Global Physiology and Pathophysiology of Cough
ACCP Evidence-Based Clinical Practice Guidelines

F. Dennis McCool, MD, FCCP

Objective: The anatomy and neurophysiology of cough has been reviewed in the preceding section. The objective of this section is to describe how the varied anatomic components of the respiratory system work in concert to produce an effective cough.

Methods: This was accomplished by reviewing (1) the factors needed to produce effective cough pressures and gas velocity in the airways, and (2) the salient features of the interaction between the airflow generated during a cough and the mucus that lines the tracheobronchial tree. The MEDLINE database was searched for this review, and the search consisted of studies published in English between 1960 and April 2004. Search terms were “cough mechanics” and “cough physiology.”

Results: Inhaling to high lung volumes and glottic closure prior to the expiratory phase of cough facilitate the generation of high intrathoracic pressures. These high intrathoracic pressures (1) provide the driving force for airstream flow during cough and (2) dynamically compress the central airways, which further enhances the cough airstream velocity.

Conclusions: High intrathoracic pressures are needed to generate the requisite cough expiratory flows and airstream velocities. However, cough may be effective in individuals with mild-to-moderate degrees of respiratory muscle weakness, as only modest increases in intrathoracic pressure are needed to dynamically compress the large intrathoracic airways and increase cough flow velocity.

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Key words: expiratory flow; intrathoracic pressure; mucociliary clearance; mucous rheology; respiratory muscles

Cough serves to clear the airways when there are (1) large amounts of inhaled material, (2) large amounts of mucus due to excessive secretions or impaired mucociliary clearance, and (3) large amounts of abnormal substances such as edema fluid or pus. Each cough involves a complex reflex arc. The neurophysiology of this reflex has been reviewed in the previous section. An effective cough depends on the ability to drive gas at high linear velocities through the airways, and on an effective interaction between the flowing gas and mucus lining the airways. These events depend on the capacity of the respiratory muscles to increase intrathoracic pressures and dynamically compress the airways. The MEDLINE database was searched for this review, and the search consisted of studies published in English between 1960 and April 2004. Search terms were “cough mechanics” and “cough physiology.”

Review of the Global Physiology of Cough

Cough Mechanics

Cough mechanics can be evaluated by considering the timing of the varied events that constitute cough. The sequence of events that lead to an effective cough has been previously described, and the phases have been classified as inspiratory, compressive, and expiratory (Fig 1).1-7 The initial phase of cough is characterized by the inhalation of gas. The volume of gas that is inhaled may be as little as 50% of tidal volume or as great as 50% of vital capacity.8-9 During
Inspiration, the expiratory muscles are lengthened and “strengthened.” The inhalation of a large volume of gas will produce greater lengthening and will optimize the expiratory length-tension relationship. Thus, inhaling to high lung volumes will enable the expiratory muscles to generate greater positive intrathoracic pressures for a given degree of neural activation. Although a modest degree of positive intrathoracic pressure is needed to generate expiratory flow, an effective cough can be achieved at pressures much lower than the maximal pressure that the expiratory muscles are capable of producing. Thus, this initial phase of cough is not critical because an effective cough can be accomplished by inhaling small volumes.

The compressive phase of cough follows the initial inspiratory phase. After inhaling a volume of air, the glottis is closed and an expiratory effort ensues. At the onset of the expiratory effort, the glottis closes for about 0.2 s. Glottic closure maintains lung volume as intrathoracic pressures are building. Glottic closure minimizes expiratory muscle shortening, thereby promoting an “isometric” contraction of the expiratory muscles, and allowing the expiratory muscles to maintain a more advantageous force-length relationship and to generate greater positive intra-abdominal and intrathoracic pressures. The high intrathoracic pressures developed during glottic closure may be as great as 300 mm Hg. The high intra-abdominal and intrathoracic pressures developed during this phase of cough can be transmitted to the CNS and mediastinum, and underlie some of the adverse cardiovascular, GI, genitourinary, musculoskeletal, and neurologic complications associated with cough (which are described in more detail in their respective sections in these guidelines).

Once the glottis is opened, the expiratory phase of cough ensues, and the high intrathoracic pressures developed during the compressive phase of cough promote high expiratory flow rates. Initially, there is a very brief blast of turbulent flow. This initial peak of expiratory flow lasts about 30 to 50 ms and may reach flow rates as great as 12 L/s. This burst of air is due to the additive effects of the gas expired from the distal parenchymal units and the gas displaced by the central airways, which are compressed by the high intrathoracic pressures. Although glottic closure enhances this phase of cough, it is not essential for an effective cough. For example, individuals with a tracheostomy or endotracheal tube can produce an effective cough by performing a huffing maneuver, which is performed with an open glottis. Accordingly, in patients with endotracheal tubes, a tracheostomy need not be performed for the express purpose of improving cough efficiency.

**Recommendation**

1. In patients with endotracheal tubes, tracheostomy need not be performed to improve cough effectiveness. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

Following the initial blast of air, there is a more prolonged period characterized by lower expiratory flows. This stage lasts 200 to 500 ms with sustained flows in the range of 3 to 4 L/s. During this timeframe, lung volume falls, transpulmonary pressure decreases, and cough expiratory flows fall. As expiratory flows diminish, the velocity of the airstream is reduced. Because the relationship between expiratory flow and airstream velocity depends on the cross-sectional area of the airways (velocity = flow/cross-sectional area), the velocity of the airstream increases as the net cross-sectional area of the airways decreases for a given rate of expiratory airflow. It follows that, as air flows from the periphery of the lung to the central airways the velocity of the gas increases. The velocity of gas in the more central airways can be further enhanced by the dynamic compression of these airways. For example, when the tracheal cross-sectional area is dynamically compressed to one fifth of its static cross-sectional area, as may occur during the expiratory phase of cough, the linear velocity of the gas would increase by fivefold. Because the kinetic energy of the airstream is proportional to the square of the velocity of
the airstream, this degree of dynamic compression increases its kinetic energy 25-fold. Increasing kinetic energy, in turn, enhances the removal of mucus adhering to the airway wall.

Dynamic compression during cough results from differences between intraluminal and extraluminal airway pressures (called transmural airway pressure). During a forced expiration, the transmural pressure at the alveolus is the same as the recoil pressure of the lung; namely, the increase in pleural pressure is transmitted to the alveolus. However, as expiratory flow ensues, the intraluminal pressure becomes lower, due to the viscous forces, while extraluminal pressure (pleural pressure) remains elevated. Thus, the airways downstream from the alveolus are subject to dynamic compression. Normally, dynamic compression is initiated in the trachea and mainstem bronchi at high lung volumes, and extends to the more peripheral airways as lung volume decreases, ensuring that the whole length of the tracheobronchial tree is “coughed.” For this to occur, high intrathoracic pressures must be sustained throughout the expiratory effort.

Gas-Mucus Interactions

The purpose of cough is to clear the airways. For cough to effectively remove mucus and particulates, the secretions that line the airways must be dispersed into the expiratory gas. The major physical forces affecting the removal of secretions include the mean velocity of the air stream and the rheologic properties of the mucus. The mean velocity of the air stream is a major determinant of the type of airflow that occurs in liquid. The generation of high gas velocities promotes the dispersion of liquid mucus into the air stream. At the high velocities that are commonly encountered during cough (ie. > 2,500 cm/s), mucus is torn off and droplets are suspended within the airway lumen. This flow pattern is termed misty flow. At lower velocities, the mucus-gas interaction is less effective. Other factors may also be operant in removing mucus at the high gas velocities associated with misty flow. First, airflow, in the range seen during a cough, can create waves of mucus. These waves may further enhance particle clearance. Second, the airways behave more as collapsible tubes than rigid pipes. During cough, they may vibrate and their walls approximate each other, further aiding in loosening mucus and promoting clearance.

The physical properties of mucus also affect cough efficiency. In the framework of two-phase gas-liquid flow, mucus clearance is directly proportional to the depth of the mucus, and is inversely proportional to its viscosity and elasticity. Mucus properties that enhance transport by coughing may retard transport by cilia. For example, increased elasticity has a negative effect on mucus clearance by cough, but it enhances the removal of secretions by ciliary beating. To accommodate both mechanisms of mucus clearance, mucociliary and cough, native mucus may exhibit intermediate levels of viscosity. In healthy individuals, cough may be effective in clearing secretions down to the 7th to 12th of the total of 23 airway generations. It is possible that under conditions of excess mucus production, in which the serous layer has low viscosity close to that of water, the effect of coughing can extend down to the level of the respiratory bronchioles.

An alternate theory asserts that the removal of airway secretions with cough has more to do with the stimulation of ciliary activity rather than the dispersion of liquid into gas. The high-velocity of air attained during cough may promote mucus clearance by stimulating the mucociliary apparatus, changing the rheologic characteristics of the periciliary fluid, or increasing ciliary beat frequency. These changes may be due to neural reflexes or to physical forces acting directly on airway cells. Stress has been known to open potassium channels in vascular endothelial cells, increasing potassium flux out of the cell, resulting in hyperpolarization. The goblet cells may respond similarly to shear stresses associated with the rapid flows of cough or rapid inhalations. Neural reflexes may be mediated by rapidly adapting receptors in the lung that respond to rapid deflation or inhalation by increasing mucus secretions. The observed increase in mucociliary clearance induced by high-frequency oscillatory flows may be due to a similar mechanism. This alternate theory to enhanced ciliary function, however, is less likely than the two-phase liquid gas theory as a mechanism underlying the clearance of secretions with cough. First, mucociliary clearance seems to operate at optimum levels under circumstances in which there is no cough, and, second, the removal of pathologic secretions requires that they are physically detached from the airway lining fluid.

Cough Inefficiency

Altered Cough Mechanics

Several factors may interfere with the capacity of the respiratory system to produce the requisite pressures and gas velocities needed for effective cough. The initial phase of cough is accompanied by inhaling a volume to near total lung capacity. Inhaling to high lung volumes will optimize expiratory pressures, and will enhance expiratory airflow and velocity. At high lung volumes, the expiratory muscles are near their optimal length and respiratory system elastic
recoil is increased; both factors will increase expiratory pressure during cough.\textsuperscript{27} Patients with neuromuscular disease and inspiratory muscle weakness will inhale only a limited volume of air. Because the inhaled volume is reduced, expiratory pressures, airflow, and velocity will be diminished. However, inspiratory muscle weakness must be profound to affect this phase of cough as mild-to-moderate degrees of weakness may not result in restriction. By contrast, expiratory muscle weakness may have more severe ramifications regarding cough efficiency. Even mild-to-moderate degrees of expiratory muscle weakness will adversely affect the expiratory pressures and thereby the expiratory flows needed for an effective cough.\textsuperscript{28,29} Thus, individuals with lower cervical spinal cord injuries who exhibit profound expiratory but mild inspiratory muscle weakness will have a compromised cough. The inability to effectively cough increases their risk of developing atelectasis and pneumonia, which are frequent causes of morbidity in patients with neuromuscular weakness.\textsuperscript{30} Protussive mechanical aids may be especially useful in augmenting cough by providing a negative pressure at the mouth and enhancing expiratory flow. However, these devices are only useful when expiratory flow is not limited by airways collapse when suction is applied at the airway opening. Thus, individuals with neuromuscular weakness, and no concomitant COPD, may benefit from these mechanical aids (see section on “Nonpharmacologic Airway Clearance Therapies” in these guidelines).

**Recommendation**

2. **Individuals with neuromuscular weakness and no concomitant airway obstruction may benefit from mechanical aids to improve cough.**

   Level of evidence, low; net benefit, intermediate; grade of recommendation, C

Expiratory muscle weakness also contributes to cough inefficiency by limiting dynamic airway compression, a condition that augments expiratory gas velocity. Dynamic compression is needed to increase gas velocity for a given flow rate and thereby enhance the kinetic energy available to clear secretions. The relationship between expiratory muscle weakness and cough expiratory flows has been explored in healthy individuals and in those with neuromuscular weakness. Expiratory muscle weakness has a more profound effect on expiratory pressures than expiratory flow. In partially curarized healthy subjects, expiratory pressures are markedly reduced, whereas expiratory flows are only minimally reduced.\textsuperscript{31} However, the spike in peak flow normally seen on cough flow-volume curves during expiration is absent (Fig 2). Individuals with profound expiratory muscle weakness due to cervical spinal cord injury (ie, expiratory pressures in the range of only 8 to 36 cm H\textsubscript{2}O) also have reduced expiratory flows.\textsuperscript{32} However, the expiratory pressures are sufficient to cause dynamic airway compression, as suggested by the presence of plateaus of flow on isovolume pressure-flow curves.\textsuperscript{32} Weakness of the abdominal expiratory muscles may also impair cough by impeding dynamic compression of the airways. When the abdominal wall expands rather than contracts during cough, the expiratory muscles perform work shortening the muscle rather than generating pressure. In addition, because the passive abdomen is very compliant and expands during cough, some of the pressure generated by the expiratory muscles is dissipated across the abdomen. Both factors limit the rise in intrathoracic pressure, thereby hindering dynamic airway compression.\textsuperscript{10,31}

**Altered Mucus Rheology**

Cough ineffectiveness may occur when the rheological properties of mucus are altered. An effective cough requires that mucus is detached from the epithelial surface and mobilized into the airstream. Thus, sputum clearability depends on sputum tenacity, which is the product of adhesiveness and cohesiveness. Increasing viscosity and elasticity will increase tenacity and reduce cough effectiveness. When the water content of mucus is decreased, viscosity,\textsuperscript{33} and elasticity\textsuperscript{34} are increased, thereby inhibiting mucus clearance. The finding of decreased
cough effectiveness in asymptomatic smokers compared with nonsmokers supports the notion that altered rheologic properties may initially impair cough clearance, but when smokers become symptomatic with excessive secretions, increases in mucus thickness will aid cough clearance. In contrast to the results of in vitro studies, cough effectiveness may be independent of mucus viscoelasticity in patients with COPD. The lack of a correlation between mucus clearance by cough and the viscoelasticity of expectorated secretions may be explained by the narrow range of viscosity of the sputum specimens in comparison to the previous in vitro studies (0.3 to 1.7 vs 1 to 77 Pa/s, respectively).

Altered Mucociliary Function

The mucociliary apparatus serves to transport secretions from the periphery to the more proximal airways where they can then be cleared by cough. Smoking inhibits ciliary beating and would therefore be expected to adversely affect mucociliary clearance. The effect of smoking on mucociliary clearance, however, is controversial. Mucociliary clearance is reduced in young, asymptomatic cigarette smokers with normal pulmonary function. However, clearance from the peripheral airways of asymptomatic smokers was no different than that of healthy age-matched nonsmokers. The inability to find a difference in mucociliary clearance between these two groups may be due to the opposing effects of smoking. It can either decrease mucociliary clearance by inhibiting ciliary beating or increase it by increasing peripheral airway secretions. However, when smokers develop airways obstruction, mucociliary clearance becomes impaired as this system is overloaded with excessive secretions. Once smoking leads to the development of COPD, cough becomes a necessary adjunct to mucociliary clearance.

Conclusions

An effective cough constitutes an important host-defense mechanism. High intrathoracic pressures promote dynamic airway compression and are needed to generate the requisite expiratory flows and airstream velocities. However, only modest increases in intrathoracic pressure are needed to narrow the large intrathoracic airways and increase cough flow velocity. Thus, cough may be effective in individuals with mild-to-moderate degrees of respiratory muscle weakness. Cough ineffectiveness may occur when the respiratory muscles are severely weakened such that the volume of air inhaled during the first phase of cough is limited and/or the rise of intrathoracic pressures is severely limited during the second and third phases of cough. Thus, in patients with diseases that are likely to be associated with cough ineffectiveness, the clinician should have a high index of suspicion that such patients are at increased risk of pneumonia, atelectasis, and respiratory failure, and should monitor closely for these complications.

Recommendation

In patients with ineffective cough, the clinician should be aware of and monitor for possible complications, such as pneumonia, atelectasis, and/or respiratory failure. Level of evidence, low; net benefit, substantial; grade of recommendation, B

Summary of Recommendations

1. In patients with endotracheal tubes, tracheostomy need not be performed to improve cough effectiveness. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

2. Individuals with neuromuscular weakness and no concomitant airway obstruction may benefit from mechanical aids to improve cough. Level of evidence, low; net benefit, intermediate; grade of recommendation, C

3. In patients with ineffective cough, the clinician should be aware of and monitor for possible complications, such as pneumonia, atelectasis, and/or respiratory failure. Level of evidence, low; net benefit, substantial; grade of recommendation, B

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