

# Bronchial Mucus Transport

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## Summary

**Effective clearance of inhaled particles requires mucus production and continuous mucus transport from the lower airways to the oropharynx. Mucus production takes place mainly in the peripheral airways. Mucus transport is achieved by the action of the ciliated cells that cover the inner surface of the airways (mucociliary transport) and by expiratory airflow. The capacity for mucociliary transport is highest in the peripheral airways, whereas the capacity for airflow transport is highest in the central airways. In patients with airways disease, mucociliary transport may be impaired and airflow transport may become the most important mucus transport mechanism. *Key words: mucus clearance, cilia, cough, mucociliary transport.* [Respir Care 2007;52(9):1150–1156. © 2007 Daedalus Enterprises]**

## Introduction

The inner surface of the airways is exposed to at least 10,000 L of air per day. Besides air, also dust, toxic gases,

and microorganisms are inhaled, many of which are deposited in the lower airways. Effective defense mechanisms are therefore needed to clear the airways of alien materials and keep the lung sterile. One of the most important defense mechanisms is the production of bronchial secretions and the continuous transport of these secretions from the peripheral airways to the oropharynx. Bronchial secretion is a heterogeneous fluid that consists mainly of water and macromolecular constituents.<sup>1–4</sup> The most specific part of bronchial secretion is mucus, which is a highly oligomerized and entangled mucin polymer, with water and various macromolecular glycoproteins as part of the gel structure.<sup>3,4</sup> Mucus is produced throughout the bronchial tree by serous cells, goblet cells, Clara cells, and type II alveolar cells.<sup>3</sup> The amount of mucus produced at a given level in the bronchial tree depends on the number of mucus-producing cells at that level, which is related to

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Fig. 1. Mucus production is higher in the peripheral airways than in the central airways. The capacity for mucociliary transport is higher in the peripheral than in the central airways. The capacity for mucus transport by expiratory airflow is higher in the central airways than in the peripheral airways.

the total airway surface, so more mucus is produced in the peripheral airways than in the central airways (Fig. 1). In normal situations the total amount of mucus that reaches the trachea is about 10–20 mL/d.<sup>5</sup>

### Mucus Transport

Mucus transport is governed by the mechanical forces of ciliary beating and airflow, which are counteracted by the frictional and inertial forces of the mucus. The bronchial secretions form at least 2 layers, possibly 3. The cilia reside in the sol layer, and the mucus layer lies atop the cilia. It is hypothesized that the sol and mucus layers might be separated by a layer of surfactant. The sol contains glycoproteins, but these glycoproteins are not highly oligomerized, so the sol has very low viscosity and elasticity (it behaves as a liquid). However, the mucus has a high concentration of oligomerized glycoproteins and is therefore both elastic and viscous (a gel). Probably only the mucus layer is transported, but the sol layer is essential for mucus transport<sup>6</sup> because it provides the conditions necessary for the cilia to beat effectively.

The transporting surface area at a given level in the bronchial tree is determined by the number and diameter of the airways. From the central to the peripheral airways, the airway diameter decreases and the number of airways increases exponentially, so the total airway diameter and the transporting surface decrease from the peripheral to the central airways, and is somewhat reduced at bifurcations.<sup>7</sup> Because of the smaller transporting surface in the central airways, in theory, mucus might accumulate in the central airways, but such accumulation is prevented by a higher mucus transport rate in the central airways,<sup>8</sup> and by reduction of the mucus volume by reabsorption of the watery constituents.<sup>9</sup>

### Mucociliary Transport

In health, mucus is transported partly by the coordinated beating of the cilia. Ciliated cells are found in the airways

from the trachea to the terminal bronchioles. Each ciliated cell has about 200 cilia, and the cilia have “claws.” The cilia beat at 8–15 Hz. During the beat, the “claws” reach the mucus gel layer and push it toward the oropharynx. The cilia’s recovery motion takes place in the sol layer, below the mucus layer. The coordinated ciliary beat delivers a small force to the mucus blanket with a relatively high shear rate, because of the beat frequency, which creates favorable rheological conditions to transport the mucus toward the oropharynx. The decrease of the total airway surface from the peripheral to the central airways is proportionally related to a decrease in the number of ciliated cells. That is, the number of ciliated cells per unit of airway surface decreases from the peripheral to the central airways, so the central airways have less mucociliary transport capacity than the peripheral airways (see Fig. 1). This is partly compensated by a somewhat higher beat frequency in the central airways,<sup>10</sup> but in the central airways, airflow is the primary mechanism of mucus transport.

### Expiratory Flow Transport

Both tidal breathing and forced expiration propel mucus cephalad. This is described as 2-phase gas-liquid flow.<sup>11</sup> Airflow transport depends mainly on the airflow velocity, which is determined by the airway diameter and the airway pressure created by the expiratory muscles. Mucus is transported especially if flow velocity is  $> 1$  m/s.<sup>12</sup> The total airway diameter depends on the airway generation and the dynamic compression of the airways during expiration. The total airway diameter decreases from the peripheral to the central airways, so the airflow velocity is higher in the central airways, and airflow transport is greater in the central airways. During a forced expiration, the airways are compressed by the transmural pressure (Fig. 2). Airway narrowing increases airflow velocity, which increases mucus transport. With a simulated cough machine, Zahm et al<sup>13</sup> found that the displacement of artificial mucus after a single simulated cough was higher when the airway diameter was narrower (Figs. 3 and 4). Hasani et al found that mucus transport due to expiratory airflow is more efficient in the central than in the peripheral airways<sup>14</sup> (Fig. 5).

During a forced expiration, high expiratory flow develops within approximately 0.1 second, which creates a high shear rate. Mucus transport varies inversely with shear rate. This phenomenon is called pseudoplastic flow or shear thinning. Mucus viscosity in a given sample may vary by a factor of up to 500, depending on the applied shear. The decrease in viscosity can be explained by a temporary realignment of macromolecular glycoproteins by the applied force,<sup>3</sup> so repeated forced expirations with short intervals between the expirations may reduce viscosity and improve mucus transport more than coughs with longer

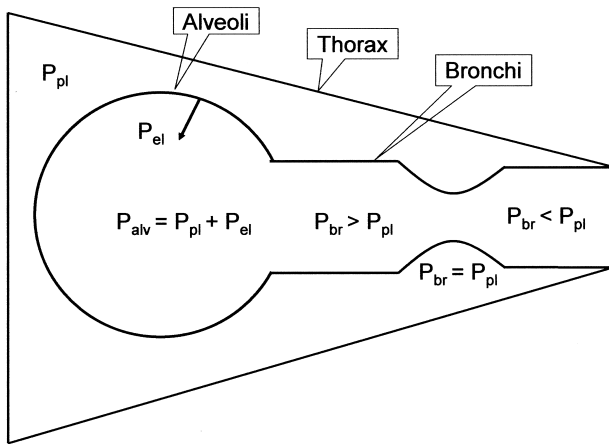


Fig. 2. During a forced expiration, expiratory airflow is generated by a high alveolar pressure ( $P_{alv}$ ), which is the sum of pleural pressure ( $P_{pl}$ ) and elastic recoil pressure ( $P_{el}$ ). The bronchial pressure ( $P_{br}$ ) decreases toward the mouth. The point where  $P_{br}$  equals the surrounding  $P_{pl}$  is called the equal pressure point. Downstream of the equal pressure point, airway compression can take place and cause high linear airflow velocity.

intervals. This concept is supported by the findings of Zahm et al,<sup>13</sup> who found in a model study that repetitive forced expirations are more efficient with shorter intervals.

Forced expirations can be done with cough or huff. A cough begins with glottis closure, then a more or less isometric contraction of the expiratory muscles, which creates high intrathoracic pressure, then sudden opening of the glottis creates a burst of expiratory airflow. A huff starts with the glottis open, and the glottis remains open throughout the huff. Huff requires a fast, dynamic contraction of the expiratory muscles. Cough or huff can begin at low, middle, or high lung volume. Lung volume and expiratory force can be more easily adjusted during huff than during cough. However, huff technique is more difficult for some patients.

### Mucus Transport in Airways Disease

Mucus transport is often decreased in patients with pulmonary diseases such as asthma,<sup>15</sup> chronic obstructive pulmonary disease (COPD),<sup>16–18</sup> and cystic fibrosis,<sup>19,20</sup> and in patients with dysfunctional cough or glottic control. Impaired mucociliary transport may arise because of impaired cilia function,<sup>21–25</sup> which mainly impairs transport in the peripheral airways and thus causes secretion stasis in the peripheral airways. Aikawa et al found that mucus retention occurred especially in the peripheral airways<sup>26</sup> (Fig. 6).

### Asthma

Asthma is characterized by sudden episodes of dyspnea and bronchospasm, which can usually be almost completely

reversed by medical therapy. The hypersecretion that is usually present during asthma episodes is a result of mediator release after antigen exposure. Even with resolution of dyspnea and pulmonary dysfunction, there is ongoing airway inflammation and hyperplasia of the mucus glands and cells. Bronchodilation probably has no effect on mucus transport in these patients.<sup>27</sup> It has been postulated that during an asthma episode a cilia-inhibiting factor reduces cilia activity, disorganizes ciliary beating, and thereby reduces ciliary efficacy,<sup>24,28,29</sup> but the cilia-inhibition may be caused by abnormal physical properties of the mucus rather than an intrinsic ciliary inhibitor. Mucus hypersecretion and changes in the flow or surface properties of mucus may also reduce ciliary activity.<sup>30–32</sup> Mucociliary transport, therefore, can be severely reduced in patients with asthma, and there is a further reduction during sleep. After an exacerbation, when the patient is symptom free, mucus transport can recover and be comparable to that in healthy subjects, or it may remain reduced<sup>15,33–35</sup> despite favorable changes in mucus viscoelasticity.

### Chronic Obstructive Pulmonary Disease

Patients with COPD have day-to-day variability in the extent of airway obstruction and collapse. About 10–15% of these patients have a measurable decrease in airway obstruction with medical therapy. Although mucociliary transport may be normal in patients with emphysema associated with alpha-1 antitrypsin deficiency,<sup>36</sup> in other forms of COPD mucociliary transport is usually reduced. Mucus transport may also be decreased by smoking-induced ciliary paralysis<sup>23,24</sup> and by bacterial infections.<sup>37,38</sup> Airway collapse during coughing, or the inability to generate effective cough flow can also contribute to mucus retention. In contrast to patients with asthma, mucociliary transport does not fully recover, and it may progressively decrease due to a loss of ciliated epithelium because of recurrent infections and progressively severe airway instability.<sup>25</sup> Hypersecretion, which is usually present in these patients, may also further reduce mucociliary transport.

### Cystic Fibrosis

Patients with CF initially have normal functioning cilia and an efficient cough.<sup>19</sup> During the course of the disease, however, the bronchial mucus transport rate decreases along with the pulmonary function.<sup>39</sup> There is an inverse correlation between residual volume as a percentage of total lung capacity and bronchial mucus clearance rate.<sup>39</sup> Although bronchial mucus is considered a bigger problem in CF than in COPD, the rheological characteristics of CF mucus are comparable to those of mucus from patients with chronic bronchitis.<sup>40</sup> Mucus hydration was postulated to be decreased in CF, but experimental evidence did not

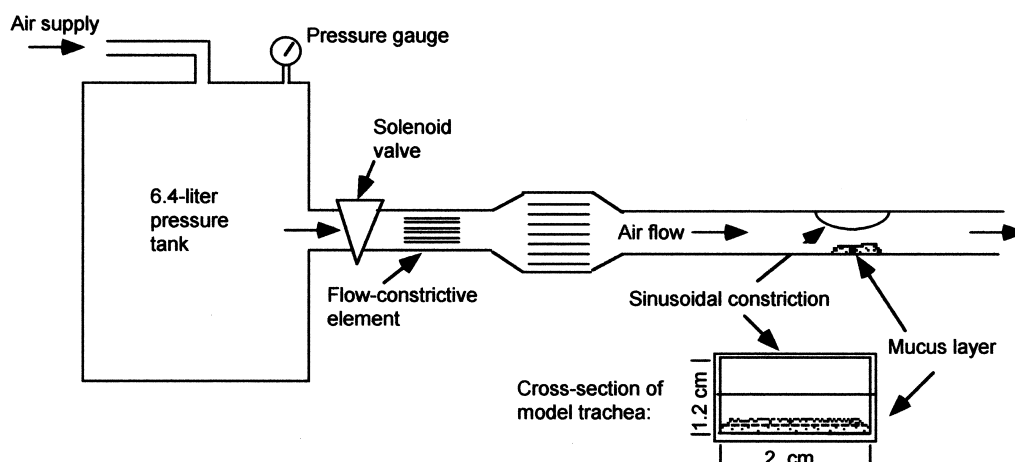


Fig. 3. A simulated cough machine to measure the airflow-dependent clearability of sputum. The model trachea is  $1.2 \times 2$  cm in cross-section. Forty  $\mu\text{L}$  of artificial mucus is placed in approximately 0.5-mm thick line across the base of the artificial trachea. The artificial cough is at about 11 L/s, through a flow-constrictive element that mimics the airflow pattern of a natural cough. The movement of the mucus is measured after each of 3 artificial coughs. The tube can be narrowed to simulate airway compression. (From Reference 13, with permission.)

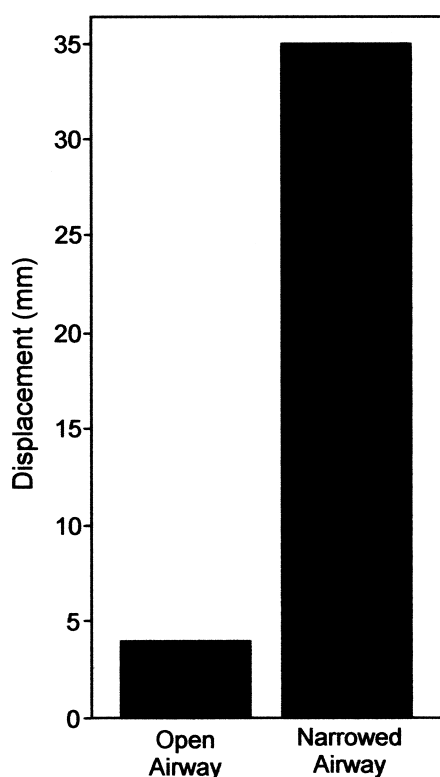


Fig. 4. Displacement of an artificial mucus sample in an open versus a narrowed airway (in the simulated-cough setup in Figure 3) after one simulated cough. Narrowing the airway significantly increased mucus transport. (From data in Reference 13.)

support that contention.<sup>41</sup> It is more likely that poor mucus clearance in CF airways results from abnormal mucus adhesiveness and tenacity.<sup>42</sup> In CF, the small peripheral air-

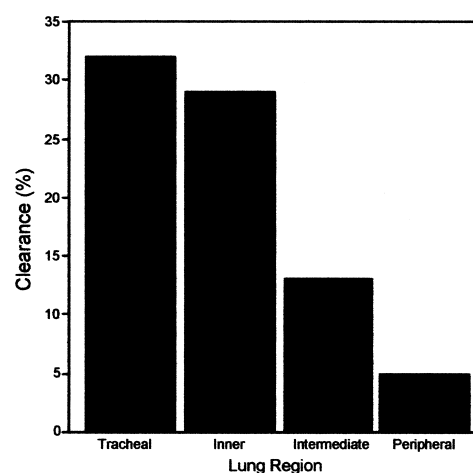


Fig. 5. Cough clearance of mucus in 4 lung regions. (From data in Reference 13.)

ways can be completely obstructed by mucus. Hypersecretion and chronic obstruction can cause recurrent respiratory infections that can further reduce mucociliary transport and cause dysfunctional cough.

### Neuromuscular Dysfunction of the Cough Mechanism

Airway mucus clearance can also be impaired by factors external to the lungs and airways. Patients with bulbar or expiratory muscle weakness may not be able to generate peak flow sufficient for an effective cough. Severe bulbar dysfunction most commonly occurs in patients with amyotrophic lateral sclerosis, spinal muscular atrophy type 1,



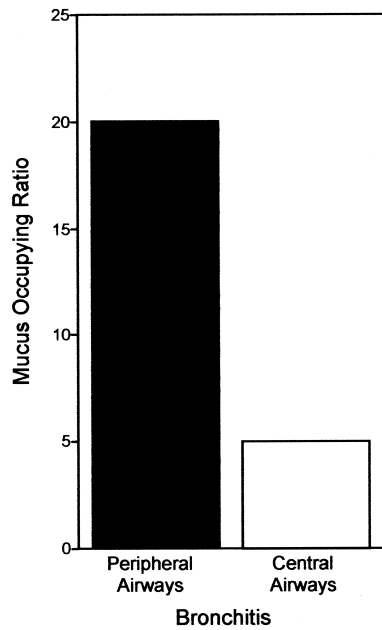


Fig. 6. Mucus occupying ratio (percentage of the cross-section of the airway occupied by mucus) in patients with chronic bronchitis. This ratio reflects the mucus retention in the peripheral and central airways. (From data in Reference 26.)

and the pseudobulbar palsy of central nervous system etiology. Inability to close the glottis can result in complete loss of cough ability. Patients with certain central nervous system diseases, such as multiple sclerosis, can lose volitional cough but retain effective reflex coughs. Cerebellar and basal ganglia diseases often result in ineffective, uncoordinated cough.

#### Risk From Insufficient Mucus Transport

When mucus transport is insufficient, mucus can turn into a risk factor instead of a defense mechanism. Prescott et al<sup>43</sup> found that chronic mucus hypersecretion is a significant predictor of COPD-related death when pulmonary infection is implicated (relative risk 3.5), but not of death without pulmonary infection (relative risk 0.9). This suggests that mucus stasis may lead to infection and thereby to death.

#### Compensating for Insufficient Mucus Transport

Impaired mucociliary transport can be partly compensated by mucus transport by expiratory airflow. The effectiveness of airflow transport is illustrated in patients with primary cilia dyskinesia, who have no effective mucociliary transport because of a defect of the cilia. Figure 7 shows the deposition and airflow clearance of radioactive aerosol particles in a patient with immotile cilia syndrome

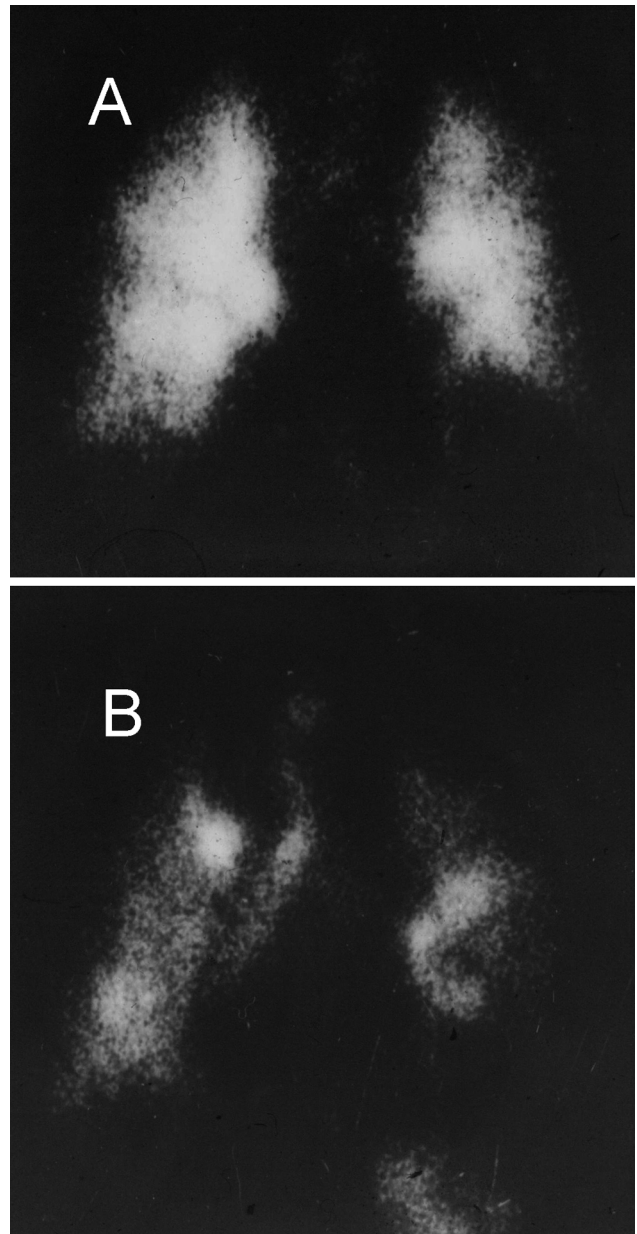


Fig. 7. A: Deposition of radiolabeled particles in the lungs of a patient with primary ciliary dyskinesia. B: Clearance of the radiolabeled particles after a period of directed coughing. Because the patient has ciliary dyskinesia, the mucus and radiolabeled particles were transported only by the airflow from the directed coughing. Some of the particles were swallowed, so the stomach contains some of the radioactive tracer.

before and after a period of directed coughing. With only airflow transport the airways can be cleared of a large percentage of the inhaled particles. However, the effectiveness of forced expirations (cough or huff) may be limited in patients with airflow obstruction and/or dynamic airway collapse, because obstructions limit airflow and airflow velocity in the airways peripheral to the obstruc-

tion and lower velocity means less effective mucus transport. In patients with unstable airways (eg, patients with emphysema), dynamic compression (which is usually favorable for mucus transport) may cause complete airway collapse and no local airflow. This airway collapse is caused by the low elastic recoil pressure, which shifts the point of dynamic compression to the peripheral airways, and to larger transmural pressures. In some patients, frequent coughing can have adverse effects, such as costal fractures and vomiting. And coughing increases energy expenditure and can cause fatigue. In those patients cough should be suppressed to some extent, or huff should be considered as an alternative.

### Summary

Mucus production and transport is an important defense mechanism of the lower airways. However, in pulmonary disease, mucociliary transport may be impaired and inadequate mucus transport can become a risk factor for pulmonary infection. Mucus transport by expiratory airflow is the most important alternative to mucociliary clearance.

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## Discussion

**Hess:** I wonder if you could help me to understand the mechanism of the airway narrowing during coughing and how that improves mucus clearance. Is it because there's an increased velocity of gas flow? Is it because there's more pressure behind it? Does it affect the properties of mucus in some way?

**van der Schans:** Yes, the airway narrowing takes place by pressure differences between the pressure in the airways and the surrounding pressure. So when the surrounding pressure is higher than the pressure in the airways, the airways are narrowed. It depends a little bit on the stiffness of the airways, of course; when the airway is very stiff, there is more pressure difference with. . . the pressure difference is responsible for airway narrowing.

**Hess:** But my question, then, is, how does that improve mucus clearance? Is it because there is more velocity of gas flow through the airways? Or, does it affect the structure of the mucus in some way? I assume it's just the physics of gas flow and the effect of that on moving secretions?

**van der Schans:** The velocity of the airflow is much higher when the airways are narrow. Yes.

**Rubin:** I'll add to that that not only are you increasing the velocity and increasing the Reynolds number, but the equal pressure point isn't a fixed point; that that moves, and it tends to move proximally, and as it moves, you

get carried-along secretions. So you have 2 things operating, an increased flow, but a change in that flow profile that would tend to bring things more toward the trachea.

**Rogers:** I was fascinated by the image you showed of the collapsed trachea. The trachea has got massive C-shaped cartilage rings around it, which, you would think, would limit collapse, but clearly doesn't. Perhaps the collapse would be even greater without the cartilage?

**van der Schans:** Still they can collapse.

**Rogers:** But how does that happen?

**van der Schans:** Just because of the pressure differences and because of the fact that in some patients, like the patient with emphysema, the airways are not so stable anymore. But if you look through a bronchoscope in the airways, you can just see that there is complete collapse of large airways.

**MacIntyre:** Help me understand—what actually triggers the cough? If you have a lot of mucus down there, I can see why, teleologically, you would want to cough. But what actually stimulates this rather complex reflex? And then to take that a step further, what about the person who doesn't have mucus, but coughs like crazy—a classic example would be somebody, perhaps, with asthma, the cough variant of asthma, where there's no mucus, or very little mucus. So what actually triggers this mechanism, both with and

without mucus? Or is that too complicated?

**van der Schans:** What triggers it, I don't know. Even patients who don't have a history of producing mucus still need to clear their airways. So when the mucociliary system is not enough, these patients need to cough. For instance, patients with primary ciliary dyskinesia, they need expiratory flow to compensate for the immotile cilia. So, they need to cough even when they don't have a history of really producing mucus. Does that answer your question?

**MacIntyre:** It just confuses me, and because I am a pulmonologist, cough is a very, very common presenting symptom. And certainly, during an episode of acute bronchitis or where there's clearly gunk in the airway, you can understand why we have a cough reflex, although apparently I don't understand what triggers it. But what really confuses me are these patients who don't have a lot of mucus. As I said, sometimes in an asthma-like syndrome, patients with interstitial lung injury—where there's very little, if any, mucus present—often are bothered by these horrific coughs. And I'm just trying to figure out why that happens.

**Wojtczak:**\* Neil, there are lots of different receptors in the airway that

\* Henry Wojtczak MD, Naval Medical Center, San Diego, California, representing Monaghan/Trudell Medical.



account for cough. For instance, the concept of stretch and/or compression. If the airway is subjected to either of these physical forces, then the mechanical and/or tactile receptors could initiate cough. So, for instance, in somebody who has got a cough-variant form of asthma, their cough may be coming from airway stretched, or it may be coming from inflammatory mediators. Mucus is just one potential stimulant for cough.

**MacIntyre:** As I get older, I think more teleologically, and I wonder why on earth we evolved into a system that would make us cough even though there was no mucus there.

**van der Schans:** Even when there is no mucus, there are inhaled particles, and you need to clear your lungs from the inhaled particles.

**Howard:\*** My reading of the literature actually suggests that the most common reason for chronic cough is postnasal drip. And gastroesophageal reflux disease has been indicated as well. But actually having a cough due to mucus hypersecretion is one of a more restricted domain, as you've indicated. It's a complicated question.

**Rubin:** I was just going to actually say something similar to Bill [Howard]: a year ago January the ACCP [American College of Chest Physicians] published evidence-based guidelines on cough that Richard Irwin edited.<sup>1</sup> In adults, the Irwin studies have shown that upper airway cough syndrome (this used to be called postnasal drip), gastroesophageal reflux, and asthma really represent the 3 major causes of cough within patients who don't have bronchiectasis or chronic bronchitis.<sup>2</sup> Very few of those patients with chronic cough, otherwise, have a lot of secretion down

there. Only about 2% or less, and they call that "persistent bacterial bronchitis."<sup>3</sup>

In children, it may be different. It's not at all clear that reflux is associated with cough in children, or that cough-variant asthma is a significant problem, according to Anne Chang in Australia.<sup>4</sup> But there still exists some problem of persistent or chronic cough.

The other comment is that the failure to expectorate secretions doesn't necessarily mean that there is mucus hypersecretion, and that coughing a lot or coughing up a lot of junk doesn't necessarily tell you whether you're clearing the airways, whether you're producing an excessive amount in the airways, or whether you're just coughing it up. So when we've looked at volume of expectorated secretions outcome, it hasn't really correlated well with anything that could be considered clinical outcomes, such as days of hospital, exacerbations, or pulmonary function, making this that much more difficult, and harkening back to Mike Schechter's earlier question.

1. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al; American College of Chest Physicians (ACCP). Diagnosis and management of cough. ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):1S-23S.
2. Irwin RS, Madison JM. The diagnosis and treatment of cough. *N Engl J Med* 2000; 343(23):1715-1721.
3. Schaefer OP, Irwin RS. Unsuspected bacterial suppurative disease of the airways presenting as chronic cough. *Am J Med* 2003; 114(7):602-606.
4. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. *Chest* 2006;129(5):1132-1141.

**Rogers** Just to also say that in a number of these diseases, the cough reflex can become sensitized and the response becomes heightened. Experimental studies have shown that, for example, bradykinin, which is generated in asthma, sensitizes the nerves that cause cough to subsequent exposure to tussive stimuli.<sup>1</sup> It looks as if the inflammatory processes associated

with some of these respiratory disease conditions upregulate the cough-inducing nerves, such that you don't need so much of a stimulus to activate them.

1. Fox AJ, Laloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. *Nat Med* 1996;2(7):814-817.

**MacIntyre:** Can a "dry" cough, in fact, irritate the airways to the point where it stimulates mucus?

**Rogers:** Yes, I think that would be possible.

**MacIntyre:** So you start off with a dry cough, and end up producing the mucus.

**Schechter:** I also savor teleologic explanations. And I think that probably the main reason for cough is to reverse aspiration and maybe also to stop people from smoking. But smoking is actually a great example of desensitization of the cough reflex, because when kids first start smoking, they can barely inhale, because they cough, and then after awhile, they can continue to smoke because they've desensitized themselves. So I think that progressive desensitization of the cough reflex is what allows people to smoke.

It's also what allows children who have swallowing dysfunction and other things that lead to aspiration to do that in a clinically silent way. They aspirate but don't necessarily cough that much when they aspirate. As an anecdote, we once misplaced a pH probe into the trachea of a child and didn't realize it until we saw the x-ray, because it didn't bother him; he was completely desensitized from all the chronic aspiration he had been doing.

**Hess:** So, then the question I ask the group is, when is a cough abnormal and it when should it be suppressed?

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**MacIntyre:** That's where I was going.

**Hess:** That's the logical question from the question Neil was asking.

**Myers:** I have a question. It's not an answer to Dean's or Neil's question, but you actually showed a slide that talked about the ability of constriction or bronchoconstriction potentially to help or enhance mucus mobilization and clearance. I guess this is a clinical application question. Routinely, in our patients, when we're performing airway clearance, we provide

$\beta$  agonists or bronchodilators to those patients prior to airway clearance. Is that actually being counterproductive?

**van der Schans:** No, I don't think so, because that airway dilation takes place in very peripheral airways, so it decreases flow. And this narrowing of the airways I showed you is more in central airways—the larger airways. Although I think there is one study group from Austria<sup>1</sup> who showed that it may decrease the airway stability when you use airway dilators. It may decrease the stability of the airways and may make the airways collapse.

1. Zach MS, Oberwaldner B, Forche G, Polgar G. Bronchodilators increase airway instability in cystic fibrosis. *Am Rev Respir Dis* 1985;131(4):537-543.

**Rubin:** They did some studies a few years back at Philadelphia<sup>1</sup> in children with tracheomalacia, showing that if you used bethanechol it may prevent collapse, and actually improve their malacia, as opposed to  $\beta$  agonists, which have been shown to collapse the airways.

1. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. *Pediatr Pulmonol* 1990;9(3):170-176.



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