Inhaled Adrenergics and Anticholinergics in Obstructive Lung Disease: Do They Enhance Mucociliary Clearance?

Ruben D Restrepo MD RRT

Introduction

Innervation of Airway Secretory Structures
- Adrenergic Innervation
- Cholinergic Innervation
- Non-Adrenergic and Non-Cholinergic Pathway

Adrenergics
- Short-Acting β Agonists
  - Terbutaline
  - Albuterol
  - Levalbuterol
  - Fenoterol
- Long-Acting β Agonists
  - Salmeterol
  - Formoterol

Anticholinergics
- Ipratropium
- Tiotropium
- Glycopyrrolate

Effects of Common Adrenergics and Anticholinergics on Mucociliary Clearance

Summary

Pulmonary mucociliary clearance is an essential defense mechanism against bacteria and particulate matter. Mucociliary dysfunction is an important feature of obstructive lung diseases such as chronic obstructive pulmonary disease, asthma, cystic fibrosis, and bronchiectasis. This dysfunction in airway clearance is associated with accelerated loss of lung function in patients with obstructive lung disease. The involvement of the cholinergic and adrenergic neural pathways in the pathophysiology of mucus hypersecretion suggests the potential therapeutic role of bronchodilators as mucocative agents. Although anticholinergics and adrenergic agonist bronchodilators have been routinely used, alone or in combination, to enhance mucociliary clearance in patients with obstructive lung disease, the existing evidence does not consistently show clinical effectiveness. Key words: anticholinergic, adrenergic, airway clearance, bronchodilator, chronic obstructive pulmonary disease,
**Introduction**

Mucociliary clearance is an effective and essential biological barrier against microorganisms and particulate matter. This specialized apparatus consists of secretory cells and ciliated cells that beat in a coordinated and metachronal fashion. Their propulsive force mobilizes the mucus blanket toward the larynx for elimination.

In the presence of infection and inflammation, the airway mucosa typically responds by increasing the amount of secreted mucus, due to goblet cell and submucosal gland hyperplasia and hypertrophy, a phenomenon also known as secretory hyperresponsiveness. Additionally, inflammation causes loss of cells and ciliary function, destruction of the surfactant layer by airway phospholipases, and alteration of the biophysical properties of the mucus.

Dysfunction of the mucociliary clearance is a common respiratory disturbance in patients with obstructive lung disease (OLD) such as chronic bronchitis, asthma, bronchiectasis, and cystic fibrosis (CF). This dysfunction is an important marker of accelerated loss of lung function in chronic obstructive pulmonary disease (COPD). Cough and adequate airflow are of critical importance when hypersecretion is severe, prolonged, and associated with extensive ciliary damage, because airflow may become the primary means of airway secretion clearance. Since cough is most effective with high expiratory flow, bronchodilators may have a therapeutic role in airflow-dependent clearance.

There is variability in the abnormalities of secretions produced by patients with obstructive lung disease. In CF the composition of the secretions is similar to pus, with almost no mucin or mucus, whereas secretions from patients with asthma are more viscous than those from patients with COPD, CF, or bronchiectasis. The abnormal secretion and retention of mucus in asthma has been confirmed by postmortem studies of patients with status asthmaticus that showed obstructed airways with gelatinous mucus plugs.

Although β2 adrenergics are important in the management of symptomatic obstructive lung disease, it appears that only the long-acting β adrenergics provide sustained improvement of mucociliary clearance. Evaluation of short-acting β adrenergics for the improvement of mucociliary clearance in patients with OLD has shown that their effect is generally less than that seen in normal airways.

Since neural control of mucus secretion is believed to be predominantly cholinergic, anticholinergics have the potential to inhibit the neurogenic mucus secretion pathway by blocking the cholinergic muscarinic receptor subtype M3. However, their clinical benefit as mucokinetic agents has been difficult to demonstrate.

The effect of β2 adrenergics and anticholinergics in modifying human-neutrophil-elastase-induced impairment of mucociliary clearance common to OLD has been confirmed in animal studies. Human neutrophil elastase is a known mucus secretagogue with cilia-inhibiting properties that can stimulate epithelial sodium channels, reducing the periciliary fluid layer and thus contribute to mucus stasis. Human neutrophil elastase depresses mucociliary clearance, as measured by tracheal mucus velocity in animals. Several studies have shown that human neutrophil elastase is an important inflammatory mediator in OLD and that disease severity is linked to the concentration of human neutrophil elastase in the airways.

**Innervation of Airway Secretory Structures**

The sympathetic (adrenergic), parasympathetic (cholinergic), and non-adrenergic non-cholinergic pathways are the main neural pathways responsible for the modulation of airway diameter and the innervation of secretory cells. Figure 1 shows photomicrographs of normal airway epithelium and secretory cell innervation. Darkfield illumination shows the presence of cholinergic muscarinic receptors in the submucosal glands and non-adrenergic non-cholinergic tachykinin receptors binding to epithelium and glands.

**Adrenergic Innervation**

Based on histological analyses, the sympathetic-adrenergic innervation of human airway smooth muscle and secretory structures is sparse or nonexistent and plays little or no role in regulating airway caliber. Adrenergic control appears to be restricted to the interaction of circulating catecholamines, such as adrenaline, with adrenoceptors on the secretory cells to increase mucus production.

**Cholinergic Innervation**

The cholinergic system is the dominant neural pathway in the airways, primarily by stimulation of the muscarinic M3 pathway. The muscarinic receptors are classified into M1–M5 subtypes. The M1 receptors are widely distributed throughout the parasympathetic ganglia and exocrine glands. The prejunctional muscarinic M2 autoreceptors are found in the smooth muscle and the myocardium.
and provide negative presynaptic feedback to reduce further release of acetylcholine.\textsuperscript{40–44} The \( M_3 \) receptor subtype in the airway smooth muscle mediates bronchoconstriction and secretion of mucus with a low concentration of mucin.\textsuperscript{24,45–47} When coupled to G-proteins, \( M_1, M_3, \) and \( M_5 \) muscarinic receptors have a stimulatory effect on the target tissue, whereas the \( M_2 \) and \( M_4 \) subtypes are inhibitory.\textsuperscript{43}

The increased release of acetylcholine from cholinergic nerve terminals in OLD is thought to be the result of an abnormal muscarinic receptor expression.\textsuperscript{48} Stimulation of the \( M_2 \) receptors explains the increased acetylcholine release and the potentiation of cholinergic-induced bronchoconstriction and hypersecretion in patients with asthma.\textsuperscript{47} CD8\textsuperscript{+} T lymphocytes induced by viral infection appear to cause \( M_2 \) receptor dysfunction and cholinergic activation in asthmatics.\textsuperscript{49–52} The ideal anticholinergic mucoactive drug for OLD should then antagonize \( M_1 \) and \( M_3 \) receptors but have little affinity for the \( M_2 \) receptor.

**Non-Adrenergic and Non-Cholinergic Pathway**

The non-adrenergic and non-cholinergic pathway appears to be a potent mucus secretagogue system.\textsuperscript{53,54} Neurotransmitters of the non-adrenergic non-cholinergic pathway include peptides such as vasoactive intestinal peptide, the tachykinins substance P and neurokinin A, and gases such as nitric oxide. Most gland secretion is stimulated by vasoactive intestinal peptide and tachykinins,\textsuperscript{55} whereas nitric oxide has no effect on mucus secretion in animals.\textsuperscript{38}

---

**Fig. 1.** Photomicrographs of secretory cells, nerves, and receptors in the airways. A: Normal respiratory epithelium (Ep). L = lumen. G submucosal glands. B: Intra-epithelial nerve fiber (N) between 2 goblet cells that contain mucin granules (MG) in guinea-pig trachea. The arrow points to the intercellular junction. C: Muscarinic receptors in ferret trachea. Darkfield illumination of tracheal section incubated with the muscarinic receptor antagonist \([\textsuperscript{3}H]\)quinuclidinylbenzilate, which shows localization of binding sites to submucosal glands (G) and, to a lesser extent, epithelium. D: Tachykinin receptors in ferret trachea. Darkfield illumination of tracheal section incubated with \([\textsuperscript{125}I]\)-Bolton-Hunter-SP, which shows localization of substance P binding sites to epithelium (Ep) and glands (G). Photograph A courtesy of David E Martin, PhD, Cardiopulmonary Care Sciences, Georgia State University, Atlanta, Georgia. (Photographs B, C, and D from Reference 24, with permission.)
Whereas vasoactive intestinal peptide innervation is decreased in patients with severe asthma, the number of vasoactive intestinal peptide nerves in COPD is increased. Unfortunately, the properties of vasoactive intestinal peptide nerves have no significant effect on secretion production of patients with chronic bronchitis.

Sensory non-adrenergic non-cholinergic C-fibers contain substance P, which is a tachykinin that causes bronchoconstriction and increases mucus secretion. Although the non-adrenergic non-cholinergic excitatory C-fibers have been thought to have an important role in the airway hyperresponsiveness in asthma, their presence in the human airways is not as critically important as in rodent species.

Though the non-adrenergic non-cholinergic pathway seems to play a critical role in respiratory mucus production, the description of agents that modulate that system is beyond the scope of this article. The reader is encouraged to search the reports provided in this section.

**Adrenergics**

The available data conflict regarding the benefits of $\beta_2$ adrenergics on mucociliary clearance. The effects of the $\beta_2$ adrenergics on the airways are mediated by stimulation of the $\beta_2$ receptors, which increases cyclic adenosine monophosphate, which is a regulator of ciliary beat frequency in human airway epithelia. Because of their effect on ciliary beat frequency, $\beta_2$ adrenergics have been considered mucokinetic medications and cough clearance promoters. $\beta_2$ adrenergic agonists increase passive movement of water across the airway surface, via active transport of ions across the airway epithelium. They also stimulate secretion production, primarily from their action on mucus-secreting cells and submucosal glands. These actions combined increase the amount of mucus in the airways. In fact, Daviskas et al found that the majority of the patients with chronic asthma in their study had mucociliary clearance abnormalities to the same degree as in patients with bronchiectasis and CF. Enhanced mucociliary clearance, measured by mucin secretion, with $\beta_2$ adrenergics in animal models is significantly less than that observed after administration of $\alpha$ adrenergics and $\beta_1$ adrenergics. There is, however, little evidence to suggest that there are increased proportions of mucins in the airway secretions of patients with OLD, except in patients with asthma.

**Short-Acting $\beta$ Agonists**

Though short-acting $\beta$ adrenergics have mucociliary-enhancing effects in healthy individuals, their effect in subjects with depressed clearance is minimal (Fig. 2).

**Terbutaline**

A study by Sutton et al on the effect of nebulized terbutaline, as an adjunct to chest physiotherapy in patients with stable bronchiectasis, found no significant difference in either sputum volume or radioaerosol mucus clearance between saline solution and terbutaline treatment administered prior to chest physiotherapy. Similarly, Mortensen et al found a decreased mucus production with terbutaline delivered via metered-dose inhaler in healthy subjects and patients with asthma or bronchiectasis or CF.

Two studies have evaluated the mucoactive properties of terbutaline in a group of patients with pseudohyperaldosteronism. These patients have a dysfunction of the pulmonary epithelial sodium channel. Terbutaline stimulated chloride ion secretion toward the lumen, in a dose-dependent manner, which suggests enhanced water secretion.
onto the airway surface. Daviskas et al investigated baseline mucociliary clearance and the short-term effect of terbutaline in 16 patients with chronic asthma with sputum production while on long-term treatment with salmeterol in combination with inhaled corticosteroids. Although terbutaline improved mucociliary clearance in a few of the patients, mucociliary clearance remained impaired in the majority of patients, probably because of persisting inflammation and hypersecretion of abnormal mucus (Fig. 3).

**Albuterol**

Sabater et al measured tracheal mucus velocity (a marker of mucociliary clearance) in sheep before and for 12 hours after treatment with salmeterol, albuterol, ipratropium, or placebo, to determine the effects on normal mucociliary clearance. They found that only albuterol and salmeterol can stimulate normal mucociliary clearance and reverse human-neutrophil-elastase-induced mucociliary dysfunction, and that salmeterol has a longer duration of action in these models of normal and abnormal mucociliary clearance (Fig. 4). Human neutrophil elastase contributes to mucus stasis because it decreases the tracheal mucus velocity.

Jones and Reid found that isoproterenol and albuterol increase the number of secretory cells in rats, particularly in the most peripheral airways. This hyperplasia and/or hypertrophy of mucus-secreting cells may be counterproductive in maintaining effective mucociliary clearance.
Though albuterol can be associated with bronchodilation in asthma, it has been suggested that larger-than-usual doses are needed for maximal short-term effects on mucociliary clearance, which increases the risk of increased viscous mucus secretion (Fig. 5).21

Guleria et al used cine-scintigraphy of inhaled radioactive aerosol to evaluate the effect on mucociliary clearance of a single inhalation of albuterol, ipratropium bromide, and beclomethasone in 8 patients with OLD, on 4 separate days. Quantitative indices for the 3 drugs were comparable to placebo, and there was no significant increase in mucociliary clearance on any of the days. There was no significant difference between any of the 3 drugs in short-term improvement of mucociliary clearance, as compared to placebo.88,89 Devalia et al also found that, while albuterol had a less potent, slower, and shorter duration of action than salmeterol on stimulation of ciliary beat frequency in cultured human bronchial epithelium, both agonists produced only slight (< 20%) increases in ciliary beat frequency above baseline.88

In a recent study, Laube et al measured radioactivity from inhaled particles labeled with technetium-99m in the central and peripheral regions of 7 transplanted lungs. A single administration of albuterol significantly improve mucociliary clearance, compared with the baseline values, in those lung-transplant patients (Fig. 6).90

Levalbuterol

Frohock et al used digital videomicroscopy to evaluate the differences in effect of racemic versus single-enantiomer albuterol on mucociliary clearance of single ovine airway epithelial cells. R-albuterol was associated with a dose-dependent stimulation of ciliary beat frequency significantly higher than that of the racemic S-albuterol.91

O’Riordan et al assessed the clinical importance of standard doses of the S-enantiomer on airway secretions in 14 stable long-term intubated patients by comparing a racemic formulation of albuterol, an R-enantiomer formulation, and normal saline solution. Tracheal aspirates were analyzed for volume, sodium, chloride, bicarbonate, interleukin-8, interleukin-1β, soluble intercellular adhesion molecule, and tumor necrosis factor alpha. Although all the agents were associated with increased secretion volume after the first dose, this effect was not apparent on subsequent doses. There was no significant difference in the concentrations of the electrolytes or the inflammatory indexes.92

A recent randomized double-blind placebo-controlled trial with 10 healthy adult subjects evaluated the effects of inhaled nebulized levalbuterol (1.25 mg), albuterol (2.5 mg), or placebo, for 7 days, 3 times daily. Gamma camera images of the lungs were obtained after inhalation of radiolabeled aerosol. Cleary et al found that inhaled levalbuterol does not increase mucociliary clearance or cough clearance, compared to albuterol or placebo.93
Fenoterol

In an in vivo canine preparation, Wong et al found a 4-fold increase in ciliary beat frequency 30 min after administration of fenoterol. In a study of 26 subjects with chronic bronchitis, airways reversibility of >15% after fenoterol administration was associated with faster tracheobronchial clearance, more coughs, lower sputum viscosity and elasticity, and larger 24-hour sputum production than those airways with reversibility of <15%. In a similar study by Weich et al, mucociliary clearance was measured with a scintillation camera after inhalation of a technetium-99m labeled aerosol. The increase in percentage clearance after fenoterol administration for the left and right whole lung was 35% and 36% per hour, respectively.

Long-Acting Agonists

Though some in vitro and in vivo studies suggest that long-acting agonists significantly improve mucociliary clearance, compared to short-acting agonists, others suggest only a modest improvement.

Salmeterol

Salmeterol is the most thoroughly investigated long-acting agonist, in regard to measuring the effect of β2 adrenergic agonists on mucociliary clearance. It has been suggested that lipophilic agonist proportionally prolongs its duration of action. Salmeterol is more lipophilic than the short-acting agonists, formoterol, and arformoterol. In vitro and in vivo studies show that salmeterol stimulates a faster and stronger ciliary beat frequency than does albuterol.

A study by Piatti et al, with patients with COPD and pneumonia, confirmed the ability of salmeterol to enhance “only to a modest degree” ciliary beat frequency in both normal and COPD nasal epithelium. This minimal stimulatory effect of β2 adrenergics in chronic bronchitis was confirmed by Mossberg et al, in a study in which patients with the least ventilatory impairment had the greatest enhancement of clearance. However, there have been no reports on the in vivo effect of salmeterol pretreatment on either the quantity or quality of airway secretions in chronic bronchitis.

Bennett et al compared the short-term effect of salmeterol (42 μg) to placebo on mucociliary and cough-enhanced secretion clearance in 14 patients with mild chronic bronchitis. A radiolabeled aerosol (technetium-99m sulfur colloid) and gamma camera analysis was used to measure mucociliary and cough clearance on 2 study days: a placebo/control day, and a salmeterol treatment day. There were no significant correlations between the average clearances over any period, relative to placebo and either baseline lung function or improvements in lung function (eg, percent increase in forced expiratory flow in the middle half of the forced vital capacity) associated with salmeterol treatment. Although mean whole-lung clearance was higher with salmeterol than with placebo, only peripheral lung clearance was significantly enhanced by salmeterol (Fig. 7). The distribution of β agonistic aerosol particles and their impact on mucociliary clearance may be particularly important in patients with mild to moderate airway obstruction. Bennett et al has suggested that the observed enhanced clearance with salmeterol may be primarily from its effect on the mucociliary apparatus, as opposed to the cough mechanism.

A crossover study by Hasani et al found no significant enhancement of mucociliary clearance in patients with asthma following 2 weeks of salmeterol versus placebo, and concluded that salmeterol’s mucociliary clearance benefit was a result of increased airway patency.

One more mechanism by which long-acting β adrenergics might benefit mucociliary clearance is by reducing neutrophil adhesion and accumulation in airway epithelium in patients with asthma. The reduction in epithelial damage is associated with a decrease in total number of bacteria that adhere to the respiratory mucosa. Salmeterol...
has a longer inhibition of the secretagogue human neutrophil elastase than does albuterol.24

Although over 80% of patients with CF receive bronchodilators,104 it is controversial whether bronchodilators benefit mucociliary clearance.105,106 Some patients with CF report recurrent wheezing after receiving bronchodilators.107–109

A review by Colombo et al on the use of long-acting β adrenergics in CF revealed that some of the mechanisms implicated in the response of CF to bronchodilators include direct smooth muscle relaxation, increased mucociliary clearance, improved peripheral deposition of nebulized antibiotics or mucolytics, direct effects on inflammatory cells and bacterial adherence, and a possible direct effect on CF transmembrane conductance regulator function.106,110 Particularly important to patients with CF is the study by Taouil et al, who found that β2 receptors have the same localization in the apical region of airway epithelial cells as does the CF transmembrane conductance regulator.110 The CF transmembrane conductance regulator protein is a cyclic-adenosine-monophosphate-regulated chloride channel.111 Stimulation of human airway mucosa with salmeterol produces a time-dependent increase in apical CF transmembrane conductance regulator protein expression in human airway epithelial cells. The maximum response is typically reached after 24 hours of treatment with salmeterol.107

Mortensen et al suggested that β2 adrenergic agonists do not significantly improve airway clearance because they do not stimulate cyclic-adenosine-monophosphate-dependent chloride secretion in the lung, which is affected by CF, and thus do not improve hydration of the airway surface.112

**Formoterol**

Melloni and Germouty113 evaluated inhaled formoterol in 10 patients with stable chronic bronchitis. After 6 days of treatment, mucociliary clearance had significantly increased to 46% versus placebo. The improvement was linked to better functioning of the mucociliary apparatus, not to bronchodilation, since the airway resistance was only slightly (nonsignificantly) reduced. Formoterol significantly reduces the absolute number of airway neutrophils, compared with placebo. There is a significant correlation between the percentage of neutrophils and sputum interleukin-8 and the improvement of lung function, as measured by FEV1 (forced expiratory volume in the first second).114

**Anticholinergics**

Although inhaled anticholinergics are considered mucoregulatory agents that inhibit mucus secretion by blocking cholinergic muscarinic M3 subtype receptors,71 there is historical evidence of mucociliary clearance impairment after administration of old anticholinergic drugs.115,116 The M2 receptor is not involved with mucus output,117 but in conjunction with the M3 receptor, the M1 receptor may control water secretion.118 Stimulation of the cholinergic muscarinic M2 subtype receptor inhibits further release of acetylcholine into the synaptic space, so the use of M2 receptor antagonists is associated with increased mucus secretion.24 Cholinergic control of mucus secretion might be augmented in asthma because of dysfunctional airway muscarinic M2 receptors.119 and airways with hypertrophic submucosal glands have a significantly lower response to atropine and higher than normal response to acetylcholine in vitro.120

**Ipratropium**

Large doses of the short-acting anticholinergic ipratropium bromide caused no significant changes in the volume or viscoelastic properties of tracheal mucus in animal studies.121 Current evidence on the effect of inhaled ipratropium on mucociliary clearance in normal subjects, adult patients with asthma, and patients with chronic bronchitis suggests that sputum volume does not change.97,122–126 Bennett et al previously reported that ipratropium has a tendency to slow cough-associated mucus clearance in patients with severe COPD. Using a radiolabeled (technetium-99m iron oxide) monodisperse aerosol and gamma camera analysis, Bennett et al127 investigated the effect of inhaled ipratropium bromide (40 µg) on cough-enhanced clearance of mucus from the airways of 15 subjects with stable, moderate-to-severe COPD. Clearance was measured during 2.5-hour periods on 3 separate days: a control day, a cough day with ipratropium, and a cough day with placebo. Ipratropium diminished the effectiveness of cough in clearing the radiolabeled particles from the airways. Analysis of the data from the 2 study days (placebo versus ipratropium) also showed significantly faster cough clearance on the placebo study day. This effect of ipratropium on cough clearance may be due to changes in the airflow dynamics induced by bronchodilation, altered rheology, or depth of airway secretions.127,128

Miyata et al had reported that neither oxtropium nor ipratropium depressed the normal mucociliary clearance in animals.129 Those results were confirmed in 2 separate studies by Guleria et al, who found no appreciable effect on mucociliary clearance after inhalation of ipratropium in patients with chronic stable asthma88 and COPD.89

Pavia et al reported a decrease in 6-hour sputum weight from patients with reversible airway obstruction.125 A similar reduction in the volume of airway mucus in patients with chronic bronchitis was found by Tamaoki et al after long-term administration of a short-acting anticholinergic,
oxitropium bromide. Sabater et al found that ipratropium did not affect the response to inhaled human neutrophil elastase, whereas the human-neutrophil-elastase-induced depression in tracheal mucus velocity was reversed with only albuterol and salmeterol, not with ipratropium.

**Tiotropium**

Although the long-acting anticholinergic tiotropium binds to all 3 muscarinic receptors, its prolonged pharmacologic activity is the result of its slow dissociation from the M1 and M3 receptors. Hasani et al conducted a 3-week randomized double-blind placebo-controlled tiotropium study with 34 subjects (age range 40–75 years) with stable COPD. Aerosol deposition, defined as the proportion of particles deposited in the non-ciliated airways and therefore not available for mucociliary clearance, was significantly greater with tiotropium (Fig. 8).

Based on a significant decrease in cough frequency, Hasani et al hypothesized that tiotropium produces a shift from cough to mucociliary action. Because effective bronchodilation led to deeper penetration of the radioaerosol, they concluded that the transit pathway for mucus was lengthened. These findings suggest that tiotropium does not adversely affect mucus transport, and may marginally enhance mucociliary transport efficiency. In a recent review, Keam et al found that aerosol particle penetration was improved with tiotropium, without delaying mucus clearance from the lungs.

**Glycopyrrolate**

Glycopyrrolate is a quaternary ammonium derivative with minimal mucosal absorption and minimal systemic toxicity when inhaled. Its oral absorption is less than 5%. Although poorly studied, there is a resurging interest in glycopyrrolate’s potential role as a long-acting anticholinergic for treating stable and unstable OLD. A study by Pahl et al on human primary monocytes found that glycopyrrolate acts synergistically with anti-inflammatory drugs in inhibiting inflammatory mediators commonly secreted in patients with asthma and COPD. Additionally, administration of nebulized racemic glycopyrrolate has been associated with longer bronchodilation and bronchoprotection against methacholine-induced bronchospasm in patients with asthma, when compared to ipratropium bromide or placebo. In combination with albuterol, nebulized glycopyrrolate significantly improves FEV1 in patients with COPD exacerbations.

Although glycopyrrolate injection is more frequently used preoperatively, to reduce cholinergic symptoms such as sialorrhea, bronchorrhea, and excessive pharyngeal secretions, there has been little research on glycopyrrolate’s role in mucociliary clearance. “Death rattle” is a term commonly used to describe the respiratory noise in dying subjects due to sialorrhea and bronchorrhea. Hugel et al compared glycopyrrolate and hyoscine hydrobromide in 72 dying subjects with respiratory noise due to death rattle. Glycopyrrolate provided a greater and more prolonged improvement of respiratory tract secretions.

However, a similar study by Back et al found glycopyrrolate less effective than subcutaneous administration of hyoscine hydrobromide. In a mini-review, Lawrey evaluated the effectiveness of hyoscine hydrobromide and glycopyrrolate in drying respiratory secretions in terminally ill patients, and found no clear evidence to support the choice of hyoscine hydrobromide over glycopyrrolate.

**Effects of Common Adrenergics and Anticholinergics on Mucociliary Clearance**

Table 1 shows a chronological summary of human and animal studies on the effects of the most common adrenergics and anticholinergics on mucociliary clearance. There are several important limitations to summarizing the results and making recommendations. First, the differences in research design may explain the variability of findings in these studies. There are several techniques to evaluate mucociliary clearance. Second, some studies measured mucociliary clearance by creating central regions of analysis for the gamma scintigrams, whereas others created and measured peripheral radioaerosol deposition and particle clearance to assess regional differences. Third, a limited number of clinical studies have been adequately powered to show significant differences. The small statistical differences reported are of questionable clinical relevance. And, finally, the possible effects of different dosing regimens relative to the time when mucociliary clearance measurements were made may have affected the comparisons and clinical recommendations. Longer mucociliary clear-
Table 1. Summary of Human and Animal Trials on the Effects of β2 Adrenergics and Anticholinergics on Mucociliary Clearance.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Agent(s)</th>
<th>n</th>
<th>Subjects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mossberg</td>
<td>1976</td>
<td>Terbutaline</td>
<td>12</td>
<td>Asthma vs healthy subjects</td>
<td>Significant increase in mucociliary clearance but significantly less than in healthy subjects. Significantly less response in subjects with impaired mucociliary clearance.</td>
</tr>
<tr>
<td>Sutton</td>
<td>1988</td>
<td>Terbutaline</td>
<td>8</td>
<td>Bronchiectasis</td>
<td>Significantly increased sputum production</td>
</tr>
<tr>
<td>Mortensen</td>
<td>1991</td>
<td>Terbutaline</td>
<td>10</td>
<td>Asthma vs healthy subjects</td>
<td>Significant increase in mucociliary clearance in healthy subjects</td>
</tr>
<tr>
<td>Mortensen</td>
<td>1993</td>
<td>Terbutaline</td>
<td>10</td>
<td>Cystic fibrosis</td>
<td>No significant increase in mucociliary clearance</td>
</tr>
<tr>
<td>Mortensen</td>
<td>1994</td>
<td>Terbutaline</td>
<td>62</td>
<td>Healthy subjects</td>
<td>Significant increase in mucociliary clearance</td>
</tr>
<tr>
<td>Daviskas</td>
<td>2005</td>
<td>Terbutaline</td>
<td>16</td>
<td>Asthma</td>
<td>Little or no stimulation of mucociliary clearance</td>
</tr>
<tr>
<td>Jones</td>
<td>1979</td>
<td>Albuterol</td>
<td>62</td>
<td>Healthy subjects</td>
<td>Significant increase in number of secretory cells</td>
</tr>
<tr>
<td>Devalia</td>
<td>1992</td>
<td>Albuterol</td>
<td>16</td>
<td>Asthma</td>
<td>Albuterol produced a transient but significant increase in ciliary beat frequency. Salmeterol produced a significantly rapid and prolonged increase in ciliary beat frequency.</td>
</tr>
<tr>
<td>Frohock</td>
<td>2002</td>
<td>Albuterol</td>
<td>8</td>
<td>Chronic airway disease</td>
<td>No significant difference in mucociliary clearance vs placebo</td>
</tr>
<tr>
<td>Galeria</td>
<td>2003</td>
<td>Albuterol</td>
<td>8</td>
<td>Asthma</td>
<td>No significant difference in mucociliary clearance vs placebo</td>
</tr>
<tr>
<td>Sabater</td>
<td>2005</td>
<td>Albuterol</td>
<td>6</td>
<td>Sheep</td>
<td>Significant increase in tracheal mucus velocity and reversion of human-neutrophil-elastase-induced depression of tracheal mucus velocity with salmeterol and albuterol. Ipratropium had no effect.</td>
</tr>
<tr>
<td>O’Riordan</td>
<td>2006</td>
<td>Albuterol</td>
<td>14</td>
<td>Long-term ventilated patients</td>
<td>No significant differences in volume, electrolyte concentration, or inflammatory indexes of sputum</td>
</tr>
<tr>
<td>Cleary</td>
<td>2007</td>
<td>Albuterol</td>
<td>10</td>
<td>Healthy subjects</td>
<td>No significant differences in mucociliary clearance vs placebo</td>
</tr>
<tr>
<td>Laube</td>
<td>2007</td>
<td>Albuterol</td>
<td>7</td>
<td>Lung transplant</td>
<td>Significant improvement in mucociliary clearance</td>
</tr>
<tr>
<td>Wong</td>
<td>1988</td>
<td>Fenoterol</td>
<td>9</td>
<td>Healthy beagles</td>
<td>Significant increase in ciliary beat frequency</td>
</tr>
<tr>
<td>Weich</td>
<td>1988</td>
<td>Fenoterol</td>
<td>12</td>
<td>Chronic bronchitis</td>
<td>Significant increase in mucociliary clearance</td>
</tr>
<tr>
<td>Moretti</td>
<td>1997</td>
<td>Fenoterol</td>
<td>26</td>
<td>Chronic bronchitis</td>
<td>Patients with FEV1 changes &gt; 15% had significant increase in mucociliary clearance, more coughs, and larger 24-h sputum production</td>
</tr>
<tr>
<td>Hasani</td>
<td>2003</td>
<td>Salmeterol</td>
<td>11</td>
<td>Asthma</td>
<td>No significant increase in mucociliary clearance</td>
</tr>
<tr>
<td>Piatti</td>
<td>2005</td>
<td>Salmeterol</td>
<td>10</td>
<td>COPD</td>
<td>Significant dose-dependent increase in ciliary beat frequency in all groups. No rheological changes.</td>
</tr>
<tr>
<td>Bennett</td>
<td>2006</td>
<td>Salmeterol</td>
<td>14</td>
<td>Chronic bronchitis</td>
<td>No significant overall increase in mucociliary clearance vs placebo. Significant increase in lung periphery clearance.</td>
</tr>
<tr>
<td>Melloni</td>
<td>1992</td>
<td>Formoterol</td>
<td>10</td>
<td>Chronic bronchitis</td>
<td>Significant increase in mucociliary clearance</td>
</tr>
<tr>
<td>Francis</td>
<td>1977</td>
<td>Ipratropium</td>
<td>12</td>
<td>Healthy subjects</td>
<td>No significant difference in mucociliary clearance vs placebo</td>
</tr>
<tr>
<td>Pavia</td>
<td>1979</td>
<td>Ipratropium</td>
<td>12</td>
<td>Reversible airway obstruction</td>
<td>No significant difference in mucociliary clearance vs placebo</td>
</tr>
<tr>
<td>Miyata</td>
<td>1989</td>
<td>Ipratropium</td>
<td>14</td>
<td>Pigeons and rabbits</td>
<td>No depression of mucociliary clearance with ipratropium and oxtitropium</td>
</tr>
<tr>
<td>Bennett</td>
<td>1993</td>
<td>Ipratropium</td>
<td>15</td>
<td>COPD</td>
<td>Significant decrease in cough clearance vs placebo</td>
</tr>
<tr>
<td>Tamaoki</td>
<td>1994</td>
<td>Oxtitropium</td>
<td>17</td>
<td>Chronic bronchitis</td>
<td>Significant decrease in sputum production</td>
</tr>
<tr>
<td>Hasani</td>
<td>2004</td>
<td>Tiotropium</td>
<td>34</td>
<td>COPD</td>
<td>No depression of mucociliary clearance</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in the first second
COPD = chronic obstructive pulmonary disease.
Inhaled observation times may be needed to evaluate the short-term, medium-term, and long-term cumulative effect of bronchodilators.

Inhaled $\beta_2$ adrenergics appear to stimulate mucociliary clearance in normal airways.\textsuperscript{21,86,91,121} Because the mucociliary enhancing effect of these agents in patients with depressed clearance is much less than in healthy individuals,\textsuperscript{2,20,64,65} routine administration of $\beta_2$ adrenergics to patients with mucociliary dysfunction or patients undergoing mechanical intubation, to change the volume and composition of airway secretions, is not supported by current evidence.\textsuperscript{92} Although short-acting $\beta_2$ adrenergics may cause significant bronchodilation in some patients with airway obstruction, higher-than-usual doses may be required to obtain maximal benefits on mucociliary clearance,\textsuperscript{21,78} which increases the risk of adverse effects, such as increased mucus secretion.\textsuperscript{146} High doses or continuous $\beta_2$ adrenergics quickly saturate receptors, and a patient in a severe asthma attack could literally drown in secretions.\textsuperscript{17–20} Patients who receive $\beta_2$ adrenergics for acute severe asthma should be closely monitored for mucus obstruction.

Zach et al suggested that $\beta_2$ adrenergic agonists may decrease cough secretion of secretions by decreasing airway tone and thus causing dynamic collapse of the airways or nonhomogeneous emptying of lung regions. Between 15% and 26% of patients with CF report asthma-like symptoms, primarily recurrent wheezing, after receiving bronchodilators.\textsuperscript{108,109} $\beta_2$ adrenergics may be considered in patients with demonstrated airway reversibility to enhance mucociliary clearance. However, a decreased response in mucociliary clearance to a second dose of albuterol suggests that prolonged maintenance with long-acting $\beta_2$ adrenergics may be more effective than the periodic increases in mucociliary clearance obtained with subsequent doses of short-acting $\beta_2$ adrenergics in these patients.\textsuperscript{24}

$\beta_2$ adrenergics can reverse the depression in tracheal mucus velocity induced by human neutrophil elastase and may be more beneficial than anticholinergics in improving mucociliary clearance in respiratory diseases associated with high levels of elastase. Human neutrophil elastase level correlates well with airway disease severity.\textsuperscript{35–37}

A clinical aspect of $\beta_2$ adrenoceptor pharmacology in recent years has been the recognition of genetic receptor polymorphism that could change the physical properties and composition of the sputum matrix.\textsuperscript{147,148} The potential role of this polymorphism on the pharmacologic properties of the $\beta_2$ adrenergics may have important therapeutic implications for patients with OLD. This requires further evaluation.

Anticholinergics are mucoregulatory agents that can reduce mucus secretion by affecting the neural pathway.\textsuperscript{4} The available evidence shows no improvement in mucociliary clearance, in either healthy subjects or patients.\textsuperscript{97,125,126} Opposite to the $\beta_2$ adrenergic agents, anticholinergics do not modify the human-neutrophil-elastase-induced depression in tracheal mucus velocity,\textsuperscript{24} and do inhibit cough clearance. Cough might be of critical importance to enhance mucociliary clearance in some patients with severe COPD.\textsuperscript{127} Although tiotropium is associated with a minimal enhancement in mucociliary clearance,\textsuperscript{133} more studies are required to draw conclusions on tiotropium’s effects on cough and mucociliary clearance. Based on existing evidence, routine administration of anticholinergics is not recommended to improve mucociliary clearance.

The effect on mucociliary clearance of $\beta_2$ adrenergics and anticholinergics combined with inhaled corticosteroids and other mucoactive agents has not been extensively studied. It is clear that a better understanding of the pathophysiology of mucus hypersecretion in obstructive airway disease is the key to identifying therapeutic targets in the respiratory tract and the development of mucoactive agents.

**Summary**

Bronchodilators are important in the management of OLD. The benefit of $\beta_2$ adrenergic and anticholinergic bronchodilators has typically been measured by lung function improvement. Their effects on mucociliary clearance need to be further evaluated in a much larger group of patients. Excessive respiratory secretions may be an important dysfunction of the mucociliary transport system in patients with OLD, and excessive secretions considerably increase the risk of respiratory infections and exacerbations. A better understanding of the role of bronchodilators in mucociliary clearance is critical to establish a new therapeutic profile to optimize airway clearance. It appears that no single mucoactive agent is appropriate or enough for all patients with OLD. Combination therapy may provide synergism to improve mucociliary clearance, but this requires further evaluation.

**REFERENCES**

7. King M. Role of mucus viscoelasticity in cough clearance. Bio-
MUC5AC and MUC5B mucins increase in cystic fibrosis airway
secretions during a pulmonary exacerbation. Am J Respir Crit Care
9. Henke MO, Renner A, Huber RM, Seeds MC, Rubin BK. MUC5AC
and MUC5B mucins are decreased in cystic fibrosis airway secre-
10. Henke MO, Ratjen F. Mucolytics in cystic fibrosis. Paediatr Respir
11. Rogers DF, Barnes PJ. Treatment of airway mucus hypersecretion.
12. Lopez-Vidriero MT, Reid L. Chemical markers of mucous and
serum glycoproteins and their relation to viscosity in mucoid and
purulent sputum from various hypersecretory diseases. Am Rev
13. Charmain J, Reid L. Sputum viscosity in chronic bronchitis, bron-
chictasis, asthma and cystic fibrosis. Biochimie 1972;9(3):185–
199.
14. Shimura S, Sasaki T, Sasaki H, Takishima T, Umeya K. Viscoelas-
tic properties of bronchorrhoea sputum in bronchial asthmatics.
15. Rogers DF. Airway mucus hypersecretion in asthma: an underval-
16. Sheehan JK, Richardson PS, Fung DC, Howard M, Thornton DJ.
Analysis of respiratory mucus glycoproteins in asthma: a detailed
study from a patient who died in status asthmaticus. Am J Respir
17. Hogg JC. Pathology of asthma. J Allergy Clin Immunol 1993;92(1
Bai TR. Characterization of airway plugging in fatal asthma. Am
19. Rubin BK, Tomkiewicz R, Fahy JV, Green FH. Histopathology of
fatal asthma: drowning in mucus. Pediatr Pulmonol 2001;Suppl
23:885–89S.
20. Dicipingilatis PV. Cough: 4. Cough in asthma and eosinophilic bron-
21. Rogers DF. Mucociliary dysfunction in COPD: effect of current
1–8.
22. Bennett WD. Effect of beta-adrenergic agonists on mucociliary
23. Tamaoki J, Chiyotani A, Tagaya E, Sakai N, Konno K. Effect of
long term treatment with oxisprotonium bromide on airway secretion
in chronic bronchitis and diffuse panbronchiolitis. Thorax 1994;
24. Rogers DF. Pharmacological regulation of the neuronal control of
25. Miyata T. Novel approach to respiratory pharmacology: pharmaco-
cological basis of cough, sputum and airway clearance. Yakugaku
26. Sabater JR, Lee TA, Abraham WM. Comparative effects of salme-
terol, albuterol, and ipratropium on normal and impaired mucocil-
27. Fischer BM, Voynow JA. Neutrophil elastase induces MUC5AC
gen expression in airway epithelium via a pathway involving re-
452.
28. Nadel JA. Role of mast cell and neutrophil proteases in airway secre-
Effect of human neutrophil elastase and Pseudomonas aeruginosa
proteases on human respiratory epithelium. Am J Respir Cell Mol
30. Smallman LA, Hill SL, Stockey RA. Reduction of ciliary beat
frequency in vitro by sputum from patients with bronchiectasis: a
31. Caldwell RA, Boucher RC, Stutts MJ. Neutrophil elastase activates
near-silent epithelial Na⁺-channels and increases airway epithelial
L813–L819.
32. O’Riordan TG, Otero R, Mao YM, Lauroedo I, Abraham WM. Elas-
tase contributes to antigen-induced mucociliary dysfunction in ovine
33. Hill AT, Bayley D, Stockley RA. The interrelationship of sputum
inflammatory markers in patients with chronic bronchitis. Am J
Neutrophilic inflammation in severe persistent asthma. Am J
35. Little SA, MacLeod KJ, Chalmers GW, Love JG, McSharry C,
Neutrophil recruitment and airway epithelial cell involvement in
135.
37. Qiu Y, Zhu J, Bandi V, Atmar RL, Hattotuwa K, Guntupalli KK,
Jeffery PK. Biopsy neutrophilia, neutrophil chemokine and receptor
gene expression in severe exacerbations of chronic obstructive pul-
38. Kim JS, Okamoto K, Arima S, Rubin BK. Vasoactive intestinal
peptide stimulates mucus secretion, but nitric oxide has no effect on
486–491.
40. Haddad el-B, Roussel J. Regulation of the expression and function of
322–327.
41. Barnes PJ. The role of anticholinergics in chronic obstructive pul-
42. Gross NJ, Barnes PJ. A short tour around the muscarinic receptor.
43. Roffel AF, Elzinga CR, Zaagsma J. Muscarinic M receptors me-
diate contraction of human central and peripheral airway smooth
44. Lefkowitz RJ, Hoffman BB, Taylor P. Neurohormonal transmis-
sion: the autonomic and somatic motor nervous system. In: Gilman
AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman’s
the pharmacological basis of therapeutics, 8th ed. Elmsford, NY:
45. Disse B, Raichl R, Speck GA, Travnecker W, Rominger KL, Ham-
rer R. Ba 679 BR, a novel anticholinergic bronchodilator. Life Sci
46. Witek TJ. The fate of inhaled drugs: the pharmacokinetics and
pharmacodynamics of drugs administered by aerosol. Respir Care
2000;45(7):826–830.
47. Iosso GF. Potential usefulness of inhibiting neural mechanisms in
48. Barnes PJ. Modulation of neurotransmission in airways. Physiol
49. Ayala LE, Ahmed T. Is there loss of protective muscarinic receptor
50. Fryer AD, Jacoby DB. Parainfluenza virus infection damages inhibi-
itory M₃-muscarinic receptors on pulmonary parasympathetic


INHALED ADRENERGICS AND ANTICHOLINERGICS IN OBSTRUCTIVE LUNG DISEASE


Restrepo: That is a very good question. They actually quoted a limitation for long-acting β agonists, and that is the inability to study even longer mucociliary clearance effect, or chronic beneficial effect on mucociliary clearance of human subjects because there is not an easy way to keep these patients for longer periods of time in this type of study.

In animals, salbutamol versus salmeterol, must be difficult to do in terms of the protocol. For example, salbutamol will have a quick onset of action and a relatively quick offset of action compared with salmeterol, which has a slower onset of action and, of course, a much slower offset. How are those studies conducted so that they are comparing like for like, for example, in terms of concentration and time course?

Rogers: The studies comparing the differences in mucociliary clearance between short- and long-acting β-agonists that you showed, salbutamol versus salmeterol, must be difficult to do in terms of the protocol. For example, salbutamol will have a quick onset of action and a relatively quick offset of action compared with salmeterol, which has a slower onset of action and, of course, a much slower offset. How are those studies conducted so that they are comparing like for like, for example, in terms of concentration and time course?


Restrepo: I don’t have a good answer for that. I don’t know if Bruce...

Rubin: I don’t know. I saw that and was wondering if, in fact, the very long duration that the salmeterol remains on the receptor might actually allow the propranolol, which has a fairly short on-and-off as well, to be washed out, and so you are getting a blunting, but because of the relatively long action and the long signaling you then begin to pick up some of the β agonists action later on in the course. But I don’t think that’s actually been studied.

Homnick: In cystic fibrosis, it’s sort of been a knee-jerk for us to start β agonists prior to using airway clearance. I think that this emphasizes the importance of individualizing β agonist use or bronchodilator use in CF patients. Some will have more airway obstruction following the β agonists, so that the use of spirometry before and after, before you decide to use them on a chronic basis, I think is important. It looks to me like the lipophilic β agonists are those that have the most potential for increasing mucociliary clearance. Is that correct?

Restrepo: Yes, that is correct. The short-acting β agonists are more hydrophilic, and the salmeterol more lipophilic than the formoterol. The great majority of studies include the long-acting β agonist salmeterol versus the formoterol. It will be interesting to see what kind of effects we will see with the arformoterol (Brovana). The lipophilic property has a lot to do with the action of these agents due to the ability to spread across the epithelium versus the cleavage of the hydrophilic agents and their short term effect.

MacIntyre: You mentioned arformoterol. Is there any effect on these L- and R-isomers on these mucus activities you’ve been talking about?

Restrepo: I couldn’t find any data on it.

Rubin: Not on the arformoterol, but there was a study done by Tom O’Riordan’s group looking at levalbuterol versus albuterol. Assessing the effects of racemic and single-enantiomer albuterol on airway secretions in long-term intubated patients. And both of them were identical in onset of action, inflammation, and mucus secretion. This is similar to other human studies comparing albuterol to levalbuterol.


MacIntyre: This may be way out on the fringe, but all this discussion about these mutations on the β receptor, do those have effects with mucus secretion as well as with bronchial smooth muscle relaxation?

Restrepo: That’s been mentioned in probably 2 discussions. Those different phenotypes of the β2 receptors have to be looked at—that, along with the different changes in the rheology of the mucus. But I don’t think it has been addressed.

Myers: I want to go back to Bruce Rubin’s comments. There actually are a couple of studies out there, cellular studies that look at the S-isomer from albuterol. They potentially showed that it does increase mucus or mucus production, also impacts ciliary beat frequency, and actually makes it very dysfunctional. A lot of the studies looked at racemic mixtures of albuterol. And it would be interesting to see some of those reproduced with a single-isomer albuterol, to see if this cellular mechanism truly does impact the airway clearance mechanism in the human model.


Rogers: I think what they found with the separate isomers was that the active isomer worked and the nonactive isomer didn’t. In fact, it made things worse, as you so rightly say. They found that it was due to an irritant effect of the drug formulation. But, without the protective effect of the active isomer, the bronchodilation effect was lost. Thus, in the racemic mixture there is a combination of an irritant, bronchoconstrictor effect that is offset by the protective bronchodilator effect of the active isomer. In contrast, with the single, inactive isomer, there is just the irritant effect without the protective effect. Is that true?

Myers: That is correct, when you give it as a dual-isomer mixture, the R offsets the S, but you have to remember that the metabolism clearance of the R-isomer really clears the lungs in about 2–4 hours, where the S-isomer (in other studies) has been shown to hang around as long as 10–12 hours. So, potentially, you do have the single-isomer, the S-albuterol, which theoretically is the nonproductive part of the isomer that’s hanging around 6-fold longer.

Schechter: I want to make a technical comment about statistical testing, if people will bear with me, because I think it’s important in the context of all the studies that you showed. When a study concludes that there’s no discernible difference between treatment groups, really what’s going on is it’s failing to prove that there’s a difference. It’s different, and much more difficult, to prove that there’s equivalence, and especially when you’re looking at studies that were designed to look for a difference.

Also, while some of the studies were somewhat larger, you referenced studies with 4, with 8, with 10 subjects, and so failure to find a difference between groups might be due primarily to a lack of statistical power. Even in the studies with a larger number of subjects, if there’s a wide range of variation in measurements, the $n$ value might not be enough. With all the small studies that have been looking at this topic, it looks like it’s a ripe area for a meta-analysis, where you could potentially combine the results of these different studies, and potentially draw some more clear-cut conclusions.

Restrepo: I completely agree. I think one of the major limitations is how to translate findings of poorly powered studies into practice, as well as how you translate the fact that well-powered studies could have resulted in good clinical response but no statistically significant differences. In other words it would be very nice to run a meta-analysis just to see what you end up with. Because at this point, it is a very limited number of subjects, which again creates a limitation on studies of medications we use on a regular basis. This is actually relatively poor evidence to extrapolate.

Hess: I have some clinical questions. Should I ever use $\beta$ agonists to improve airway clearance? Should I ever use anticholinergics in patients who have a bronchorrhea? Should I think about using anticholinergics in a patient with sialorrhea, like a patient with ALS?

Restrepo: My answer would be that, based on the evidence that I presented today, the beneficial effect of $\beta$ agonists is limited when you have baseline impairment of the mucociliary clearance. In terms of the anticholinergics, the potential inhibition of cough will be important to remember on those patients who depend so much on the cough mechanism for mucociliary clearance (not so much on bronchodilation). By providing bronchodilation, the anticholinergics compensate their effect on cough. Evidence for both bronchodilators is poor; therefore, their routine recommendation is still very questionable.