The Effect of Inflammation on Mucociliary Clearance in Asthma*
An Overview

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Mucociliary clearance (MCC) is one of the most important nonspecific defense mechanisms of the respiratory tract, and its impairment is a well-documented feature of chronic respiratory diseases, including asthma. In vitro and in vivo data suggest that several inflammatory mediators influence the mucociliary apparatus. Epithelial damage and functional abnormalities have been described in bronchial asthma, along with changes in mucus-secreting cells and the chemical and rheological properties of airway fluid. Although the mechanisms of MCC impairment in asthma are not clearly understood, data in the recent literature suggest that airway inflammation plays a major role. In this article, we review studies on MCC alterations in light of up-to-date findings on pathogenetic mechanisms in asthma.

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Key words: asthma; inflammation; mucociliary clearance

Abbreviations: CB = chronic bronchitis; ISH = isocapnic hyperventilation; MCC = mucociliary clearance; PAF = platelet-activating factor; PG = prostaglandin; TMV = tracheal mucus velocity

Human lungs represent the largest area (range, 40 to 120 m²) exposed to environmental agents, and the amount of air inhaled into the lungs is about 10 to 20 m³ in 24 h.¹ In the lung, numerous and complex mechanisms maintain cleanliness and sterility, and some are specific, while others are nonspecific mechanisms (eg, mucociliary clearance [MCC] and cough).²,³

MCC is one of the most important nonspecific defense mechanisms of the airways.⁴ The efficacy of the mucociliary apparatus is due to (1) the morphologic integrity of the cilia structure and mucus components, and (2) the functional efficacy of synchronism and the magnitude of ciliary activity, periciliary fluid depth (sol), and mucus rheological properties (gel).⁵,⁶

During a mild airway inflammation such as that occurring in acute viral infections, mucus hypersecretion and changes in the MCC are small and transient.⁷ In contrast, in chronic pathologic conditions such as chronic bronchitis (CB), cystic fibrosis and asthma, permanent changes in ciliary structure and function, mucus hypersecretion and/or rheological changes, result in mucus retention.⁸

It is well-documented that MCC is reduced in heavy smokers,⁹ and in patients with CB¹⁰ and bronchiectasis.¹¹ Although MCC also is impaired both in stable patients with asthma¹²,¹³ and during exacerbations,¹⁴ it is affected to a lesser extent than in patients with CB or bronchiectasis.¹⁵

In this review, we analyze the MCC functional changes and the contribution of mucus and cilia to the impairment of the mucociliary apparatus in patients with asthma due to the pathologic effects of airway inflammation.

MCC Impairment in Asthmatic Patients and Animal Models

MCC impairment in asthmatic patients was first described by Hilding¹⁶ in 1943 and by Dunnill¹⁷ in 1960. When the authors examined patients who had died of bronchial asthma, they found a reduced number of ciliated cells, goblet cell metaplasia, and large amounts of hyperviscous mucus. On the basis of these findings, the authors suggested that modifi-
cations occurring during asthmatic attacks are associated with a marked ciliary dysfunction and with a decrease of MCC.

To confirm this hypothesis, Santa Cruz et al.18 studied tracheal mucus velocity (TMV) in elderly patients (age range, 57 to 71 years) with obstructive lung disease. These studies, which were carried out by a cinebronchoscopic technique that measures the velocity of Teflon disks placed in the trachea, showed a considerable decrease of TMV. Moreover, Foster et al.19 found a considerable reduction both in mucus clearance and mucus speed in the trachea of symptomatic asthmatic patients. Additionally, Bateman et al.12 in a study of a large group of stable patients with mild asthma and a wide age range, showed that tracheobronchial clearance, evaluated by following the movement of the 5-μm radioaerosol polystyrene particles on a gamma-scanner, was significantly poorer than in the age-matched control group.

In contrast, by using the inhalation of Teflon particles labeled with 99mTc, Mosberg et al.20 observed no significant reduction in tracheobronchial clearance in a group of asthmatic patients who no longer experienced asthmatic attacks. Since aerosol inhalation was obtained mainly by forced inspiratory maneuvers in the central airways, those findings did not exclude some possible epithelial damage in peripheral airways with a reduction of MCC.

MCC changes are present in the asthmatic airways of the entire bronchial tree, as was demonstrated by Bateman et al.12 and confirmed by Daviskas et al.21 These results contrast with those obtained by Foster et al.22 who stated that MCC undergoes changes only in the large airways.

The discrepancies between studies are probably due to the different techniques used and different clinical stages of the disease.

Furthermore, clinical exacerbation of asthma can dramatically decrease MCC, and impairment is of longer duration than airflow obstruction. In this regard, Pavia et al.13 showed that in asthma patients who were in clinical remission and were far from acute exacerbation, a significant reduction of MCC still was present when lung function parameters returned to normal values. When Messina et al.14 evaluated MCC by radioaerosol and gamma-camera in a small group of asthmatic patients during acute exacerbation and after hospital discharge, they observed a severe decrease of MCC during the acute phase of disease, along with an improved speed of MCC during the last days of hospitalization and in the period following discharge. The authors suggested that MCC measurement could be useful for the evaluation of bronchial inflammation and the monitoring of therapeutic interaction in asthma.

Finally, the normal physiologic decrease of MCC during sleep23 becomes more pronounced in asthmatic patients,24 and the nocturnal reduction of MCC can improve after therapy with inhaled β2-agonists25 and methylxanthines26 but does not improve following the administration of oral, slow-released β2-agonist, as previously reported by Hasani et al.27

**Effects of Mediators on MCC**

The effects of inflammation have been investigated in animal models of asthma28 as well as on atopic and nonatopic patients.29 Also, several inflammatory mediators have been found and studied in the bronchial fluid of patients (Fig 1).30

Chemical mediators of anaphylaxis appear to have various and sometimes opposing effects on the two essential components for MCC, cilia and mucus. It appears, however, that the net effect of the various chemicals involved in anaphylaxis is impairment of mucus clearance31 (Table 1).

Mezey et al.32 studied six asymptomatic atopic asthmatic patients for whom the mucus velocity in the trachea, which was evaluated radiographically, was significantly reduced when compared to that of seven healthy subjects. In all patients, TMV was measured immediately and 1 h following an antigen inhalation challenge. The study showed a 28% decrease of TMV from baseline immediately after exposure to the antigen and a 53% decrease 1 h later, when both specific airway conductance and FEV1...
returned to normal values. In contrast, there was no reduction of mucus velocity when patients had been treated previously with sodium-cromoglycate even if a significant decrease in the percentage of FEV1 was evident. Thus, the authors concluded that the mechanism of TMV reduction implies a role for mast cell mediators.

A similar study carried out by Ahmed et al33 on atopic asthmatic patients confirmed the results of Mezey et al32 while also pointing out that inflammatory mediators released after antigen challenge reduced mucus transport in the trachea. Additionally, previous treatment with a slow-reacting substance of anaphylaxis antagonist (FLP-55712) prevented changes from occurring.

The inflammatory mechanism is also evident in the upper respiratory tract (ie, the nasal and oropharyngeal tract), as observed by Awotedu et al34 in a group of asthmatic subjects with and without allergic rhinitis. By using the saccharine method, the authors found a significant decrease of nasal MCC. Kurashima et al35 studied the effect of a thromboxane-A2 synthetase inhibitor (OKY-046) on the impairment of nasal MCC by saccharine testing in 19 asthmatic subjects. Since they found an increase of nasal mucociliary transport after 4 weeks of treatment with the thromboxane-A2 synthetase inhibitor, they concluded that thromboxane plays an important role in the pathogenetic mechanism of MCC in asthma.

Not all inflammatory mediators can impair and decrease MCC in asthma. In fact, Wanner et al28 found that histamine and acetylcholine can increase the transport of mucus in dog tracheas. This finding was confirmed further by consecutive studies made on sheep trachea strips. The authors found a decrease of surface liquid velocity secondary to perfusion with a platelet-activating factor (PAF) and an antigen. On the contrary, after acetylcholine perfusion, an increase of surface liquid velocity in a concentration-dependent manner occurred.36

Polosa et al37 evaluated the strong effect of bradykinin, a vasoactive nonapeptide with secretagogue properties, on the secretory cells of dog airways and of nasal mucosa in vivo, and they suggested that it acts as a mediator in the pathogenesis of bronchial asthma. They confirmed previous data by Yeates et al,38 demonstrating that in healthy subjects this compound increases MCC with respect to a control group treated with a placebo.

**AIRFLOW OBSTRUCTION AND MCC**

Despite the fact that MCC is impaired in asthmatic patients, there is no clear evidence that the severity of disease, as reflected by airflow obstruction, is correlated with the degree of impairment of MCC.39

The pathologic modifications that occur in bronchial asthma, most importantly bronchial flow obstruction, can be included among the possible causes of MCC impairment. Studies in animal models showed that the induction of a flow-limitation segment determined the reduction in mucociliary movement.40 This finding also was confirmed in humans. It is believed that flow limitation is caused by repetitive coughing in the segmental and subsegmental bronchi,41,42 and that coughing may decrease MCC in central airways.43

In 1978, Mezey and et al32 when studying TMV in subjects affected by bronchial asthma with a wide baseline FEV1 range, observed that after antigen challenge the decrease of TMV was not correlated to the fall in FEV1. Moreover, although sodium cromoglycate treatment did not prevent the bronchoconstriction that was induced by antigen challenges, an increase of mucus transport was observed. Since, with the same cumulative antigen dose, specific airway conductance and FEV1 decreased less than without cromolyn pretreatment, a partial protection against bronchoconstriction is suggested. The authors concluded that bronchial obstruction did not cause MCC changes.

### Table 1—Effects of Inflammatory Mediators on MCC, Ciliary Beat Frequency, and Mucus Secretion*

<table>
<thead>
<tr>
<th>Inflammatory Mediators</th>
<th>MCC</th>
<th>Ciliary Beat Frequency</th>
<th>Mucus Secretion</th>
</tr>
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<tbody>
<tr>
<td>Histamine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>↑</td>
<td>↑(↓)</td>
<td>↑</td>
</tr>
<tr>
<td>SRS-A</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-Hydroxyeicosatetraenoic acid</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Leukotriene C4</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Leukotriene D4</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>PAF</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Eosinophil major basic protein</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Eosinophil cationic protein</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil elastase</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral protease</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast cell chymase</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PGs</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>VIP</td>
<td>↑↑</td>
<td>↑(↓)</td>
<td>↑</td>
</tr>
<tr>
<td>Neurokinin A</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement C3a and C5</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin 1, 2, and 3</td>
<td>↑</td>
<td>↑(↓)</td>
<td></td>
</tr>
</tbody>
</table>

*↑ = increase; ↓ = decrease; ↑(↓) = increase with some reported decreasing effect or no effect.**
In addition, O’Riordan et al.\(^{39}\) in a group of stable asthmatic subjects with varying degrees of bronchial obstruction, observed that patients with significant decreases of MCC were affected by airflow limitation during tidal breathing. However, they did not find any correlation between obstruction and decreasing MCC. Also, in a later study, the same group did not experience any MCC reduction during methacholine-induced challenge.\(^{44}\)

Cilia: Structure and Functions in Asthma

In asthmatic patients, mucus hypersecretion causes a decrease of ciliary beat frequency with respect to the duration of bronchial inflammation and produces severe structural and functional epithelial damage to the mucociliary apparatus.\(^{45}\)

Ultrastructural and in vitro studies have demonstrated that cilia have claw-like projections on their tips that move secretions during the “effective stroke” and return to primary position during the “recovery stroke” by moving slowly in the periciliary fluid (sol phase).\(^{46–48}\)

The shedding of airway ciliated epithelium is one of the most significant and frequently occurring morphologic alterations of asthma.\(^{49}\) It is also a characteristic pathologic feature of asthmatic tissue obtained from autopsy,\(^{47}\) bronchial biopsy\(^{50}\) and BAL.\(^{51}\) In this regard, ciliated cells obtained in bronchial biopsy\(^{52}\) and in BAL\(^{53}\) correlate with the degree of bronchial responsiveness, and ciliary destruction is more evident with persistent disease, although it can be reversed with steroid treatment.\(^{54}\)

Structural changes, such as ciliary epithelial lesions, with cells that often appear swollen, as well as intercellular space edema have been described in the airway epithelium of asthmatic patients.

Electron microscopy has shown ciliated cells with vacuolization of both the endoplasmic reticulum and mitochondria and a loss of cilia,\(^{50,51}\) along with microtubular discontinuities.\(^{55}\) It is evident that airway inflammation is the cause of these changes, and the more severe the inflammation, the more prevalent the destruction of the mucociliary apparatus.

Although epithelial derangement is a peculiar aspect of bronchial asthma, studies carried out on chicken tracheas showed that epithelial damage of at least 50% of the bronchial ciliary apparatus is necessary to determine an evident decrease of MCC.\(^{56}\) Hence, functional alterations of cilia that can cause MCC modification should be evaluated. In this regard, Mossberg et al.\(^{57}\) assumed that the coordinated ciliary stroke is disturbed when the variation between the stroke direction of cilia is 90°, while Laitinen et al.\(^{50}\) demonstrated that the ciliated stroke deviation exceeded from 45° up to 90° in their asthmatic patients.

Regarding ciliary modifications in asthma, Frigas et al.\(^{58,59}\) were the first research group to hypothesize a functional change by isolating a characteristic protein, called the major basic protein, that can induce ciliostasis, cytolysis, and epithelial mucosa damage in the eosiophils of asthmatic patients. At a later date, Dulfano and Luk\(^{60}\) identified another ciliary inhibitory factor that seems to derive from a specific reaction between a substance present in the sputum and cilia of asthmatics. This seemingly reversible inhibitory effect is probably related to clinical exacerbations and not to functional damage of the cilia or mucosa cells. Similar inhibitory effects of sputum obtained from asthmatics also have been observed with human bronchial explants.

Furthermore, when evaluating ciliated cells that were obtained from the tracheas of allergic sheep in vitro, Maurer et al.\(^{61}\) noted a remarkable increase of ciliary beating, even though TMV was reduced. These results led the authors to conclude that during an allergic reaction, the reduction of mucus transport is not related to a decrease of ciliary beat frequency.

It is important to note, however, that inflammatory mediators do not always exert an inhibitory effect on ciliary function. A study carried out by Wanner et al.\(^{62}\) on sheep tracheas showed that leukotriene C\(_4\) and prostaglandin (PG) E\(_1\) and PGE\(_2\) are potent ciliary stimulators, whereas histamine modestly increases ciliary beat frequency only at high concentrations. Also, Seybold et al.\(^{36}\) showed that the perfusion of acetylcholine and epinephrine caused an increase of ciliary beat frequency in sheep tracheas in a concentration-dependent manner. The same effect was obtained with antigen challenge perfusion, while the opposite was obtained with PAF.

Mucus Secretion in Asthma

The efficiency of MCC depends not only on ciliary activity but also on the amount and rheological characteristics of mucus.\(^{63}\) Respiratory mucus is a complex mixture of secretions from submucosal glands, secretory cells of the epithelial surfaces, tissue fluid transudates, substances produced by specialized cells, and alveolar surfactant. In the tracheobronchial tree, mucus is produced by at least four types of secretory cells, mucous, and serous glands,\(^{64}\) and the “normal” amount of secretion ranges from 10 to 100 mL/d.\(^{65}\)

In chronic respiratory diseases, the persistence of airway inflammation can determine epithelial pathophysiologic modifications that produce excessive mu-
cus hypersecretion.66 This significant change is due to the increase of secretory cells and to the hypertrophy and hyperplasia of submucosal glands with respect to normal subjects.17,67,68

Although asthmatics in the stable phase produce unquantifiable amounts of mucus daily, highly viscous mucus plugs are commonly found at the autopsy of subjects who died of bronchial asthma.69,70

Some histologic findings suggest that the amount of mucus hypersecretion in stable asthmatics can determine airflow limitation in small airways.71 Moreover, mucus can take the place of surfactant even in bronchiolar airways. It contributes to bronchial collapse and reduces bronchial reversibility, as observed during an asthmatic attack, by modifying surface tension properties.72,73

In patients with asthma, plasma exudate is a major component of airway fluid and reflects the degree of inflammation. Plasma exudate may produce an increase of the fluid layer where cilia beat, thus impairing MCC. Protein components of plasma exudate increase mucus production, prevent hydration, and alter mucus viscosity, possibly by mucin-albumin complexes and by the activation of the coagulation system through fibrin formation. Moreover, peribronchial edema may reduce lung compliance and further facilitate bronchoconstriction by uncoupling the bronchial muscle.74

In patients with bronchial asthma, sputum becomes viscous and expectoration is always more difficult than in patients with CB, bronchiectasis, or cystic fibrosis.8,66 Airway secretions adhere to bronchial walls and, although they are quantitatively “normal,” contain large quantities of albumin, lipids, and glycoproteins that alter their rheological characteristics.75 These altered sputum characteristics are responsible for the increased adhesiveness and loss of fluidity, which in turn decreases MCC (Table 2).76

Moreover, immunologic factors, the autonomic nervous system, and the nonadrenergic and noncholinergic pathway alterations of vasoactive intestinal polypeptide releases have all been promoted as possible generators of the hypersecretory mechanism in asthmatics.77–80 Fuller et al81 showed that bradykinin and lysyl-bradykinin, inflammatory peptides that are derived from the effect of kallikrein on kininogenic molecules, stimulated sensitive nonmyelinc fibers (C fibers) in a selected manner. These fibers can cause an increase of mucus secretion by a tachykinin release.

Furthermore, by modifying biochemical components, antigenic challenge can alter mucus rheological properties and mucociliary transport. By studying the trachea of Ascaris-sensitized sheep after antigenic challenge, Phipps et al82 found an increase in the number of glycoproteins in the periciliary fluid and a subsequent interaction with the mucociliary apparatus. This effect is caused by the release of leukotrienes, as demonstrated by the blocking process that Na-cromoglycate and antileukotriene sulfopeptide antagonists exert on the secretory mechanism. Other in vitro studies carried out by Marom et al83,84 confirmed the role of potent secretory stimulants of leukotrienes C4 and D4, whereas histamine, PGE2, PGD2, PGJ1, PGE1, and PGA2 have proved to be less effective.

Sperber et al85 evaluated a new, high-molecular-weight, macrophage-derived, mucus secretagogue, which was found in BAL fluid, on 37 patients with bronchial asthma who had mucus hypersecretion. The authors hypothesized a direct correlation between hypersecretion and mucus secretagogue values.

Also, excessive amounts of mucus secretion might be caused by an increased transfer of water and electrolytes in the airway lumen, with a reduction of ciliary movement.86 In this regard, Olver et al,87 after antigenic challenge, and Marin et al,88 after histamine challenge, found an increase in the amount of electrolytes in the dog tracheal epithelium. These findings were further confirmed by experiments on sheep trachea strips previously sensitized to Ascaris. In fact, the successive antigen exposure caused a transient but marked flow of H2O, Cl−, and Na+ throughout the bronchial epithelium.82 Similarly, other compounds such as histamine,88 bradykinins,89 arachidonic acid-derived factors obtained via lipoxy-

<table>
<thead>
<tr>
<th>Physical Properties</th>
<th>Normal</th>
<th>CB</th>
<th>Bronchial Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity over 24 h, mL</td>
<td>10</td>
<td>24.7 ± 16.3</td>
<td>12.7 ± 8.7</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Usually yellow or greenish</td>
<td>Colorless</td>
</tr>
<tr>
<td>Odor</td>
<td>Nonodorous</td>
<td>Varies according to the kind of infection</td>
<td>Usually nonodorous</td>
</tr>
<tr>
<td>pH range</td>
<td>7.45–8.15</td>
<td>6.3–7.9</td>
<td>5.4–7.6</td>
</tr>
<tr>
<td>Viscosity, dyne · s · cm²</td>
<td>7</td>
<td>&lt; 400</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>Elastic recoil at 100 dyne/cm, SR units</td>
<td>4–8</td>
<td>4–8</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Dulfano and Ishikawa.76
genase cascade, and PGs can determine a trans-
epithelial transport of H₂O and Cl⁻.

Additionally, decreased amounts of periciliary fluid also might cause the rheological modification of mucus. This observation was confirmed by Daviskas et al. when they evaluated MCC with a radioaerosol technique during and after isocapnic hyperventilation (ISH) in 8 healthy subjects and 10 asthmatic patients. An analysis of initial and postintervention lung radioactivity for the whole right lung and for defined regions showed that MCC was reduced during ISH with dry air and increased after in patients from both groups when compared to the results of ISH with warm humid air and nasal breathing at rest. The authors concluded that MCC changes during and after ISH with dry air might be caused by excessive H₂O loss, which in turn causes a reduction of the periciliary fluid layer and subsequent hyperosmolarity of the airway fluid.

**CONCLUSION**

In bronchial asthma, morphologic and functional changes that occur in the airways can be due to both inflammatory and/or injury repair mechanisms. In cases of severe disease (i.e., in patients who died of asthma), desquamative areas with infiltrative edematous zones and inflammatory cells, such as eosinophils, neutrophils, mast cells, and some mononucleated cells, can be observed.

In addition, pathogenetic mechanisms of asthma define the key role of inflammation in the development of disease. Inflammatory cells as well as different types of asthma mediators in the bronchial wall damage the airway epithelium and cause muscle hyperreactivity and impairment of mucociliary function.

In conclusion, based on findings in the literature, we can state that MCC is abnormal in stable patients and in the acute phase of bronchial asthma and that inflammatory mediators influence MCC, as well as ciliary structure and function and mucus production.

Finally, not enough data are available to be able to weigh the relative contribution of each of the mentioned factors, and further research is needed to better understand the effect of inflammation on the mucociliary apparatus in asthma.

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