Pulmonary Function Is Negatively Correlated With Sputum Inflammatory Markers and Cough Clearability in Subjects With Cystic Fibrosis But Not Those With Chronic Bronchitis*

Jung-Soo Kim, MD, PhD; Kosuke Okamoto, MD, PhD; and Bruce K. Rubin, MEngr, MD, MBA, FCCP

Background: Polymorphonuclear neutrophil (PMN)-dominated inflammation is prominent in the airways of subjects with cystic fibrosis (CF) and chronic bronchitis (CB). Interleukin (IL)-8, myeloperoxidase (MPO), and DNA are markers of neutrophilic inflammation. We hypothesized that sputum MPO, DNA, and IL-8 concentrations would negatively correlate with pulmonary function and sputum transportability.

Methods: We measured pulmonary function and analyzed sputum IL-8, MPO, and DNA concentrations, as well as the transport properties of sputum samples obtained from 16 subjects with CF and 15 subjects with CB. We also evaluated changes in these measurements in paired sputum samples from these subjects obtained 2 to 12 months apart.

Results: IL-8 and MPO concentrations in the sputum of CF subjects was inversely correlated with FEV1 percent predicted (IL-8: \( r = -0.40; p = 0.003 \); MPO: \( r = -0.38; p = 0.003 \)) and FVC percent predicted (IL-8: \( r = -0.4; p = 0.02 \); MPO: \( r = -0.4; p = 0.02 \)). IL-8 and DNA concentrations were inversely correlated with sputum cough transportability (CTR) [IL-8: \( r = -0.4; p = 0.02 \); DNA: \( r = -0.36; p = 0.048 \)]. Changes in DNA concentration in sputum samples from CF subjects over time were inversely correlated with changes in FEV1 percent predicted (\( r = -0.58; p = 0.02 \)), FVC percent predicted (\( r = -0.74; p = 0.002 \)), and CTR (\( r = -0.59; p = 0.02 \)). There was no correlation among pulmonary function, sputum properties, and inflammatory markers in the sputum from subjects with CB.

Conclusions: The sputum concentrations of IL-8, MPO, and DNA appear to be closely associated with pulmonary function in subjects with CF but not in subjects with CB.

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Key words: chronic bronchitis; cystic fibrosis; DNA; interleukin-8; myeloperoxidase; neutrophils; pulmonary function testing; sputum

Abbreviations: CB = chronic bronchitis; CF = cystic fibrosis; CTR = cough transportability; ELISA = enzyme-linked immunosorbent assay; IL = interleukin; MPO = myeloperoxidase; PBS = phosphate-buffered saline; PMN = polymorphonuclear neutrophil

Cystic fibrosis (CF) and chronic bronchitis (CB) are characterized by polymorphonuclear neutrophil (PMN)-driven airway inflammation.1,2 PMNs play a critical role in pulmonary defense but have also been implicated as a cause of tissue destruction causing the progression of chronic lung disease.1,3 Thus, assessing the degree of PMN inflammation in sputum could be a means of evaluating the clinical status of patients with CB and CF.4,5

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There are a number of inflammatory markers that can be measured in sputum. Concentrations of soluble interleukin (IL)-8, myeloperoxidase (MPO), and/or DNA have been measured in the sputum of CF patients\(^5\)–\(^\text{11}\) and CB patients.\(^2\),\(^6\),\(^12\) IL-8 is a proinflammatory cytokine with a primary effect on PMN maturation, migration, and activation.\(^5\),\(^13\),\(^14\) MPO is stored in the azurophil granules of the PMN and is a direct marker of PMN activation.\(^7\),\(^15\) DNA in sputum is almost entirely derived from PMN necrosis.\(^16\) Thus, in a sense, these markers should represent different phases in the “life cycle” of the airway PMN.

Several studies have demonstrated a relationship between sputum inflammatory mediator concentration and pulmonary function in subjects with CF or CB. An increased sputum leukocyte count has been associated with decreased pulmonary function,\(^17\),\(^18\) and a negative correlation has been reported between the DNA content of sputum from CF patients and peak expiratory flow.\(^19\) In addition, there is evidence showing a negative relationship between MPO content in the sputum of CF patients and pulmonary function.\(^10\),\(^20\) Increased IL-8 concentrations in sputum have been associated with decreased pulmonary function in persons with CB\(^12\) or CF.\(^21\) Other studies\(^22\) have shown that although IL-8 concentrations decrease with the use of antibiotic therapy for an exacerbation of CF, there was no correlation between IL-8 concentrations and pulmonary function test results. Although other investigators\(^23\),\(^24\) have failed to demonstrate any relationship of airway inflammation to pulmonary function in CF subjects, these were small studies that used dithiothreitol for sputum processing potentially inactivating the enzyme-linked immunosorbent assay (ELISA)-based assays.\(^25\),\(^26\)

Much less is known about the biophysical and transport properties of sputum in CF patients\(^27\),\(^28\) or CB patients.\(^29\),\(^30\) Although sputum from CF patients does not have increased viscosity,\(^27\) it is highly adhesive, and this increase in adhesivity is associated with decreased cough transportability (CTR) \(\text{in vitro}\).\(^30\) Although overall the viscosity of subjects with CF is less than that of CB subjects, the degree of the viscosity and elasticity of sputum from CF subjects has been associated with DNA concentration\(^16\) but not with mucin concentration, perhaps because of the decreased mucin content of sputum from CF subjects.\(^31\)

In a study\(^32\) of CF subjects during stable and unstable periods, those subjects who were receiving antibiotics had higher sputum viscosity and lower mucociliary transportability than subjects who were not receiving antibiotics. In subjects with CB, quality-of-life scores correlated directly and significantly with sputum CTR but not with pulmonary function.\(^33\)

The interrelationships among inflammatory markers, pulmonary function, and the physical and transport properties of sputum has not been studied in CF or CB subjects. We evaluated these relationships, and we also wished to determine whether changes in the sputum concentration of IL-8, MPO, and DNA over time would be associated with temporal changes in pulmonary function and sputum transportability. We hypothesized that sputum MPO, DNA, and IL-8 content would negatively correlate with sputum transportability and pulmonary function.

**Materials and Methods**

**Subjects**

We analyzed spontaneously expectorated sputum samples that had been obtained from 15 subjects (29 samples) with CB and 16 subjects (31 samples) with CF (Table 1). Among CF subjects, 11 were receiving antibiotics at the time of sampling and 5 were not. Therapy with systemic (oral or domiciliary IV) antibiotics were prescribed at the discretion of the treating physician, always on an outpatient basis, and generally for a “mild exacerbation.” Subjects receiving in-hospital antibiotic therapy were excluded as

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>Age, yr</th>
<th>FVC</th>
<th>FEV(_1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>% Predicted(^\dagger)</td>
</tr>
<tr>
<td>CF</td>
<td>16</td>
<td>22 ± 2 (9–41)</td>
<td>2.3 ± 0.2</td>
<td>66 ± 5</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB</td>
<td>15</td>
<td>62 ± 1.6 (49–75)</td>
<td>3.3 ± 0.2</td>
<td>75.8 ± 2.2</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Values are given as the mean ± SEM (range), unless otherwise indicated.

\(^\dagger\)Values from the studies of the American Thoracic Society/European Respiratory Society\(^35\) for pulmonary function were used to calculate percent predicted values.
were those receiving regular inhaled tobramycin solution for inhalation (TOBI; Chiron Corporation; Emeryville, CA). None of CB subjects were receiving antibiotics at the time of sampling.

Ten CF subjects were receiving long-term therapy with dornase alfa (Pulmozyme; Genentech; South San Francisco, CA) at the time of sputum collection. The diagnosis of CF was confirmed by sweat chloride testing in all subjects. CB was diagnosed by American Thoracic Society criteria of at least 3 months of daily sputum expectoration for at least 2 years in subjects who were tobacco smokers and who had no other underlying pulmonary disease. All CB subjects had a smoking history of at least 20 pack-years. Sputum was usually collected during scheduled outpatient pulmonary function testing. Spirometry was measured at the time of sputum collection, using American Thoracic Society standards. Sputum collection for this study was approved by the Wake Forest University School of Medicine institutional review board.

To compare temporal changes in sputum properties and pulmonary function with changes in sputum inflammatory marker content, we obtained sputum samples from 16 subjects with CF and 15 subjects with CB at two discrete time points, with an interval range of 2 to 11 months (mean \[\pm\] SEM duration, 6 \[\pm\] 1 months) in CF subjects and an interval of 3 months in CB subjects. This sputum could not be fully analyzed from one subject with CF and one with CB due to small volume or poor quality associated with salivary contamination.

Sputum Processing

As previously described, a 50-\(\mu\)L sputum aliquot from each subject was diluted by adding 20 times the volume of phosphate-buffered saline (PBS) solution. This mixture was gently vortexed for 30 s and then centrifuged at 2,500 \(g\) for 20 min. The supernatant was collected and stored at \(-70^\circ\)C for later analysis. Because DNA binds both IL-8 and MPO, dornase alfa was added to the dilution mixture for these analyses but not for the measurement of DNA described below. We specifically did not add dithiothreitol to the diluting solution as this has been shown to render ELISA assays inaccurate.

Measurement of IL-8

Free IL-8 was measured using a commercially available ELISA kit (Immunootech; Marseille, France) with recombinant human IL-8 as the standard (5 to 2,000 pg/mL). The collected supernatant was further diluted 1:20 for specimens from CF subjects and 1:5 for specimens from CB subjects with PBS solution in order to be within the linear portion of the standard curve. After washing five times, the plate was incubated with 50 \(\mu\)L of biotinylated goat polyclonal anti-MPO antibody and 100 \(\mu\)L of streptavidin-horseradish peroxidase conjugate for 30 min at room temperature. The plate was then washed three times. One hundred microliters of tetramethylbenzidine substrate was added and was incubated for 20 min at room temperature in the dark. This was stopped by adding 50 \(\mu\)L of 2 N sulfuric acid. Color development was read as absorbance at 450 nm in an ELISA reader.

Measurement of MPO

MPO was measured using a commercially available ELISA kit (Calbiochem; La Jolla, CA) with human MPO as a standard (1.6 to 100 ng/mL). The collected supernatant was further diluted 1:2,000 for specimens from CF subjects and 1:100 for specimens from CB subjects with PBS solution. After washing five times with buffer (0.05 mol/L Tris-HCl buffer, pH 7.8, containing 0.15 M NaCl, 0.1% Tween-20, and 0.005% NaN3), the plate was incubated with 100 \(\mu\)L of biotinylated goat polyclonal anti-MPO antibody in diluting buffer (20 nM phosphate buffer, pH 7.4, containing 150 mM NaCl, 20 mg/mL bovine serum albumin, and 0.2% NaN3) for 1 h at 37\(^\circ\)C. Avidin-alkaline phosphatase solution (1 \(\mu\)g/mL, 1 mg/mL phosphatase) was added and incubated for 15 min at 37\(^\circ\)C. The reaction was stopped by adding 50 \(\mu\)L of stop solution (1 mol/L sodium hydroxide, containing 100 mM ethylenediamine tetraacetic acid). Color development was read as absorbance at 405 nm by an ELISA reader.

Measurement of DNA

DNA was measured by microfluorometry (33258 Hoechst fluorochrome; Calbiochem; La Jolla, CA) and was compared with a calf thymus DNA (Sigma; Saint Louis, MO) standard (0.25 to 10.0 \(\mu\)g/mL). The supernatant was further diluted 1:50 for specimens from CF subjects and 1:10 for specimens from CB subjects with a standard sodium citrate solution (0.0154 mol/L, NaCl, 0.015 mol/L Na3-citrate, pH 7.0). One milliliter of the reagent solution (1 \(\times\) 10\(^{-6}\) mol/L) was added to the sample, and fluorescence was measured by spectrophotofluorometry with an excitation wavelength at 360 nm and emission at 450 nm.

In Vitro CTR

A simulated cough machine was used to measure the air flow-dependent clearability of sputum. A model plastic (Plexiglas; Dupont; Wilmington, DE) trachea, rectangular in cross-section (1.2 \(\times\) 2 cm), was connected to a 6.4-L tank containing air pressurized to 12 lb per square inch giving a flow rate of about 11 L/s. A solenoid valve controlled air release through a flow-constrictive element that was used to mimic the air flow pattern of a natural cough. A sinusoidal constriction (length, 7.7 cm; height, 8 mm) was used to decrease the airway diameter while minimizing the turbulence of the system. A sample, 40 \(\mu\)L in volume and 0.5 mm in depth, was placed in a 1-mm line across the base of the plastic trachea. The bulk transport of the sample was measured after a single cough maneuver. Three successive measurements were made, and the results were averaged.

In Vitro Ciliary Transportability

A mature northern leopard frog (\textit{Rana pipiens}) was pithed, and the palate was removed. The excised palate was placed on a piece of gauze saturated with modified amphibian Ringers solution prepared by mixing two parts of standard Ringers injection solution with one part sterile water. The palate was allowed to deplete of mucus at 4\(^\circ\)C for 12 h and then was placed in a box with a fitted glass top. The palate was focused under a microscope so that a 5-mm micrometer scale ran between the optic bulges to the opening of the esophagus. The movement of a 4-\(\mu\)L sputum specimen was timed as the trailing edge moved across a 3-mm segment. Three measurements of mucus transport rate were taken to minimize variability, and the average transport rate was normalized to the transport rate for collected endogenous frog mucus. These studies were approved by the Wake Forest University School of Medicine Animal Care and Use Committee.

Statistical Analysis

Statistical analysis was performed using a statistical software package (StatView; version 5.0 for Macintosh; SAS Institute;
Cary, NC). Descriptive statistics were used to summarize subject demographics. The relationship between sputum inflammatory mediators and pulmonary function and physical properties was made by regression analysis after ascertaining that the data were normally distributed. A probability of < 0.05 was taken as significant, and, when multiple analyses were conducted, significance was adjusted using the Bonferroni correction; p = (α/ (number of variables). Results were given as the mean ± SE.

RESULTS

Relationship Between Inflammatory Mediators and Pulmonary Function

In CF subjects, IL-8 and MPO concentrations in sputum samples treated with dornase alfa in vitro were inversely correlated with pulmonary function, but DNA and MPO concentrations in sputum samples treated with PBS solution alone did not (Table 2, Fig 1). There was no relationship between pulmonary function and the concentrations of IL-8, DNA, or MPO in sputum from patients with CB. A subgroup analysis showed no significant difference (p = 0.79 in the sputum DNA concentration of subjects routinely using dornase alfa [1.51 μg/mL] compared with those who were not [1.45 μg/mL]).

Relationship Between Inflammatory Mediators and Sputum Transportability

IL-8 and DNA concentrations were inversely correlated with CTR (IL-8: r = −0.4; p = 0.02; DNA: r = −0.36; p = 0.048), but not with MCTR in CF (Fig 2). There was no relationship between sputum cough or mucociliary transportability and inflammatory mediators in the sputum of CB subjects.

Comparing Temporal Changes in Measurements

We compared absolute changes in sputum properties or inflammatory mediators to changes in the percent predicted of pulmonary function (FEV₁ and FVC) in 15 subjects with CF and 14 subjects with CB at two discrete time points in order to better evaluate how changes in inflammatory mediators would be associated with changes in pulmonary function and sputum physical properties. In CF subjects, a change in DNA concentration was associated with a change in FEV₁ percent predicted (r = −0.58; p = 0.02) and FVC percent predicted (r = −0.74; p = 0.002). A change in IL-8 concentration was nearly significantly correlated with a change in FEV₁ percent predicted (r = −0.47; p = 0.06). A change in DNA concentration was correlated with a change in CTR (r = −0.59; p = 0.02) [Fig 3]. There was no relationship among the changes in inflammatory mediators and the changes in pulmonary function and sputum physical properties in CB subjects.

Table 2—The Relationships Between Inflammatory Markers in Sputum and Pulmonary Function in Subjects With CF*

<table>
<thead>
<tr>
<th>Variables</th>
<th>r Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8 vs FVC</td>
<td>−0.38</td>
<td>0.03</td>
</tr>
<tr>
<td>IL-8 vs FEV₁</td>
<td>−0.36</td>
<td>0.048</td>
</tr>
<tr>
<td>IL-8 vs FVC % predicted</td>
<td>−0.40</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-8 vs FEV₁ % predicted</td>
<td>−0.40</td>
<td>0.003</td>
</tr>
<tr>
<td>MPO (DNase) vs FVC</td>
<td>−0.48</td>
<td>0.005</td>
</tr>
<tr>
<td>MPO (DNase) vs FEV₁</td>
<td>−0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>MPO (DNase) vs FVC % predicted</td>
<td>−0.40</td>
<td>0.02</td>
</tr>
<tr>
<td>MPO (DNase) vs FEV₁ % predicted</td>
<td>−0.38</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*MPO (DNase) = MPO concentration in sputum treated with dornase alfa in vitro.
Evidence suggests that the recruitment and activation of airway PMNs is a primary cause of the chronic airway inflammation in subjects with CB and CF. Because there is marked PMN degeneration in sputum, PMN counts are unreliable. However, neutrophilic inflammation is associated with the presence of proinflammatory mediators, especially IL-8. IL-8 is produced by monocytes and epithelial cells, and attracts and activates PMNs. MPO is a marker of PMN activation and can damage the airway epithelium in the presence of hydrogen peroxide. PMN necrosis releases DNA into purulent sputum, where it forms rigid polymers. Studies have shown a significant correlation between the sputum concentrations of IL-8 and MPO in persons with CB or CF. The correlation found among soluble mediators supports the hypothesis that the specific attraction, activation, and necrosis of PMNs occur concomitantly in the airways of patients with ongoing airway inflammation. The results presented here confirm that the concentrations of these mediators are correlated in sputum and, at least in CF subjects, that the concentrations of these easily measured mediators are inversely correlated with pulmonary function and poor sputum cough clearance. Thus, the measurement of these mediators may provide additional data with which to monitor the severity of disease or the response to therapeutic interventions.

Some published studies have demonstrated a significant relationship between airway inflammatory markers and pulmonary function in subjects with CF. One study showed a negative correlation between sputum DNA content and peak expiratory flow, and at the end of treatment for pulmonary exacerbations of CF DNA content was negatively correlated with FEV1 ($r = -0.44; p = 0.001$). Increased sputum MPO activity has been associated with decreased FEV1 percent predicted.

In this study, MPO concentrations in sputum samples treated with dornase alfa in vitro and IL-8 concentrations showed an inverse correlation with pulmonary function in CF subjects. In addition, the changes in IL-8 and DNA concentrations at two discrete time points were correlated with changes in pulmonary function. However, MPO concentration

**Figure 2.** The relationship between CTR and the concentrations of IL-8 and DNA in sputum from subjects with CF. **Top:** A: IL-8 concentration was inversely correlated with CTR in the sputum of CF subjects ($r = -0.4; p = 0.02$). **Bottom:** B: DNA concentration was inversely correlated with CTR in the sputum of CF subjects ($r = -0.36; p = 0.048$).

**Figure 3.** The relationship between the change in CTR and the change in DNA content in sputum from subjects with CF. We compared the change in inflammatory markers, and the change in pulmonary function and sputum physical properties in sputum at two discrete time points to evaluate how changes in inflammatory mediators might be associated with changes in pulmonary function and sputum physical properties. The change in DNA concentration over time was correlated with the change of CTR in the sputum of CF subjects ($r = -0.59; p = 0.02$).
in sputum treated with PBS solution alone did not show the relationship with pulmonary function. The concentration of MPO in sputum treated with dornase alfa \textit{in vitro} (total MPO) was about two times higher than that in sputum treated with PBS solution alone (data not shown). This result suggests that the total concentration of MPO, including that released from DNA complexes, may better reflect the clinical status of subjects.

Although we and others have shown an increase in the measured MPO concentration after CF sputum was treated with dornase alfa \textit{in vitro}, reassuringly, it has been reported\textsuperscript{40} that the long-term use of dornase alfa decreases neutrophilic inflammation in persons with CF. Thus, the increase in sputum clearance with dornase alfa is probably far more important than the “unbinding” of MPO from DNA polymers with the inhalation of the drug.

Among CB subjects, those with substantial air flow obstruction (FEV\textsubscript{1}, < 60% predicted) are reported to have significantly more PMNs in their BAL fluid than those with less air flow obstruction (FEV\textsubscript{1}, > 60% predicted).\textsuperscript{18} In subjects with COPD, IL-8 may initiate the inflammatory cycle and increase airway wall thickness, thereby decreasing air flow.\textsuperscript{12} However, in another study,\textsuperscript{2} IL-8 and MPO from BAL fluid did not correlate with pulmonary function in CB subjects. Consistent with this, our study showed no relationship between pulmonary function and these inflammatory markers in sputum samples from CB subjects. We\textsuperscript{26} and others\textsuperscript{6,11} have shown a significantly higher concentration of inflammatory markers in the sputum of CF subjects than that in CB subjects. This may be one explanation for the weaker relationship among inflammatory markers and pulmonary function in patients with CB. It may be possible that such a relationship does exist in the sputum of CB patients as well, but because of the much lower concentration of these inflammatory markers in the sputum of CB patients, this study may have been underpowered to detect statistically significant relationships.

An alternative explanation may be that in CF patients the neutrophilic inflammation is far greater and more persistent than that in CB patients. With the prolonged high-level neutrophilic inflammation in CF patients, there is PMN necrosis\textsuperscript{16} spilling both DNA and other inflammatory markers into the airway milieu. In CB patients with less severe or sustained inflammation, there is a slower progression of disease, less PMN necrosis (death favoring the apoptotic pathways), and thus less DNA and fewer inflammatory markers\textsuperscript{29} in the sputum of CB patients.

Persons who have CF and poor pulmonary function have greater sputum IL-8 concentrations, and higher sputum viscosity and elasticity.\textsuperscript{32} The sputum elasticity and viscosity of CF patients have also been reported to be associated with increases in sputum DNA concentration,\textsuperscript{16,41} although for all degrees of lung function impairment it appears that the sputum of CF patients is less viscous than that of CB patients. We found a significant inverse relationship between CTR and sputum IL-8 and DNA concentrations in CF patients. Furthermore, the changes in DNA concentration at two discrete time points are associated with changes of CTR in CF patients. In chronic lung diseases that are characterized by mucus hypersecretion, such as CB or CF, cough clearance becomes the dominant mechanism for secretion removal.\textsuperscript{27,28,42} Decreased CTR of sputum in CF patients may in part explain airway obstruction in patients with severe disease. As well, prolonged resident time of sputum due to poor cough clearance may allow inflammatory markers to accumulate.

We specifically chose to focus this study on the evaluation of three inflammatory markers associated with PMN-driven inflammation in two groups of subjects with airway disease known to be PMN dominated. We used forced expiratory flow-volume testing as the most commonly measured pulmonary function test, and assessed only \textit{in vitro} mucociliary transportability and CTR using well-established techniques as these two measurements would identify the sum of the biophysical changes that might adversely affect sputum clearance. Thus, these data cannot be extrapolated to other diseases, sputum properties, or inflammatory markers that can be measured.

These data suggest that the sputum concentrations of IL-8, MPO, and DNA are associated with the degree of airway obstruction in patients with CF and may serve as a means to evaluate the severity of airway inflammation. Although a similar association was not demonstrated for patients with CB, this may be due to the much lower concentrations of these inflammatory markers in the sputum of CB patients, making changes and relationships more difficult to detect. These data also suggest that airway inflammation is associated with poor sputum transportability, and this may in part explain mucus stasis in patients with these diseases.

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