Relationships Among Bacteria, Upper Airway, Lower Airway, and Systemic Inflammation in COPD*

John R. Hurst, MB, ChB; Tom M. A. Wilkinson, MB, BS; Wayomi R. Perera, MB, BS; Gavin C. Donaldson, PhD; and Jadwiga A. Wedzicha, MD

Study objective: The upper and lower airways are continuous. While upper airway symptoms are common in COPD patients, with accumulating evidence to suggest increased nasal inflammation, the relationships among upper airway, lower airway, and systemic inflammatory indexes have not been studied. We aimed to confirm that there is heightened nasal inflammation in COPD patients, to test the hypothesis that the degree of upper airway inflammation relates to the degree of lower airway inflammation, and to investigate the underlying associations with bacterial carriage and the systemic inflammatory response.

Design: Prospective cohort study.

Setting: Outpatient Department, London Chest Hospital, London, UK.

Participants: Forty-seven patients with COPD and 12 control subjects of similar age, sex, and smoking status.

Measurements: Serum, nasal wash fluid, and sputum samples were obtained from 47 stable patients with COPD for the analysis of inflammatory indexes and bacterial colonization. Nasal wash fluid specimens were obtained from 12 control subjects.

Results: COPD patients had an increased nasal interleukin (IL)-8 concentration compared to control subjects (difference, 97.2 pg/mL; p = 0.009). The nasal IL-8 concentration in COPD patients correlated with that in sputum (r = 0.30; p = 0.039). In both the upper and lower airways of patients with COPD, the IL-8 concentration was associated with indexes of bacterial colonization. Patients colonized with a sputum potentially pathogenic microorganism had a higher total nasal bacterial load (difference, 1.5 log cfu/mL; p = 0.016). We did not find significant relationships between the degree of upper or lower airway inflammation, or bacterial carriage, and the systemic inflammatory response.

Conclusions: COPD is associated with an increased nasal concentration of the neutrophil chemoattractant protein IL-8, the degree of which reflects that present in the lower airway. A relationship between lower airway bacterial colonization, postnasal drip, and higher nasal bacterial load may suggest a mechanism underlying this finding. This study is the first to report a correlation between the degree of upper and lower airway inflammation in COPD.

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Key words: bacterial colonization; COPD; cytokines; inflammation; nose

Abbreviations: IL = interleukin; IQR = interquartile range; PPM = potentially pathogenic microorganism

COPD is a condition that is characterized by airflow obstruction that is largely irreversible and is associated with an abnormal inflammatory response in the lung. This focus on the lung ignores the fact that there is anatomic continuity between the lower and upper airway and that both components act together as a single physiologic unit showing similar reactions to noxious stimuli.

Interactions between the upper and lower airway have been extensively studied in patients with asthma. Asthma and rhinitis commonly coexist, nasal allergen challenge in asthmatic patients results

*From the Academic Unit of Respiratory Medicine, St. Bartholomew’s Hospital, London, UK.
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in heightened bronchial reactivity, and bronchial allergen challenge in patients with rhinitis results in a nasal inflammatory reaction. Therefore, there has been increasing interest in the phenomenon of inflammatory “cross-talk” between the nose and lung, suggesting the concept of a “united airways disease” in which rhinitis and asthma are the upper and lower airway manifestations of the same disease process. In contrast, little is known about possible upper airway involvement in COPD patients, in whom cigarette smoke provides the pan-airway exposure in contrast to the allergen stimulation of allergic disease.

We have previously reported a high prevalence of chronic nasal symptoms in patients with COPD and have gone on to show that these contribute to impairment in quality of life. In our initial study, 75% of patients with moderate-to-severe COPD experienced persistent daily nasal symptoms, most commonly rhinorrhea. More recently, an analysis of matched nasal and bronchial biopsy specimens has suggested that nasal and bronchial inflammation coexist in COPD patients. Lower airway inflammation in COPD patients is known to be modulated by bacterial colonization. In contrast, the mechanisms underlying upper airway involvement in COPD patients have not been described, and, in particular, it is not known whether the degree of upper airway inflammation reflects that occurring in the lower airway or systemic circulation. Since lower airway inflammation is known to be associated with important clinical variables including FEV₁ and exacerbation frequency, a link between upper and lower airway inflammation in COPD patients could result in modulation of the lower airway disease and affect clinical outcomes. This has implications for the development of novel therapeutic strategies.

We aimed to confirm that stable COPD is indeed associated with up-regulated nasal inflammation, to test the hypothesis that the degree of this upper airway inflammation correlates with the degree of lower airway inflammation, and to investigate the underlying relationships with bacterial colonization and the systemic inflammatory response. This is the first study to investigate the inflammatory profile of upper airway, lower airway, and serum samples taken at a single time point from stable patients with COPD. A control population of similar age, sex, and smoking status was included to enable a comparison between nasal inflammatory indexes in adults with and without COPD. The use of the well-characterized East London COPD cohort allows a unique opportunity to relate upper airway indexes to important prospectively collected clinical variables, including exacerbation frequency.

**Materials and Methods**

**Study Subjects**

Forty-seven patients with COPD who were enrolled in the East London cohort were studied during the period October 2002 through July 2003. These patients with well-characterized disease recorded daily peak expiratory flow rate and any increase in symptoms on diary cards, and attended the Outpatient Clinic of London Chest Hospital for a quarterly review that included spirometry and clinical sampling. This prospectively collected daily diary card data allowed the calculation of an exacerbation frequency according to our previously published methodology. The entry and exclusion criteria have also been previously described and, in brief, consisted of a postbronchodilator FEV₁ of <80% predicted, an FEV₁/FVC ratio of <70%, β₂-agonist reversibility on baseline FEV₁ of <200 mL and/or 15%, and the absence of clinical asthma or other significant respiratory pathology. In particular, given the recognized association between bronchiectasis and sinusitis, none of the patients had clinical findings that were suggestive of bronchiectasis (such as the production of large volumes of purulent sputum or coarse inspiratory crepitations). FEV₁ was assessed as the best of three consecutive attempts using a rolling seal spirometer (Sensor-Medics; Yorba Linda, CA). Three of the 47 patients (6%) reported a history of physician-diagnosed rhinosinusitis. None were receiving therapy with nasal corticosteroids or antihistamines. Forty-four of the 47 patients were receiving regular therapy with inhaled corticosteroids. Samples of sputum, nasal wash fluid, and serum were obtained at a single clinic visit during a period of clinical stability at least 3 months after any preceding exacerbation.

Twelve control patients were recruited from an otorhinolaryngology clinic. Inclusion criteria were no history of atopy, significant lung or nasal disease, and freedom in the preceding 3 months from upper respiratory tract infection. The patients were attending the clinic for a variety of reasons including assessment for hearing aids (n = 4), tinnitus (n = 1), and Ménière disease (n = 1), or surveillance of previous mastoid cavity surgery (n = 4) or otitis externa (n = 2), which had been judged to be clinically quiescent and did not require ongoing therapy. None of the patients were receiving inhaled or intranasal therapies, or treatment with oral antihistamines or corticosteroids. None of the control subjects were current smokers. Four of the 12 subjects had never smoked, and the remaining 8 subjects had smoked a mean of 21.1 pack-years (SD, 11.2 pack-years) and had been abstinent for a mean period of 27.1 years (SD, 16.5 years). A medical history was recorded, spirometry was performed, and the nasal wash fluid sample taken. All participants gave written informed consent, and the study was approved by the local (East London and The City) Research Ethics Committee.

**Nasal Symptoms**

A simple nasal score, as used in our previous work, was used to assess the severity of chronic nasal symptoms. The presence or absence on most days of the week of the five principal nasal symptoms (i.e., rhinorrhea, postnasal drip, nasal congestion, sneezing, and impaired sense of smell) were binary coded as 1 or 0, respectively, and the scores were summed to yield a total score between 0 and 5.

**Sputum Samples**

A single sample of sputum, either spontaneous or induced, was obtained and processed according to techniques that we have
previously reported. In brief, each sample was divided into three aliquots. One portion was processed with 0.1% dithiothreitol, and was centrifuged to produce a cell-pellet for a leukocyte count using a hemocytometer and the trypan-blue exclusion method. A second sample was homogenized with glass beads in phosphate-buffered saline solution and centrifuged, and aliquots of supernatant were stored at −70°C for later cytokine analysis. The third aliquot was used for quantitative bacteriologic culture. This portion was incubated for 30 min at 37°C with an equal weight of 0.1% dithiothreitol. Tenfold serial dilutions were then made in Brain Heart infusion broth, and 100-μL aliquots were plated onto the surface of a range of culture media, including blood, chocolate, MacConkey medium, and cystine lactose electrolyte-deficient agars. These were incubated for 18 h at 37°C in air that was enriched to 5% CO₂, and bacterial colonies were counted and subcultured for identification using standard morphologic and biochemical assessments, as used in our previous studies.

Nasal Wash Procedure and Samples

Nasal wash was performed using a technique adapted from Hilding. Briefly, a 12F Foley catheter (Bard; Crawley, UK), modified by removal of the tip distal to the balloon, was inserted into the nostril and inflated with sufficient air to form a comfortable seal (typically, 7 to 10 mL). With the patients head flexed 45° forward, 7 mL warmed 0.9% saline solution was instilled through the catheter, and was washed in and out of the nasal cavity three times. A portion of the pooled wash fluid from both nostrils was processed for quantitative bacteriology, and the remainder was centrifuged to be statistically significant.

Serum Samples

A 5-mL sample of serum was collected into a sterile vacutainer and centrifuged, and the supernatant was stored for later analysis of IL-6 as described above for sputum specimens.

Sample Analysis

The inflammatory cytokines IL-6 and IL-8 were quantified using commercial sandwich enzyme-linked immunosorbent assay kits (R&D Systems; Abingdon, UK). Concentrations of cytokine are expressed in picograms per milliliter, and for sputum samples this represents a 10-fold dilution by weight of the original sample. The limits of detection were 0.7 pg/mL for IL-6 and 10 pg/mL for IL-8.

Bacteriology data are expressed as the total bacterial count (in colony forming units [cfu] per milliliter of nasal wash fluid or sputum supernatant, in logarithmic units) and the presence or absence of a range of potentially pathogenic microorganisms (PPMs) associated with exacerbations of COPD. For the purposes of this study, we defined PPM to include Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

Statistical Analysis

Data were analyzed using a statistical software package (STATA-5 software; Stata Corporation, Austin, TX). Clinical data with normal distribution are described by mean (SD), and differences between groups were tested by paired t test. Nasal wash fluid, blood, and sputum sample data are all reported for clarity as median and interquartile range (IQR). The Kolmogorov-Smirnov test of normality was employed, and relationships between groups used the Pearson or Spearman rank correlation as appropriate. Comparisons between independent groups were made with a Mann-Whitney U test, and frequency distributions were tested by χ² analysis. A probability of ≤ 0.05 was considered to be statistically significant.

RESULTS

Baseline Clinical Characteristics

The clinical characteristics of the 12 control subjects and 47 COPD patients are reported in Table 1. The control subjects, none of whom were current smokers, were compared with the 35 ex-smoking

Table 1—Clinical Characteristics of the 12 Control Subjects (6 Men), 35 Ex-Smoking COPD Patients (20 Men), and 12 Currently Smoking COPD Patients (7 Men)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Subjects</th>
<th>Ex-Smoking COPD Patients</th>
<th>Smoking COPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age, yr</td>
<td>71.8</td>
<td>7.1</td>
<td>71.1</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.3</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>% predicted</td>
<td>96.6</td>
<td>12.7</td>
<td>38.7</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.7</td>
<td>0.7</td>
<td>2.1</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, %</td>
<td>86.1</td>
<td>8.7</td>
<td>47.6</td>
</tr>
<tr>
<td>Pao₂, kPa</td>
<td>8.8</td>
<td>1.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Paco₂, kPa</td>
<td>5.6</td>
<td>0.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Smoking pack-yr</td>
<td>14.0</td>
<td>13.7</td>
<td>46.8</td>
</tr>
<tr>
<td>Nasal score</td>
<td>1.0</td>
<td>1.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Control subjects, no current smokers, were of similar age and sex distribution to the 35 ex-smoking COPD patients. There were no significant differences between the COPD patients who did and did not continue to smoke. Arterial blood gas analysis was not performed in the Control subjects.
COPD patients to avoid any effect of active cigarette smoking on nasal symptoms, inflammatory markers, or bacterial carriage. Subjects in the control population were of similar age and sex distribution to those of the ex-smoking COPD patients but had a lower total pack-year smoking history. There were no significant differences in the clinical variables between the 12 COPD patients who continued to smoke and the 35 ex-smokers (who had stopped smoking a median of 8 years previously; IQR, 3 to 15 years). The subsequent analysis, within the COPD patients, of inflammatory indexes and bacterial carriage in the upper airway, lower airway, and systemic circulation, therefore includes data from all 47 patients.

Comparison of Nasal Inflammatory Markers in Control Subjects and COPD Patients

The results of the nasal wash fluid leukocyte count and cytokine analysis for the 12 control subjects and 35 matched (ex-smoking) COPD patients are reported in Table 2. The median nasal wash fluid IL-8 concentration was significantly higher in the COPD patients than in the control subjects as illustrated in Figure 1 (COPD patients, 156.1 pg/mL; control subjects, 58.9 pg/mL; p = 0.009). The differences in leukocyte count, bacterial load, and IL-6 concentration, although higher in the COPD patients, did not reach statistical significance. Two of the 47 COPD patients (4.3%) and 1 control subject (8.3%) were colonized with a nasal PPM. These organisms consisted of one isolate each of *K pneumoniae* and *P aeruginosa* in the COPD patients, and an *M catarrhalis* isolate in the control subjects. Four of the 47 COPD patients (8.5%) were colonized with *Staphylococcus aureus*, and the remainder of the nasal wash fluid cultures in the COPD patients and control subjects grew a mixed growth of upper respiratory tract commensal organisms.

Interrelationships Among Nasal Wash Markers

We found significant correlations between the individual nasal wash fluid inflammatory markers in both the control subjects and COPD patients. In the control subjects, but not in the COPD patients, the nasal wash fluid leukocyte count correlated with the total nasal bacterial load (r = 0.60; p = 0.050). In the COPD patients, the nasal leukocyte count correlated with the nasal IL-8 concentration (r = 0.55; p < 0.001), and the IL-8 concentration correlated with that of IL-6 (r = 0.59; p < 0.001). There was a trend to correlation between the nasal IL-8 concentration and the nasal bacterial load that just failed to reach conventional statistical significance (r = 0.27; p = 0.067).

Interrelationships Among Sputum Markers

There was a significant correlation between the sputum IL-8 and IL-6 concentration in the patients with COPD (r = 0.41; p = 0.004). Twenty of the 47 COPD patients (43%) had lower airway colonization with a PPM. Of those with a PPM, 43% had *H influenzae*, 19% had *H parainfluenzae*, 14% had *S pneumoniae*, and 14% had *M catarrhalis*. One isolate each of *P aeruginosa* and *K pneumonia* was identified. Patients in whom the lower airway was colo-

### Table 2—Nasal Wash Inflammatory Markers in 12 Control Subjects and 35 Ex-Smoking COPD Patients

<table>
<thead>
<tr>
<th>Markers</th>
<th>Control Subjects</th>
<th>Ex-Smoking COPD Patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>58.9</td>
<td>13.8–81.6</td>
<td>156.1</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.9</td>
<td>1.5–2.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Leukocyte count, cells/mL</td>
<td>6,250</td>
<td>3,714–12,500</td>
<td>12,500</td>
</tr>
<tr>
<td>Bacterial load, log cfu/mL</td>
<td>2.3</td>
<td>2.0–2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>
nized with a PPM had a significantly higher median sputum IL-8 concentration than those who were not colonized (PPM group, 4,907.1 pg/mL; no-PPM group, 3,784.3 pg/mL; p = 0.041).

Relationships Among Nasal Wash Fluid, Sputum, and Serum Markers

The results of the nasal wash fluid and sputum analyses for the 47 COPD patients are reported in Table 3. The nasal IL-8 concentration correlated positively with that in sputum, as illustrated in Figure 2 (r = 0.30; p = 0.039). No significant relationships were observed for the leukocyte count, IL-6 concentration, or total bacterial load. However, lower airway colonization with a PPM was associated with a higher total nasal bacterial load (difference, 1.5 log cfu/mL; p = 0.016) [Fig 3]. Both COPD patients with a nasal PPM had the same species isolated in their sputum at the same visit.

The median serum IL-6 concentration was 4.7 pg/mL (IQR, 3.1 to 8.3 pg/mL). The serum IL-6 concentration did not correlate significantly with inflammatory indexes or markers of bacterial colonization in either the upper or lower airway samples.

Relationships Among Nasal Wash Fluid, Sputum, and Clinical Parameters

The mean nasal score was higher, but not significantly so, in COPD patients than in the control subjects and was highest in those COPD patients who continued to smoke (Table 1). The nasal score did not correlate with nasal inflammatory markers, but the presence of postnasal drip was associated with both a higher sputum cell count (p = 0.043) and the presence of a sputum PPM (p = 0.049).

We found no significant relationships between nasal inflammatory markers and clinical indexes, including smoking status, FEV1, or exacerbation frequency, over the previous 12 months. Sputum bacterial load correlated positively with exacerbation frequency, as has been previously reported (p = 0.32; p = 0.029).17

Discussion

This study has demonstrated increased levels of the neutrophil chemoattractant protein IL-8 in the upper airway of COPD patients when compared to control subjects of similar age, sex, and smoking status. The upper airway IL-8 concentration correlated with that in the lower airway, and at both sites the concentration was related to indexes of bacterial colonization. Furthermore, lower airway colonization with a PPM was associated with both postnasal drip and a higher nasal bacterial load. This study is therefore the first to suggest a correlation between the degree of upper and lower airway inflammation in COPD patients. We did not find significant relationships between upper or lower airway inflammatory cytokines, or bacterial colonization, and a marker of systemic inflammation.

We have previously described8 a high prevalence of chronic nasal symptoms in a cohort of patients with well-characterized COPD. The basis for these nasal symptoms has not been explained. Nihlen and colleagues19 have recently reported that COPD patients, particularly those with nasal symptoms, have an exaggerated nasal neutrophil response to histamine challenge. IL-8 is a potent chemotactic factor and activator of neutrophils.20 Our finding of a raised IL-8 concentration in the nasal wash fluid of COPD patients, and the highly significant correlation between nasal wash fluid IL-8 concentration and leuk-

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Table 3—Inflammatory Markers in Nasal Wash Fluid and Sputum From 47 Patients With COPD

<table>
<thead>
<tr>
<th>Markers</th>
<th>Median</th>
<th>IQR</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8, pg/mL</td>
<td>168.5</td>
<td>76.1–359.4</td>
<td>4,472.6</td>
<td>3,406.6–5,903.7</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>2.6</td>
<td>1.0–6.1</td>
<td>190.5</td>
<td>122.9–376.4</td>
</tr>
<tr>
<td>Leukocyte count, cells/mL</td>
<td>12,500</td>
<td>3,693–35,231</td>
<td>781,893</td>
<td>325,380–1,473,684</td>
</tr>
<tr>
<td>Bacterial load, log cfu/mL</td>
<td>2.3</td>
<td>1.8–3.7</td>
<td>7.4</td>
<td>7.0–8.0</td>
</tr>
</tbody>
</table>

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kocyte count, also suggests the presence of a neutrophilic inflammatory process in the upper airways of these patients. Although we did not demonstrate a direct relationship between nasal symptoms and IL-8 concentration, neutrophilic inflammation remains a plausible cause of nasal symptoms. In experimental rhinovirus infection, the nasal IL-8 concentration was related to the severity of symptoms,21 and the intranasal administration of IL-8 can induce rhinorrhea.22

A recent study by Vachier et al10 has also suggested the presence of neutrophilic inflammation in the nasal airways of patients with COPD. However, all of these patients continued to smoke, a behavior that is known to affect both nasal symptoms23 and cytokine concentrations.24 We therefore compared control subjects, none of whom were active smokers, with the subgroup of COPD patients who were ex-smokers. The finding of a raised IL-8 concentration in the nasal wash fluid of COPD patients even after prolonged smoking cessation is novel and suggests the presence of ongoing upper airway inflammation in these patients. This phenomenon is known to occur in the lower airway,25 and our results suggest that the upper and lower airways are behaving in a similar manner.

In both the COPD patient and control subject populations the degree of upper airway inflammation was related to indexes of bacterial colonization. In the COPD patients, there was a trend to correlation between the nasal bacterial load and the IL-8 concentration in nasal wash fluid that suggested a relationship between the neutrophilic response and bacterial carriage. It has been previously reported11 that lower airway bacterial colonization modulates lower airway inflammation. The demonstration of a relationship between upper airway bacterial colonization and heightened nasal inflammation is further evidence of the similarity between upper and lower airway pathology in COPD patients.

This is the first study to demonstrate a significant relationship between the degree of upper and lower airway inflammation in COPD patients, as assessed by nasal and sputum IL-8 concentration. However, while statistically significant, the correlation coefficient of 0.3 suggests that only 9% of the variance in inflammation at one site is accounted for by the degree of inflammation at the other. Other local mechanisms must therefore contribute to airway inflammation, which, as discussed above, are likely to include bacterial carriage.

There is a considerable volume of work exploring the relationships between the upper and lower airways in asthma patients. In addition to the strong epidemiologic links between rhinitis and asthma,3 there are many pathophysiologic similarities.26 This has resulted in the concept of an inflammatory “cross-talk” between the nose and the lung,6 which becomes of clinical relevance with the suggestion that treating the rhinitis of patients with asthma may improve their asthma symptoms.27 Our results suggest that in patients with COPD there is also a pan-airway inflammatory response, reflecting the pan-airway exposure to cigarette smoke. This has important implications. First, the nose may provide new therapeutic targets that could result in the modulation of lower airway inflammation, in addition to reducing nasal symptoms. Second, our findings of a similar inflammatory process in the upper and lower airways suggest that the nose deserves further study and that it may provide a more accessible site for future COPD airway research.

A number of mechanisms have been suggested to explain the link between the upper and lower airway in asthma, including the direct passage of mediators along the respiratory mucosa, blood-borne passage, and neural responses.26 Our finding of higher nasal bacterial load in patients with lower airway colonization suggests a possible mechanism for the relationship between upper and lower airway inflammation in COPD patients. We hypothesize that patients with a higher nasal bacterial load (and associated greater nasal inflammation) may be more likely to pass bacteria into the lower respiratory tract where colonization is known to be associated with increased lower airway inflammation. The demonstration of a relationship between postnasal drip and the presence of a lower airway PPM provides further evi-

![Figure 3. Comparison of nasal bacterial load in 47 COPD patients with and without a lower airway colonizing PPM. Box plot represents median, IQR, and range (p = 0.016).](image-url)
idence to support this hypothesis. Although only two patients with COPD were colonized with a nasal PPM, nasal bacterial carriage is dynamic. It is also possible that the discrepancy in colonization rates between the upper and lower airway samples could be accounted for by the nasal wash technique that was employed, which samples the nasal cavity but not, for example, the posterior nasopharynx. Since lower airway bacterial load is known to relate to clinically important variables such as the rate of decline in FEV₁, and exacerbation frequency, it is possible that strategies aimed at reducing nasal bacterial carriage could provide new therapeutic strategies in COPD patients.

In contrast to the relationships described between the upper and lower airway, we did not find a significant correlation between either upper or lower airway inflammation and the systemic inflammatory response, as assessed by the serum IL-6 concentration. We measured IL-6 because this cytokine is known to mediate the hepatic production of fibrinogen, which may represent a mechanism underlying the link between COPD and increased cardiovascular mortality. The current data suggest that in stable patients with COPD the degree of systemic inflammation is independent of airway IL-8 concentration and bacterial colonization. This is in contrast to data from a recent report by Banerjee et al describing a relationship between the presence of a lower airway PPM and higher serum fibrinogen level. The latter study used a different definition of PPM from that in the current study, which may explain the apparent discrepancy, and which serves to highlight that the links among the degree of airway inflammation, systemic inflammation, and cardiovascular morbidity also require further investigation.

In this study, we have compared soluble mediators in nasal wash fluid and sputum. An alternative approach for studying the upper and lower airways would be with matched nasal and bronchial biopsy specimens. This has been performed in asthma patients and, more recently, in patients with relatively mild COPD. However, the morbidity and mortality in COPD patients is most pronounced in those with more severe underlying disease. In these patients, biopsy studies are more difficult to perform because the greater severity of airflow obstruction precludes volunteer research bronchoscopy procedures for reasons of safety.

We have used a nasal wash technique adapted from that of Hilding. In contrast to sputum analysis, in which standard protocols have been developed, a variety of methods may be used to assess the upper airway. For the analysis of soluble mediators, the three main approaches are the collection of spontaneous secretions, absorption, or dilutional nasal wash techniques. Collecting spontaneous secretions directly or by absorption may not provide enough secretion for analysis, and we therefore elected to use a dilutional nasal wash technique. The major concern with the nasal wash technique is that the collected nasal secretion is diluted to an unknown degree. Our data suggest good reproducibility of this nasal wash methodology. A number of methods of correcting for dilution have been suggested including dividing the cytokine concentration by the total protein level. In preliminary experiments, we found that the total protein level itself correlated with IL-6 and IL-8 concentrations in nasal wash fluid, and the bacterial load, perhaps because of increased protein transudation in the inflamed noses of these patients with COPD. Correcting the cytokine concentration using total protein measurement did not enhance the differences between the control subjects and COPD patients, and diminished reproducibility between the repeat washes. Our results therefore remain uncorrected.

In conclusion, we have demonstrated that COPD is associated with an increased nasal concentration of the neutrophil chemoattractant protein IL-8 and, furthermore, that this upper airway IL-8 concentration was related to that present in the lower airway. A relationship between lower airway bacterial colonization and both higher nasal bacterial load and postnasal drip may suggest a possible mechanism for cross-talk between the upper and lower airways in COPD patients. This study is the first to report a correlation between the degree of upper and lower airway inflammation in COPD patients. These findings have implications for the use of the nose as a model of the lower airway in COPD patients, and in suggesting novel therapeutic targets to treat this common and debilitating condition.

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