Exhaled and Sputum Nitric Oxide in Bronchiectasis*
Correlation With Clinical Parameters

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Study objectives: Although there has been tremendous attention on endogenous nitric oxide (NO) production in many respiratory and systemic diseases, little is known on NO production in bronchiectasis.

Design and setting: We determined exhaled and sputum NO levels in 109 patients with stable bronchiectasis (71 women; mean ± SD age, 58.2 ± 14.1 years) and 78 control subjects (39 women; mean age, 56.7 ± 12.1 years) by using an automatic chemiluminescence analyzer.

Measurements and results: There was no significant difference in exhaled NO between patients with bronchiectasis and control subjects (p = 0.11). Bronchiectasis patients with Pseudomonas aeruginosa infection had a significantly lower exhaled, but not sputum, NO levels than their counterparts and control subjects (p = 0.04 and p = 0.009, respectively). Exhaled NO correlated with 24-h sputum volume in P aeruginosa-infected patients (r = −0.36; p = 0.002). After adjustment for sputum volume and number of bronchiectatic lung lobes, P aeruginosa-infected patients still had lower exhaled NO levels than their counterparts (p = 0.01). There was no correlation between exhaled NO with FEV₁, FVC, and the number of bronchiectatic lung lobes (p > 0.05). Sputum NO levels were not different between patients and control subjects (p = 0.64), and had no correlation with clinical parameters.

Conclusion: Exhaled NO appears to be reduced among bronchiectasis patients with P aeruginosa infection independent of other clinical parameters, and further studies on the potential mechanisms and pathogenetic implications of this reduction should be pursued.

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Key words: assessment; bronchiectasis; nitric oxide

Abbreviations: CF = cystic fibrosis; HRCT = high-resolution CT; iNOS = inducible nitric oxide synthase; NO = nitric oxide; ppb = parts per billion

Endogenous nitric oxide (NO) production has received tremendous attention in the last decade, and NO metabolism appears to be involved in the pathogenesis of many respiratory, renal, neurologic, and liver diseases. Endogenous NO is an essential physiologic signaling molecule mediating various cell functions, and also induces cytotoxic and mutagenic effects when present in excess. NO reacts extremely rapidly with superoxide anion to form another highly reactive compound, peroxynitrite, which may be cytotoxic itself or easily decompose to the highly reactive and toxic hydroxyl radical and nitrogen dioxide.

Bronchiectasis is a chronic inflammatory and infective airway disease that is very common among the Chinese. Although lung function and high-resolution CT (HRCT) assessment can define the extent of established lung destruction, markers for monitoring disease activity in patients with bronchiectasis are lacking. Measurement of the exhaled NO level allows noninvasive monitoring of NO production in the lower respiratory tract in vivo, and is technologically relatively easy to achieve. Exhaled NO is elevated in patients with diseases associated with airway inflam-
nation such as asthma and chronic bronchitis. However, exhaled NO is probably decreased in patients with cystic fibrosis (CF) despite a significant inflammatory element in its pathogenesis. There have only been two studies that evaluated the level of exhaled NO in bronchiectasis, and these studies have yielded conflicting results. In addition, little is known on the clinicopathologic correlation of exhaled and sputum NO levels in patients with bronchiectasis. We have, therefore, performed this study to evaluate these gaps of knowledge in a cohort of 109 patients with stable bronchiectasis, and compare their exhaled and sputum NO levels with 78 healthy control subjects.

Materials and Methods

Subject Recruitment

Consecutive patients with proven bronchiectasis who were not treated with inhaled steroid therapy and diagnosed by HRCT were recruited with written informed consent. Inclusion criteria included absence of asthma, COPD, tuberculosis, or other unstable systemic diseases; no alteration in medication and dosage for at least 3 months; and steady-state bronchiectasis. The latter was defined as the absence of significant (>20%) alteration of 24-h sputum volume, FEV1 and FVC, or changes in respiratory symptoms for 3 consecutive weeks. Healthy non-smoking control subjects who were receiving no regular medication and were asymptomatic of respiratory, cardiovascular, GI, renal, and neurologic diseases were also recruited. Written informed consent was obtained from each subject, and the institutional ethics committee approved these procedures.

Parameters Assessed in Patients With Bronchiectasis and Healthy Subjects

The bronchiectatic patients were questioned about the presence of respiratory symptoms, including cough, dyspnea, hemoptysis, sputum production, chest pain, and wheezing, and they were examined physically. The number of lung lobes (including lingula as an individual lobe) affected by bronchiectasis was determined by a thoracic radiologist who examined the HRCT scan of each patient using standard criteria. Very briefly, bronchiectasis was present when the bronchial segment or subsegment appeared larger than the accompanying artery on HRCT. The volume of a 24-h sputum production was also determined for each patient as the mean of three consecutive scans of each patient using standard protocols.

Exhaled NO Measurement

Exhaled NO was measured using a chemiluminescence analyzer (model 280; Sievers Instruments; Boulder, CO), before lung function assessment. This equipment was sensitive to NO from exhaled-air from seated subjects as described previously. The calibration and measurement procedures were performed according to the recommendations from the European Respiratory Society Task Force. Subjects exhaled from total lung capacity to residual volume while maintaining a mouth pressure of 10 cm H2O by instruction from a trained technician, and observing the visual display unit of a computer that controlled the analyzer. The plateau value of exhaled NO was recorded automatically with the software of the manufacturer. Participants repeated the maneuver until three consecutive acceptable tests with plateau values of exhaled NO were obtained. The mean of these readings was adopted as the exhaled NO level for a particular subject. The analyzer was calibrated daily using NO-free certified compressed air to set absolute zero and then a certified concentration of NO in nitrogen of 90 ppb and 500 ppb (BOC Special Gases; Surrey Research Park; Guildford, UK). Ambient air levels of NO were recorded immediately before assessing each subject. Similar to a recent study that employed identical methodology and equipment, the results of our pilot study showed no correlation between atmospheric with exhaled NO levels for control subjects and bronchiectasis patients (r = -0.17, p = 0.51, and r = -0.19, p = 0.36, respectively).

Collection and Microbiological Assessment of Fresh Sputum

Fresh sputum was collected by a physician in sterile clear plastic pots between 10 AM and 11 AM after thorough mouth emptying, and within 1 h of physiotherapy in the sitting position. Fresh sputum was stored at -70°C within 15 min of collection until ultracentrifugation (100,000g for 30 min at 4°C) to obtain the sol phase. Standard microbiological procedures were employed to identify all the sputum bacteria using enriched and selective media including blood agar (Oxoid CM271; Oxoid; Basingstoke, UK) with 5% defibrinated horse blood, chocolate agar supplemented with 18.9 U/mL bacillin (Sigma; St. Louis, MO), mannitol salt agar (Oxoid CMS5; Oxoid) and cetrimide-nalidixic acid agar (Oxoid CM559 and SR102; Oxoid). Incubation was performed for up to 4 days at 37°C in 5% CO2.

Measurement of Total Sputum NO contents

As NO reacts with oxyhemoglobin and superoxide anion almost immediately to form NO3- and NO2-, the latter could be converted back to NO by reduction. Standard protocol was performed to evaluate the total levels of NO3- and NO2- in sputum sol. Briefly, 100 µL of sputum sol was deproteinized by vortexing with 200 µL of 0.5 N NaOH and 200 µL of 10% aqueous zinc sulfate for 30 s, and then left standing at room temperature for 15 min. Ten microliters of this supernatant was injected into the first chamber of the Sievers chemiluminescence analyzer, where NO3- and NO2- were reduced by vanadium (III) chloride (in 1 mol/L HCl) back to NO. The latter was deaminated in 1 mol/L NaOH in the second chamber to remove HCl vapors from entering the NO analyzer. NO was mixed with ozone in the third chamber to produce ground-state NOX and excited-state NOX. The latter emitted a photon on returning to the ground state that was detected by a sensitive photomultiplier connected to the software of the manufacturer that allowed instant conversion of this reading to the corresponding concentration of NO. As NO3- is unstable and is readily oxidized to NO2- in blood or sputum, there would have been insignificant amount of NO2- present in the sample. One could therefore assume that all NO was converted to NO3- in sputum. A standard 100 mM nitrate solution was used to prepare a standard curve. Each specimen was assessed three times and the mean was taken as the value for the nitrate content for a particular specimen. As there is no evidence that sputum contains significant amounts of NO3- and NO2-...
NO$_3^-$ from sources other than NO, it was assumed that the total level of NO$_3^-$ and tiny trace of NO$_3^-$ measured by our chemiluminescence method represented the total level of NO in a particular sputum specimen.

Statistical Analysis

Preliminary inspection of data revealed that exhaled and sputum NO data were log-normally distributed and were therefore logarithmically transformed before analysis. Comparisons between groups were made using Student’s t test. Correlations were evaluated by Spearman’s method. An analysis of covariance test was performed, with adjustment made for 24-h sputum volume and number of lung lobes affected by bronchiectasis, to compare exhaled NO levels between patients who are and are not infected with Pseudomonas aeruginosa. A p value of < 0.05 was taken as statistically significant. The analysis was performed using the statistical software (SPSS version 10.0; SPSS; Chicago, IL).

RESULTS

Subject Demography and Clinical Characteristics

One hundred nine consecutive nonsmoking bronchiectasis patients (71 women; mean ± SD age, 58.2 ± 14.1 years; median, 62 years; range, 23 to 83 years) and 78 control subjects (39 women; age, 56.7 ± 12.1 years; median, 53 years; range, 36 to 83 years) were recruited prospectively between January 1999 and May 2000. Some of the relevant clinical characteristics for the bronchiectasis patients are shown in Table 1. There was no significant difference between age (p = 0.12) and gender (p = 0.53) between control subjects and patients with bronchiectasis. Of the patients with bronchiectasis, 25 patients had P aeruginosa in their sputum. Patients with P aeruginosa infection had a significantly higher 24-h sputum output and number of lung segments affected by bronchiectasis than their counterparts (Table 1). However, there was no significant difference between the two subgroups in age, FEV$_1$, FVC, and etiology of bronchiectasis (Table 1; p > 0.05). Some of the bronchiectasis patients also had diabetes mellitus (n = 5) and osteoarthritis (n = 2) but no other significant conditions known to be related to altered exhaled NO production. Medications received by patients with bronchiectasis included inhaled bronchodilators (n = 38), oral theophyllines (n = 15), oral $\beta_2$-agonists (n = 5), oral hypoglycemic agents (n = 4), and nebulized aminoglycosides (n = 3).

Exhaled NO Levels

Table 2 depicts the levels of exhaled NO in the control and bronchiectasis groups of subjects. There was no significant difference between the level of exhaled NO between control and bronchiectasis subjects (p = 0.11). However, bronchiectasis patients with P aeruginosa infection in their sputum had significantly lower exhaled NO when compared with their counterparts and the control subjects (p = 0.04 and p = 0.009, respectively). There was no significant difference between the exhaled NO levels between control subjects and bronchiectasis patients without P aeruginosa infection (p = 0.96).

Sputum NO Levels

Control subjects did not produce sputum for examination. Table 2 depicts the total NO contents in sputum in patients with bronchiectasis. There was no significant difference in sputum NO levels between bronchiectasis patients with P aeruginosa infection compared with those without P aeruginosa infection (p = 0.40).

Table 1—Clinical Features of 109 Patients With Stable Bronchiectasis*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All (n = 109)</th>
<th>P aeruginosa Infected (n = 25)</th>
<th>Non-P aeruginosa Infected (n = 84)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58.2 ± 14.10</td>
<td>56.1 ± 14.5</td>
<td>59.9 ± 13.6</td>
<td>0.12</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>72.5 ± 28.88</td>
<td>63.1 ± 30.2</td>
<td>75.6 ± 28.1</td>
<td>0.06</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>81.5 ± 23.29</td>
<td>77.2 ± 25.3</td>
<td>83.2 ± 22.4</td>
<td>0.25</td>
</tr>
<tr>
<td>24-h sputum volume, mL</td>
<td>18.3 ± 22.77</td>
<td>32.1 ± 35.4</td>
<td>12.7 ± 12.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Bronchiectatic segments, No.</td>
<td>2.5 ± 1.28</td>
<td>2.9 ± 1.5</td>
<td>2.3 ± 1.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Etiology of bronchiectasis, %</td>
<td>Idiopathic 73.4</td>
<td>76</td>
<td>72.6</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Posttuberculous 11</td>
<td>12</td>
<td>10.7</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Postpneumonic 12.8</td>
<td>4</td>
<td>15.5</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Kartagener’s syndrome 1.8</td>
<td>4</td>
<td>1.2</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Diffuse panbronchiolitis 1</td>
<td>4</td>
<td>0</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†p values obtained by comparing data between P aeruginosa-infected patients and their counterparts.
Correlation Analysis

There was no correlation between exhaled and sputum NO levels \((r = 0.02, \ p = 0.88)\). Table 3 depicts the correlations between exhaled and sputum NO with clinical parameters in patients with bronchiectasis. There was a highly significant negative correlation between exhaled, but not sputum, NO levels, and 24-h sputum volume for the entire cohort of patients with bronchiectasis. However, this significant correlation between exhaled NO and sputum volume only existed for patients with \(P\) aeruginosa infection, but not their counterparts. After adjustment for sputum volume and the number of lung lobes affected by bronchiectasis, patients with \(P\) aeruginosa infection still had a significantly lower exhaled NO level than their counterparts \((p = 0.01)\). There was no correlation between exhaled NO levels and other clinical parameters, including FEV\(_1\), FVC, and the number of lung segments affected by bronchiectasis \((p > 0.05)\). Sputum NO levels had no correlation with any of the aforementioned clinical parameters \((p > 0.05)\).

Discussion

Our results showed that exhaled NO levels were not significantly different between 109 patients with stable bronchiectasis and 78 healthy control subjects. However, there were significantly lower exhaled NO levels for patients infected with \(P\) aeruginosa, compared with their counterparts and healthy control subjects. \(P\) aeruginosa-infected patients had significantly higher 24-h sputum volume and number of bronchiectatic segments compared with their counterparts. Exhaled NO levels of patients with bronchiectasis without \(P\) aeruginosa infection were not significantly different from those obtained from control subjects. Exhaled NO levels negatively correlated with 24-h sputum volume in the entire cohort of patients and those with \(P\) aeruginosa infection, but not their counterparts. However, there was no significant difference in sputum NO levels between patients with and without \(P\) aeruginosa infection. Sputum NO levels did not correlate with any of the clinical parameters, including 24-h sputum volume, spirometry, or the number of lung lobes affected by bronchiectasis. Despite the known association of \(P\) aeruginosa infection with significantly higher 24-h sputum volume and number of lung lobes affected by bronchiectasis in patients with \(P\) aeruginosa infection,\(^1^8\) regression analysis with adjustment for these parameters still revealed significantly lower exhaled NO levels in \(P\) aeruginosa-infected patients compared with their counterparts. Our original results, therefore, indicate that exhaled NO was only...

Table 2—Exhaled and Sputum NO in Control Subjects and Patients With Bronchiectasis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects (n = 78)</th>
<th>Patients With Bronchiectasis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 109)</td>
<td>(P) aeruginosa Infected (n = 25)</td>
<td>Non-(P) aeruginosa Infected (n = 84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled NO, ppb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>24.3 (8.4–105)</td>
<td>19.9 (7.7–206.3)</td>
<td>17.0 (7.7–44.1)</td>
<td>20.7 (9.3–206.3)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.8 ± 16.6</td>
<td>26.8 ± 26.9</td>
<td>20.8 ± 10.9†</td>
<td>28.4 ± 29.5</td>
<td></td>
</tr>
<tr>
<td>Sputum NO, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>558.3 (49.9–6897.5)</td>
<td>668.6 (140.2–3579.9)</td>
<td>533.7 (49.9–6897.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1102.9 ± 1401.5</td>
<td>951.5 ± 834.4</td>
<td>1151.7 ± 1526.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*p < 0.05 when compared with control subjects without \(P\) aeruginosa infection.
†p < 0.05 when compared with patients without \(P\) aeruginosa infection.

Table 3—Relationship Between Exhaled NO and Total Sputum Nitrates (\(NO_3^-\)) and Nitrites (\(NO_2^-\)) With Clinical Parameters in Patients With Steady-State Bronchiectasis

<table>
<thead>
<tr>
<th>Variables</th>
<th>24-h Sputum Volume, (r (p \text{ Value}))</th>
<th>No. of Lobes With Bronchiectasis, (r (p \text{ Value}))</th>
<th>FEV(_1) % Predicted, (r (p \text{ Value}))</th>
<th>FVC % Predicted, (r (p \text{ Value}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaled NO, ppb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>(-0.34 (0.009)*)</td>
<td>0.01 (0.93)</td>
<td>0.11 (0.29)</td>
<td>0.19 (0.06)</td>
</tr>
<tr>
<td>Patient with (P) aeruginosa infection</td>
<td>(-0.36 (0.002)*)</td>
<td>(-0.07 (0.57))</td>
<td>0.08 (0.50)</td>
<td>0.20 (0.08)</td>
</tr>
<tr>
<td>Patients without (P) aeruginosa infection</td>
<td>(-0.03 (0.91))</td>
<td>0.20 (0.40)</td>
<td>0.18 (0.47)</td>
<td>0.33 (0.17)</td>
</tr>
<tr>
<td>Sputum NO, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>(-0.07 (0.52))</td>
<td>0.05 (0.68)</td>
<td>0.03 (0.80)</td>
<td>(-0.07 (0.57))</td>
</tr>
<tr>
<td>Patient with (P) aeruginosa infection</td>
<td>(-0.22 (0.38))</td>
<td>(-0.05 (0.70))</td>
<td>0.07 (0.59)</td>
<td>(-0.07 (0.60))</td>
</tr>
<tr>
<td>Patients without (P) aeruginosa infection</td>
<td>(-0.02 (0.98))</td>
<td>(-0.26 (0.33))</td>
<td>(-0.26 (0.31))</td>
<td>(-0.12 (0.65))</td>
</tr>
</tbody>
</table>

*Statistically significant comparison.
reduced in bronchiectasis patients with *P. aeruginosa* infection, and this downregulation was independent of other markers of disease activity and severity, namely 24- sputum volume and the number of lung lobes affected by bronchiectasis.

Bronchiectasis is a very common and largely idiopathic disease among the Chinese. Similar to CF, there are prominent chronic inflammatory and infective elements in the pathogenesis of bronchiectasis. Although our group has recently shown that sputum elastase levels correlate with sputum production, proinflammatory cytokine expression, and spirometry in patients with bronchiectasis, objective and convenient markers for the assessment of disease activity in bronchiectasis are lacking. While exhaled NO has been clearly shown to reflect disease activity in patients with asthma, and is reduced with inhaled steroid treatment, evaluation of clinical correlation of exhaled and sputum NO levels has not been performed in patients with bronchiectasis previously.

As exhaled NO is elevated in inflammatory airways diseases such as asthma and COPD, exhaled NO should theoretically also be elevated in bronchiectasis and CF. There have only been two small studies on the levels of exhaled NO in patients with bronchiectasis. Exhaled NO was reported to be higher in 20 noninhaled steroid-treated patients with bronchiectasis, compared with control subjects. In addition, there was a significant correlation between the CT score for severity of lung damage and exhaled NO in the bronchiectasis patients. A more recent study performed on 16 bronchiectasis and 36 CF patients showed no significant difference in exhaled NO when compared with control subjects. For unknown mechanism(s), children with primary ciliary dyskinesia, in whom bronchiectasis usually develops, have very low levels of exhaled NO. Several reports suggested that there is a reduction in exhaled NO levels in CF patients, although other studies showed no such difference.

Potential mechanism(s) for the reduction of exhaled NO in patients with CF, which might also apply to bronchiectasis patients, include downregulation of NO synthase in CF, consumption of NO by its rapid reaction with superoxide to form the unstable peroxyynitrite, NO<sub>3</sub>−, NO<sub>2</sub>−, and poor diffusion of NO through diseased tissue. Although the results of these CF studies are inconsistent in whether or not exhaled NO is truly reduced in patients with CF, they collectively pointed out that exhaled NO is not raised in patients with CF. Our results, which were derived from the largest study on bronchiectasis so far, also showed that non- *P. aeruginosa*-infected patients have no significant difference in exhaled NO compared with control subjects. It therefore appears that bronchiectasis itself probably does not affect exhaled NO levels unless there is concomitant *P. aeruginosa* infection. Our demonstration of a lack of difference in sputum NO production between *P. aeruginosa*-infected and non-*P. aeruginosa*-infected patients also suggest that the reduction in exhaled NO in *P. aeruginosa*-infected patients was probably not due to conversion of gaseous NO to NO<sub>3</sub>− and NO<sub>2</sub>− in the bronchiectatic airways.

It is possible that *P. aeruginosa* infection itself or factor(s) promoting its existence, such as severity of bronchiectasis, could be the cause of reduced exhaled NO production in *P. aeruginosa*-infected patients with bronchiectasis. However, there was still significantly lower exhaled NO levels in *P. aeruginosa*-infected patients, compared with their counterparts, after adjustment for sputum volume and the number of lung lobes affected by bronchiectasis. While our results suggest that *P. aeruginosa* infection leads to reduced production of exhaled NO in bronchiectasis in vivo, which might also apply to CF, the underlying mechanism(s) remains obscure.

NO is derived endogenously from the amino acid L-arginine by three isoforms of the enzyme NO synthase, and inducible NO synthase (iNOS) is involved in the inflammatory diseases of the airways and in host defense against infection. The role of NO in the pathogenesis of bronchiectasis and CF appears to be vastly complex and is likely to be that of a double-edged sword. The presence of tumor necrosis factor-α, which is found in abundance in bronchiectatic and CF airways, upregulates iNOS expression. Inhalation of bacterial lipopolysaccharide, which is present in the chronic infected airways of bronchiectasis and CF, also induces iNOS expression leading to NO-induced potentiation of neurogenic plasma leakage in guinea pig airways. NO upregulates interleukin-5 production and increases mucus hyperemia in patients with asthma, and these effects could also be detrimental to the bronchiectatic airways. A decrease in NO formation might be relevant in bronchiectasis, as the inhibition of NO production will perturb mucociliary clearance and also phagocytosis, thus favoring microbes in their interactions with the host respiratory mucosa. As NO is an endogenous neurotransmitter for human bronchodilator nerve endings, the reduced NO production in patients with bronchiectasis could also contribute to the presence of obstructive lung defects in patients with bronchiectasis. Downregulation of iNOS and thus NO production has been shown to occur in a murine model of CF, which is associated with reduced *P. aeruginosa* clearance. There is also downregulation of iNOS expression in bronchial epithelium, although this finding could not be extended to inflammatory cells, in patients with CF.
Several studies have been performed to evaluate the clinicopathologic correlations for exhaled NO in respiratory diseases. Exhaled NO correlated with FEV₁ in patients with COPD, although this has not been confirmed by another study, eosinophilic airway inflammation and airway hyperresponsiveness in patients with asthma; and lymphocyte counts of the BAL fluid obtained from patients with fibrosing alveolitis. Exhaled NO is also higher in more severely affected COPD patients with FEV₁ < 35% predicted, compared with their counterparts. These together suggest that exhaled NO could be a marker for inflammatory airways diseases. Our results showed that exhaled NO could be a convenient disease marker for assessment of disease activity (sputum production) and status of *P. aeruginosa* infection in bronchiectasis. Further studies on the potential mechanisms and pathogenetic implications of reduction of exhaled NO production by *P. aeruginosa* infection should be pursued in patients with bronchiectasis.

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