Safety of Bronchoscopy, Biopsy, and BAL in Research Patients With COPD*

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Background: Bronchoscopy with biopsy and BAL is being performed increasingly in patients with COPD as a research tool. Previous reports have shown these procedures to be safe in asthmatic patients, but there is little safety data specific to COPD.

Methods: We studied 57 patients with COPD (11 women and 46 men; median FEV₁, 1.2 L [range, 0.64 to 2.69 L]; percent predicted FEV₁, 44.5% [range, 25 to 74.8%]). Eleven patients had mild disease, 28 patients had moderate disease, and 18 patients had severe disease according to British Thoracic Society classification. Ninety-eight bronchoscopies were performed according to American Thoracic Society guidelines: 68 procedures with endobronchial biopsy and BAL and 30 procedures with biopsy alone. Controlled oxygen was administered via nasal cannula, and pulse oximetry and vital signs were monitored.

Results: Five adverse events occurred. One patient in the moderate-disease group had severe bronchospasm requiring 4 days of inpatient treatment. One patient in the severe-disease group had a pneumothorax requiring 7 days of inpatient treatment. There were three episodes of hemoptysis, two with pleuritic pain (in the BAL group) that settled without intervention. No deaths or prolonged morbidity were observed. We found a 2.0% incidence of adverse events requiring hospital treatment and a 3.1% incidence of minor hemoptysis requiring no intervention.

Conclusions: Bronchoscopy, biopsy, and BAL can be performed safely in patients with COPD, including those with severe disease, provided careful assessment is performed and guidelines are adhered to. (CHEST 2002; 122:1909–1912)

Key words: adverse effects; BAL; biopsy; bronchoscopy; safety

COPD is a major health problem in the United Kingdom and worldwide. Its prevalence is increasing, and it is associated with significant morbidity and mortality. In the United Kingdom, it is the third most common cause of death. Currently, COPD ranks as the sixth most common cause of death worldwide and is expected to increase to the third position by the year 2020.1

Over the last decade, there have been a number of studies using bronchial biopsies obtained at fiberoptic bronchoscopy in patients with COPD.2–5 These studies have yielded valuable information about the inflammatory process in large airways in this disease. Such studies increase our understanding of the disease process in COPD, and this mechanistic understanding can contribute to the development of new treatments. Bronchial biopsies may then be used to evaluate the anti-inflammatory effects of any treatments.

Less invasive methods can also be used to assess inflammation in patients with COPD. In particular, induced sputum has been widely used. This technique has been shown to be valid and reproducible.6 In addition, sputum supernatant can be used to measure inflammatory cytokines and mediators.7 In COPD, the predominant cell seen in induced sputum is the neutrophil.8 This is in contrast with bronchial biopsies, in which the predominant cell type is the CD8+ T lymphocyte.4,5 Epithelial integrity, basement membrane thickness, mucous gland hyperplasia/hypertrophy, lymphocyte subsets, and their predominance in the airway epithelium or subepithelium cannot be assessed from sputum samples. Furthermore, since patients with COPD have a higher incidence

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of carcinoma of the lung, unsuspected endobronchial lesions may be visualized at bronchoscopy leading to earlier diagnosis. Sputum analysis provides useful data about airway inflammation, which is different and complementary to that provided by bronchial biopsies. This probably reflects a difference in inflammatory cell distribution between the airway wall and lumen.

Fiberoptic bronchoscopy is being used increasingly as a diagnostic and research tool in patients with COPD to assess airway pathology and the effects of treatment. Bronchoscopic biopsy provides airway wall tissue from which the morphology can be assessed, inflammatory cells can be quantified, and gene products identified. Most of the literature regarding the investigative use of bronchoscopy and bronchial biopsy relates to its use in asthma. After the procedure, oximetry and clinical status should be monitored and clear discharge instructions given with a telephone contact in case of problems. Guidelines suggest that bronchoscopy may be safer in patients with COPD than with asthma because of lower levels of bronchial hyperresponsiveness. However, there is no consensus regarding what is a safe lower limit of FEV$_1$ for bronchoscopy in patients with COPD. We were unable to find any specific reports of the safety of research bronchoscopy and biopsy in patients with COPD.

**Materials and Methods**

**Subjects**

Fifty-seven patients with COPD (11 women and 46 men) were recruited for three studies. Study 1 evaluated the effect of inhaled steroids on the inflammatory profile of COPD. This was a single-center, randomized, double-blind, placebo-controlled study using fluticasone propionate. This study required subjects to undergo two bronchoscopies with biopsies and BAL 12 weeks apart. Study 2 was a multicenter, double-blind, placebo-controlled study using a novel phosphodiesterase type 4 inhibitor (Cilomilast; GlaxoSmithKline; Greenford, London, UK); subjects underwent two bronchoscopies 10 weeks apart with biopsy alone. Only subjects who underwent bronchoscopy at the London Chest Hospital are included in the present report. Study 3 was a single-center study to compare the inflammatory profile in smokers with COPD with chronic bronchitis without airflow obstruction and healthy volunteers; subjects underwent one bronchoscopy with biopsy alone.

Subjects were recruited from chest clinics at the London Chest Hospital and by advertisement. Ethics committee approval was obtained from the East London and City Health Authority research ethics committee for each study, and subjects gave written informed consent. Eligible subjects were male or female, aged 40 to 80 years, current or ex-smokers with > 10 pack-years smoking history, with an FEV$_1$ of 25 to 80% of predicted that improved by > 15% or 200 mL from baseline following 200 µg of inhaled salbutamol, and an FEV$_1$/FVC ratio < 70%. Subjects with severe concurrent medical problems, psychological impairment, receiving immunosuppressive treatment, or with a chest infection within 8 weeks were excluded. Subjects receiving inhaled corticosteroids had the drug withdrawn and were required to be in stable state for at least 8 weeks prior to the first biopsy. Patients received salbutamol and/or ipratropium bromide for symptomatic relief.

At recruitment, all subjects underwent a full physical examination, baseline pulmonary function testing including FEV$_1$, FVC, and peak flow by rolling seal spirometer (SensorMedics; Yorba Linda, CA), and reversibility to salbutamol. Physiologic tests were carried out in accordance with American Thoracic Society guidelines. Ears capillary blood gases (Model 278 Blood Gas Analyzer; Ciba-Corning; Medfield, MA) were performed on all patients in group 1 and severe-disease patients in group 2. In addition, full blood count, clotting screen ECG, and chest radiography as defined by the research protocol were performed. Descriptive statistics were obtained using the SPSS statistical software package (SPSS; Chicago, IL).

**Bronchoscopy**

Fiberoptic bronchoscopy was performed on an outpatient basis at the endoscopy unit at the London Chest Hospital by for all groups. Subjects underwent bronchoscopy according to American Thoracic Society recommendations. Following overnight fasting, patients were admitted to the day case unit and had baseline observations checked. All bronchoscopies were performed in the morning. All subjects, except those with mild disease, received 2.5 µg of nebulized salbutamol. At bronchoscopy, subjects had continuous monitoring of pulse oximetry and received oxygen via nasal cannula as required. All subjects received lignocaine spray to the oropharynx and 2.5 to 10 mg of midazolam IV administered by the bronchoscopist. Four percent lignocaine was instilled via the bronchoscope to the vocal cords, and further 2% lignocaine was used for the tracheobronchial tree. The bronchoscope was inserted nasally when possible, and the oral route was used as a second choice. Bronchial biopsies were obtained from the carinae of the second-order bronchi of the right middle and lower lobes using a bronchoscope (Pentax FB 19TX; Pentax; Tokyo, Japan) and cup forceps (Pentax x1718A; Pentax) or Olympus FB 20-C (Olympus; Tokyo, Japan). BAL was performed by instilling up to 180 mL of saline solution, with a dwell time of up to 30 s, followed by aspiration. Following bronchoscopy, subjects were observed with regular monitoring of oximetry and vital signs. Patients were discharged after a minimum of 2 h of observation, once safe swallowing had returned and observations were satisfactory. All were given an emergency contact number and followed up within 2 weeks. Adverse events were documented either at the time of bronchoscopy or at clinic review.

**Results**

Patient characteristics and lung function data are given in Table 1. Pulmonary function results at entry to the studies are as follows: mean FEV$_1$, 1.3 L (SEM, 0.006 L) and percent predicted FEV$_1$, 46.1% (SEM, 2.1%). Eleven patients had mild disease, 28 patients had moderate disease, and 18 patients had severe disease using British Thoracic Society criteria.

Five documented adverse events occurred. One patient in the moderate-disease group had severe bronchospasm requiring 4 days of inpatient treatment with nebulized bronchodilators, antibiotics,
and oral prednisolone. He had no significant bronchodilator response at recruitment to the study. He was later re-randomized to join the study and underwent a second bronchoscopy without complications. One patient in the severe-disease group had a pneumothorax requiring 7 days of inpatient treatment with intercostal drainage. Both of these patients underwent both biopsy and BAL. There were three episodes of hemoptysis, two with pleuritic pain (in the BAL group) that settled without intervention. There were no deaths, and all patients recovered fully and without long-term sequelae.

All patients were monitored during bronchoscopy by pulse oximetry. Falls in oxygen saturations (lowest 88%) were observed during BAL and with prolonged coughing. These falls were transient and were treated successfully with supplemental oxygen. Flumazenil was administered to reverse sedation on one occasion for the patient who had severe bronchospasm. A study patient had type 2 respiratory failure treated with long-term oxygen therapy. He underwent bronchial biopsy and lavage on two occasions 3 months apart without complications.

In the primary hemorrhage group, one patient had severe COPD and had a hemorrhage on his second bronchoscopy, which was controlled with cold saline solution bronchial wash. He was discharged home on the same day after observation. The other two patients required no intervention.

The three significant adverse events occurred in the moderate-to-severe COPD group with none in the mild-disease group. We found a 2.0% incidence of adverse events requiring hospital treatment and a 3.1% incidence of hemoptysis requiring no intervention.

Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SEM</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>40</td>
<td>78</td>
<td>63.4</td>
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<td>Pack-yr</td>
<td>14.5</td>
<td>196</td>
<td>53.8</td>
<td>4.8</td>
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<td>Peak flow, L</td>
<td>70</td>
<td>420</td>
<td>256</td>
<td>10</td>
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<tr>
<td>FEV₁, L</td>
<td>0.64</td>
<td>2.7</td>
<td>1.39</td>
<td>0.064</td>
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<tr>
<td>FEV₁ % predicted</td>
<td>23</td>
<td>75</td>
<td>47.9</td>
<td>1.8</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>25</td>
<td>70</td>
<td>49</td>
<td>0.01</td>
</tr>
<tr>
<td>Reversibility</td>
<td>2.5</td>
<td>17.1</td>
<td>10.4</td>
<td>1.69</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ %</td>
<td>8.2</td>
<td>30.4</td>
<td>17.0</td>
<td>1.0</td>
</tr>
<tr>
<td>KCO, %</td>
<td>17.8</td>
<td>110.0</td>
<td>53.9</td>
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<td>pH</td>
<td>7.37</td>
<td>7.46</td>
<td>7.4</td>
<td>0.04</td>
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<td>PaO₂ on room air, kPa</td>
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<td>10.6</td>
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<tr>
<td>PaCO₂, kPa</td>
<td>4.8</td>
<td>6.7</td>
<td>5.7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*FEF₂₅₋₇₅% = maximal midexpiratory flow; KCO = transfer coefficient. The subject with reversibility of 17.1% had an FEV₁ of 1.05 L and an absolute increase in FEV₁ of only 0.18 L after receiving salbutamol.

Discussion

This study demonstrates that research bronchoscopy can be safely performed in selected patients with COPD, even in those with severe airflow obstruction. Our patients were carefully selected to exclude subjects with significant concomitant diseases, and to be in a stable phase of disease (free from recent exacerbations), and hence considered safe for bronchoscopy. The minimum amount of sedation was used to enable the patient to tolerate the procedure. Topical lignocaine was administered as a local anesthetic to suppress cough.

For safety reasons, biopsies and lavage were performed only the right middle and lower lobes, although the remaining lobes were also inspected in order to exclude other endobronchial pathology. Six biopsies specimens were obtained in accordance with previous guidelines, although more recent experience suggests that up to 10 biopsy specimens can be obtained safely.

We observed no problems with respiratory failure, either during or after the procedure, that were not amenable to correction with oxygen at low flow rates. This is an interesting observation, considering that we administered midazolam to patients with severe COPD who might be more susceptible to its respiratory depressant effects.

The patient who had a pneumothorax at his second bronchoscopy had severe COPD with extensive bullous emphysema and an FEV₁ of 25% predicted. We analyzed the biopsy specimens carefully and found no evidence of inadvertent transbronchial biopsy. We hypothesized that the pneumothorax was due to increased coughing during the procedure causing raised intrathoracic pressure leading to the rupture of a bulla. The patient made a full recovery with no further loss of lung function.

The patient who was admitted with severe bronchospasm had moderate COPD. He was a current smoker who had numerous previous hospital admissions with exacerbations. He showed no evidence of a significant bronchodilator response either at recruitment or at any other time. His inpatient stay following bronchoscopy did not exceed his usual duration of stay, and he continued with the trial and underwent a second bronchoscopy without complications.

Fiberoptic bronchoscopy is a relatively invasive procedure for investigating patients with COPD, but it allows for the detection of coexisting endobronchial pathology and allows multiple samples of both tissue and fluid phase material to be obtained for research or diagnostic purposes. In addition to this, bronchial brushing may be applied. This may prove to be a useful technique for sampling the epithelium.
and has even been used, with the aid of an ultrafine bronchoscope, to obtain samples from peripheral airways.\textsuperscript{16}

We have shown a BAL volume of 180 mL to be safe in this group. The use of larger volumes would need further evaluation. For safety reasons, we would recommend avoiding research bronchoscopy in patients with multiple pathologies, particularly concurrent cardiac disease. We recommend the monitoring of pulse oximetry during the procedure and observation for at least 2 h after the procedure. It is also important to provide patients with an emergency contact number to allow the reporting of symptoms after the procedure.

We have shown a 2.0\% incidence of adverse events requiring hospitalization and a 3.1\% incidence of hemorrhage not requiring treatment in a group of patients with COPD of mixed severity, including subjects with severe disease (lowest FEV\textsubscript{1}, 0.64 L [23\% predicted]). We conclude that fiberoptic bronchoscopy, endobronchial biopsies, and BAL up to 180 mL of saline solution can be carried out in selected patients with COPD with a low incidence of adverse effects.

\textbf{REFERENCES}

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