Lung Function and Bronchial Responsiveness After Bronchoalveolar Lavage and Bronchial Biopsy Performed Without Premedication in Stable Asthmatic Subjects*

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We evaluated tolerance, safety, and effects on lung function and bronchial responsiveness of BAL (4 x 50 ml) combined with BB (three to five specimens) performed without premedication in 13 mild and stable asthmatics and eight healthy volunteers. All subjects tolerated bronchoscopy procedures well and without serious side effects. During procedures, no supplemental oxygen was administered and no ECG abnormalities were noted. The PEFR was measured before and immediately after bronchoscopy and at 5-min intervals up until recovery. The maximal percentage fall in PEFR after bronchoscopy was significantly greater in asthmatics (23.1 ± 13.9 percent) compared to normal subjects (7.8 ± 8.2 percent, p<0.01). Changes in PEFR returned to baseline values within 120 min in all asthmatics. The tcPO2 was recorded at baseline, during and after bronchoscopy. In both groups, a significant change in tcPO2 was measured during the infusion of BAL aliquots, and persisted throughout the procedure. A significant difference in asthmatics compared to healthy subjects was evident during BB and at the end of the procedure (p<0.05). In asthmatics, M challenge was performed on three different days over a three-week period prior to bronchoscopy, and was repeated at intervals of 2, 6, and 24 h following procedure. The PC20 M values measured before bronchoscopy were found to have a very high reproducibility (intraclass correlation coefficient = 0.93). The PC20 values measured during experiment times after bronchoscopy were not significantly different from baseline values. These data demonstrate that in mild and stable asthmatics, BAL combined with BB can be safely performed following administration of only local anesthesia. In carefully selected asthmatic subjects, transient bronchoconstriction and a lowering of oxygen tension can be induced by BAL and BB, whereas changes in bronchial responsiveness are more unlikely to occur. (Chest 1992; 101:1563-68)

Procedures using fiberoptic bronchoscopy have been increasingly used in the last years to investigate the basic mechanisms of bronchial asthma. Bronchoalveolar lavage and bronchial biopsies have proved to be safe and well tolerated by asthmatic subjects. These techniques have opened up research in asthma pathogenesis. The BAL and BB studies have demonstrated the key role played by airway inflammation in asthma and its close relationship to bronchial hyperresponsiveness. Since severe bronchoconstriction induced by fiberoptic bronchoscopy has been reported in asthmatic subjects, BAL and BB have been restricted to subjects with mild to moderate asthma and are usually performed after premedication with drugs, capable of preventing this side effect. Although bronchoscopy procedures carry minimal risk in selected and pretreated patients, there is still some debate about the effects of these procedures on lung function and bronchial responsiveness. Following BAL, some authors reported relevant changes in pulmonary function in asthmatic patients, while others did not confirm these results. No significant changes in bronchial responsiveness have been found in asthmatic patients after BAL, even when this procedure has been carried out in patients with dual asthmatic reactions and increased responsiveness after allergen challenge. On the contrary, it has been reported that BAL may increase bronchial responsiveness.

Bronchial responsiveness to methacholine was measured just once, either 12 or 24 h after BAL, and it is still unknown whether changes in bronchial responsiveness may occur earlier. In addition, only one study recently reported the effect of BB, combined with BAL, on bronchial responsiveness and lung function in asthmatic subjects. Since premedication can affect cellular findings in airways, bronchoscopy performed for research purposes should be undertaken without any pretreatment. However, unlike findings in nonasthmatic subjects, there is no tolerance, safety, or functional effect data are available concerning bronchoscopy procedures performed with-

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BB = bronchial biopsy; PEFR = peak expiratory flow rate; tcPO2 = transcutaneous oxygen tension; M = methacholine; PC20 = provocative concentration causing a 20% fall in FEV1.
out preventive treatment in asthmatic patients.

The purpose of this study, therefore, was as follows:
to evaluate BAL and BB tolerance and safety without
premedication, in asthmatic subjects selected by strict
clinical and functional criteria; to assess BAL and BB
effects on resting lung function, and on bronchial
responsiveness; and to ascertain the time course of
lung function and bronchial responsiveness changes,
following bronchoscopy procedures.

MATERIAL AND METHODS

Subjects

Thirteen asthmatic subjects were studied in our outpatient clinic
(Table 1). We only included lifetime nonsmoking subjects with a
history of asthma, age range between 18 and 45 years, with no acute
respiratory infection or spontaneous asthmatic relapses within the
month preceding the study. Respiratory symptoms were controlled
with bronchodilator therapy on a daily basis, or as needed. Subjects
could withhold their medication for a 24-h period before bronchos-
copy. Subjects requiring corticosteroids, theophylline or cromolyn
were excluded. Diurnal variability of PEFR, monitored over a
period of three weeks prior to bronchoscopy, had to be lower than
20 percent. Presence of atopy, evaluated by skin prick testing with a
standard battery of six common inhalant allergens, was not a
prerequisite for selection. The control group included eight healthy
volunteers recruited among medical students and hospital staff
(Table 1). They were lifetime nonsmokers and did not experience
any acute respiratory illness in the four weeks prior to the study.

All subjects denied any personal or family history of allergic and
respiratory disease, including asthma. Each subject gave informed,
signed consent. Part of the overall population was included in a
study to investigate the relationship between cellular findings in
lavage and bronchial biopsy.*

Methacholine Challenge Studies

Bronchial responsiveness to M was measured according to the
dosimeter method (slightly modified) proposed by Chai et al.*
Methacholine was dissolved in phosphate buffered saline solution
to obtain double increasing concentrations from 0.03 to 64 mg/ml.
Solutions (5 ml volume) at room temperature were administered
into a mouthpiece from a French Rosenthal dosimeter connected
to a nebulizer (DeVilbiss 646). The dosimeter was activated for 0.6
s and driven by compressed air at 138 kPa. This gave a 9.9 ml ± 0.3
(mean ± SD of five determinations) output. Before the challenge
study, each patient performed three maximal forced expiratory
maneuvers with a dry spirometer connected to a computer for data
analysis (Spiroflow, P.K. Morgan, U.K.). Phosphate buffered saline
solution was inhaled first and followed by increasing concentrations
of M. Subjects inhaled slowly from near functional residual capacity
reaching total lung capacity. Spirometric measurement was repeated
at 30-, 60-, and 90-s intervals after each inhalation, and the
percentage change in FEV1 was calculated from the lowest value
recorded after buffered saline. The response was expressed as PC20
FEV1, (mg/ml). In each asthmatic subject inhalation challenge with
M was performed three times within a period of three weeks, and
the last test was carried out at least three days before bronchoscopy.
Methacholine challenge was repeated at 2-, 6-, and 24-h intervals
after bronchoscopy. In healthy subjects, M challenge was performed
only once, three days before bronchoscopy.

Table 1—Subjects’ Characteristics

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*Highest value-lowest value/highest value.
†Measured on bronchoscopy day.
Bronchoscopy Procedures and Pulmonary Function Testing

In all subjects, local anesthesia was obtained by sucking a lidocaine tablet (30 mg) 15 min before bronchoscopy. The procedure was performed between 8 and 9 a.m. On each occasion, a flexible fiberoptic bronchoscope (Olympus IT10, Japan) was used. No other anesthetic or bronchodilator drug was administered either before, during, or after bronchoscopy. The BAL was performed by injecting four 50-ml aliquots of sterile saline solution, warmed to 37°C, in the middle lobe. The fluid was gently aspirated immediately after introducing each aliquot. Following BAL, three to five mucosal biopsy specimens were taken with a forceps at three different sites: at the carina of the right upper lobe, at the opening of the right middle or lower lobe, and inside the lower lobe.

Before bronchoscopy, both asthmatic and normal subjects performed three flow-volume curves, then the lowest FEV1 and PEFR values were taken. The PEFR values were measured immediately after bronchoscopy procedures, and at 5-min intervals up until recovery. The tcPO2 (mmHg) was continuously monitored throughout the study with a Microspan Combo (Biochem, International, USA). The tcPO2 was recorded at baseline conditions, at insertion of the bronchoscope, during the infusion of first, second, third, and fourth aliquots of BAL, at time of BB, and at the end of the procedure. During the procedure, ECG was continuously monitored.

Statistical Analysis

Values of PC2O M were log transformed for analysis and reported as geometric mean ± SEM. Bartlett's test was used to assess homogeneity of variance of the data. Differences between groups in baseline values of recovery fluid, FEV1, and PEFR and corresponding values measured after bronchoscopy were evaluated by analysis of variance. Differences between groups and within groups, baseline values of tcPO2, and corresponding values measured during and at the end of bronchoscopy were evaluated by analysis of variance and the Dunnett t-test. The reproducibility of PC2O values measured before bronchoscopy was evaluated by calculating the intraclass correlation coefficient. Differences in PC2O M measured at baseline condition and after the procedures, were estimated by using variance and covariance analysis (baseline FEV1 as covariate). Correlations were estimated by calculating linear regression analysis. A p value less than 0.05 was considered to be statistically significant.

Results

Subjects' characteristics are listed in Table 1. In the asthmatic subjects, maximal daily PEFR variability measured during the last three weeks prior to bronchoscopy ranged between 2.8 and 15.9 percent. All subjects tolerated bronchoscopy procedures well and without serious side effects. During procedures, no supplemental oxygen was administered and no ECG abnormalities were noted. After bronchoscopy, all subjects were kept under observation for at least 2 h. During this time, 5 out of 13 asthmatic subjects and one healthy subject complained of mild breathlessness. Bronchodilator therapy was not required, and the condition reversed itself spontaneously. The remaining subjects experienced mild coughing. Following recommendations for fiberoptic bronchoscopy and BAL use in patients with asthma, procedures involving instrument insertion, BAL, and BB were carried out expeditiously and lasted (mean ± SD) 16.0 ± 3.1 min and 13.2 ± 1.6 min in asthmatic subjects and healthy subjects, respectively. The percentage of BAL fluid recovery in the asthmatic group was significantly lower (43.8 ± 7.2 percent, range 31 to 55 percent) than in the control group (58.1 ± 6.7 percent, range 48 to 70 percent), (p<0.001).

The FEV1 and PEFR baseline values, expressed as percentage of predicted values, measured in asthmatic (102.1 ± 16.6 percent and 108.1 ± 14.1 percent) and control subjects (108.5 ± 10.8 percent and 99.7 ± 10.2 percent) were not statistically different. The maximal percentage fall in PEFR was measured immediately after bronchoscopy in both groups. This change was significantly higher in asthmatics (23.1 ± 13.9 percent, range 2.2 to 41.9 percent), compared to control subjects (7.8 ± 8.2 percent, range 0.5 to 25 percent, p<0.05) (Fig 1). In seven asthmatic subjects and in one normal control subject, the PEFR fall was greater than 20 percent. In asthmatics, PEFR values recovered within 60 min in eight subjects and within 90 to 120 min in the remaining group. In the healthy subject who developed bronchoconstriction, PEFR value returned to baseline values within 15 min. In asthmatic subjects, the maximum fall in PEFR was not related to PEFR baseline values, PEFR variability, or PC2O values of the last M challenge before bronchoscopy.

Mean values of tcPO2 measured at baseline, during, maximal fall in PEFR (%)

FIGURE 1. Maximal fall in PEFR, expressed as percentage of baseline, (open squares individual values and closed squares mean) measured after BAL and bronchial biopsy in 13 asthmatic subjects and 8 control volunteers. Asterisk is p<0.01 by one-way analysis of variance.

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and after bronchoscopy are reported in Figure 2. Baseline values of tcPO₂ in asthmatic and normal subjects were not statistically different (88.3 ± 3.1 mm Hg and 91.2 ± 5.2 mm Hg, respectively). Instrument insertion did not significantly reduce tcPO₂ values in either the asthmatic group (84.7 ± 6.8 mm Hg) or the control group (87.8 ± 6.1 mm Hg) compared to the corresponding baseline values. The sequential aliquots of BAL caused a progressive and significant change in tcPO₂ values compared to baseline values in both groups. The observed values in asthmatics were 74.3 ± 14.4, 65.2 ± 18.7 (p<0.01), 62.5 ± 19.8 (p<0.01), and 62.8 ± 16.6 mm Hg (p<0.01), and in healthy subjects 74.5 ± 5.3 (p<0.01), 70.2 ± 6.6 (p<0.01), 70.4 ± 6.5 (p<0.01), 72.6 ± 10.4 mm Hg (p<0.01), at first, second, third, and fourth aliquot, respectively. The tcPO₂ values were not further reduced by bronchial biopsies in either asthmatic (62.1 ± 15.8 mm Hg, p<0.01) or control group subjects (76.4 ± 7.3 mm Hg, p<0.01). Upon removal of bronchoscope, tcPO₂ values were still significantly reduced compared to baseline values both in asthmatic (69.1 ± 12.7 mm Hg, p<0.05) and in normal subjects (80.7 ± 7.1 mm Hg, p<0.05). Throughout the study, the fall in tcPO₂ was slightly greater in asthmatic subjects than in control subjects, and the difference between groups was statistically significant during BB and at the end of the procedure (p<0.05).

In asthmatic subjects, PC20 M values (mg/ml) measured on three different days before bronchoscopy were 1.14 ± 1.51 (range 0.15 to 13.40), 1.12 ± 1.46 (0.19-16.0), and 1.15 ± 1.49 (0.20-14.40) (Table 2). These measurements were highly reproducible (intra-class correlation coefficient = 0.93). In the normal

| Table 2—Values of FEV₁ and PC20 Methacholine Measured at Baseline and After Bronchoscopy in Asthmatic Subjects |
|--------------------|------------------|------------------|------------------|------------------|
|                   | 1st              | 2nd              | 3rd              |
|                   | FEV₁, PC20M      | FEV₁, PC20M      | FEV₁, PC20M      | FEV₁, PC20M      |
| No.               |                  |                  |                  |
| 1                 | 4.87 ± 13.38     | 4.97 ± 16.00     | 5.11 ± 13.98     |
| 2                 | 2.95 ± 0.26      | 3.01 ± 0.56      | 2.96 ± 0.19      |
| 3                 | 2.74 ± 2.39      | 2.63 ± 2.78      | 2.87 ± 1.64      |
| 4                 | 4.10 ± 1.90      | 4.11 ± 1.10      | 4.43 ± 1.58      |
| 5                 | 3.00 ± 2.39      | 2.49 ± 4.45      | 2.91 ± 5.08      |
| 6                 | 3.06 ± 0.25      | 3.08 ± 0.19      | 2.91 ± 0.50      |
| 7                 | 3.13 ± 0.83      | 3.32 ± 0.76      | 3.31 ± 0.53      |
| 8                 | 3.80 ± 0.96      | 3.42 ± 0.38      | 3.80 ± 0.94      |
| 9                 | 3.48 ± 1.05      | 3.39 ± 0.52      | 3.61 ± 0.81      |
| 10                | 4.52 ± 0.15      | 4.39 ± 0.38      | 4.14 ± 0.26      |
| 11                | 3.35 ± 13.40     | 3.15 ± 7.24      | 3.54 ± 14.40     |
| 12                | 5.17 ± 2.20      | 4.91 ± 1.90      | 4.84 ± 1.13      |
| 13                | 2.65 ± 0.16      | 2.71 ± 0.27      | 2.77 ± 0.20      |
| Mean              | 3.68 ± 1.14      | 3.65 ± 1.13      | 3.65 ± 1.15      |
| ± SE              | 0.23 ± 0.24      | 0.23 ± 0.23      | 0.26 ± 0.27      |
| ± GSEM            | 1.51 ± 1.46      | 1.49 ± 1.49      | 1.56 ± 1.57      |

*FEV₁ expressed as L; PC20 M as mg/ml.
subjects, PC20 M values were always greater than 64 mg/ml. In asthmatic subjects, bronchoscopy procedures (BAL and BB) did not significantly change airway responsiveness to methacholine. Values of PC20 M measured at 2-, 6- and 24-h intervals after bronchoscopy were 0.89 ± 1.56 (range 0.06 to 16.0), 1.00 ± 1.57 (0.13-24.8) and 1.27 ± 1.46 (0.36-20.23) (Table 2). These values were not statistically different from baseline values.

**DISCUSSION**

The present study confirms that BAL is a safe and well tolerated procedure in patients with mild and stable asthma, even when performed with bronchial biopsies and without premedication. Transient bronchoconstriction and worsening of oxygen tension were measured in the asthmatic group after bronchoscopy. Changes in oxygen tension in the asthmatics were comparable to those observed in healthy subjects. In spite of lung function changes, BAL and BB did not appear to significantly modify bronchial responsiveness.

In asthma, a variable effect of BAL on lung function has been reported. Significant changes in lung function measurements were observed immediately after BAL in mild to moderate asthmatic subjects. These lung function changes restabilized within 2 h, or persisted after 2 h or up until 24 h after BAL. Other reports did not confirm these findings. Subjects with mild asthma did not show evidence of changes either in spirometric and plethysmographic parameters after BAL. Similar conflicting results were reported concerning the effect of BAL on bronchial responsiveness. Kirby and co-workers did not observe any significant effect of BAL on methacholine responsiveness in stable asthmatics 24 h after BAL. Moreover, in atopic asthmatics, it has been recently demonstrated that BAL performed after allergen challenge did not change bronchial responsiveness. On the contrary, Kelly and co-workers showed that BAL may significantly increase bronchial responsiveness, and the increase was greater in subjects with the lowest PC20 M.

Differences in preventive treatments and in the selection of patients may likely explain these contradictory findings. Several premedications affecting bronchial tone were given before BAL and BB. They included steroids, theophylline, atropine, [13][14][15] ipratropium bromide, and salbutamol. Moreover, because fiberoptic bronchoscopy performed on patients with unstable asthma presents increased risk, different criteria of selection were followed.

We administered only local anesthesia to subjects who underwent bronchoscopy to avoid the effects of drugs active on bronchial tone. Premedication is not essential to the comfort and safety of patients undergoing bronchoscopy. On the other hand, we stated accurate clinical and functional criteria to identify mild asthmatic patients in stable conditions. Thus, only asthmatic patients in prolonged clinical remission, treated with only β2 agonists, with a very low PEFR variability, and stable PC20 M values were enrolled in the study.

The absence of premedication did not compromise subjects' safety and/or their tolerance to the procedures. No relevant side effects were observed. In most asthmatics and in one healthy subject, we found that BAL and BB induced a transient bronchoconstriction. However, this effect was spontaneously reversed and its magnitude did not appear to differ from that observed in pretreated subjects.2

We could not demonstrate any relation between the degree of bronchoconstriction developed after bronchoscopy and any physiologic indices of asthma severity, including the degree of M responsiveness. In asthma, acute bronchoconstriction can be provoked either by direct stimulation of the bronchial smooth muscle, eg, methacholine, or indirectly by stimulating the sensory nerve receptors and by releasing mediators of inflammatory cells.20 Bronchoscopy procedures, involving BAL and BB, seem to act as an indirect stimulus on bronchial airways either via reflex mechanisms, or by inducing bronchial wall edema and dilution of surfactant, thereby reducing small airway patency. The poor relationship between direct and indirect bronchial responsiveness can explain the lack of correlation we observed between bronchoconstriction induced by bronchoscopy procedures and the degree of M responsiveness.

In our study, a significant lowering in oxygen tension was found during and immediately after bronchoscopy procedures, both in asthmatic and normal subjects. In all subjects, neither arrhythmias nor other ECG abnormalities were recorded. However, changes in PEF, even when 100 percent oxygen is administered to the subjects throughout the procedure. The BAL fluid may increase the fall in oxygen tension induced by bronchoscopy alone. The alveolar filling together with removal of the surfactant may produce a mismatching of ventilation/perfusion ratio and shunt. Therefore, to prevent and to avoid possible cardiovascular side effects during bronchoscopy procedures, ECG tracing and oxygen tension monitoring is necessary.

In subjects with mild asthma, in spite of changes in respiratory function, it would seem that bronchoscopy procedures alone do not significantly enhance the degree of bronchial responsiveness. In mild asthmatic subjects, we found no evidence of increased methacholine responsiveness after BAL and BB, not only at 12- and 24-h intervals, as previously reported, but also at 2- and 6-h intervals. An enhancement in
bronchial responsiveness after bronchoscopy procedures could be due either to a secondary effect of bronchoconstriction, or to epithelial damage. In experimental animal subjects, mucosal damage was observed after flexible fiberoptic bronchoscopy and was related to procedure trauma.

In conclusion, our study further demonstrates the safety and tolerability of BAL as an investigative technique for mild asthmatic patients, whose respiratory function and bronchial responsiveness are stable. In addition, our data on methacholine responsiveness show that in selected subjects, the combination of BAL and BB can be performed following the administration of only local anesthesia, without increasing the severity of asthma. Finally, we would suggest that premedication is not essential, whereas criteria patient selection and oxygen tension monitoring are crucial to ensure patient safety and comfort during bronchoscopy procedures in asthma.

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