Original Study

Safety of research bronchoscopy in mild-moderate and severe asthma

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- safety
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SUMMARY. OBJECTIVES: Fiberoptic bronchoscopy (FB) as a research tool has contributed considerably to the understanding of the pathogenesis of asthma, but there are concerns regarding its safety, especially in patients with severe asthma. The aim of this study was to document safety data on FB and sampling techniques in asthma research. **METHODS:** A total of 75 subjects (36 mild-moderate asthmatics, 25 severe asthmatics and 14 healthy control subjects), participating in three studies, underwent research FB. Depending on the study, endobronchial and nasal biopsy, bronchioalveolar lavage (BAL) and bronchial brushing were performed, according to established guidelines. Pulmonary function tests were performed prior to bronchoscopy and 2 hours after the procedure. Daily peak expiratory flow (PEF) measurements were recorded 5 days before and 5 days after bronchoscopy in the 30 patients participating in the first two studies. **RESULTS:** FB was tolerated well. None of the patients or healthy control subjects developed severe adverse reactions during or after bronchoscopy. Only two patients with severe asthma presented mild adverse events; one demonstrated immediate and complete occlusion of the middle lobe segmental bronchial lumen after BAL instillation and another developed mild desaturation (SaO_2 91%). There were no significant changes in FEV_1 and PEF measurements after bronchoscopy. **CONCLUSIONS:** Research FB can be performed safely in patients with asthma, including those with severe disease, with careful assessment and adherence to guidelines. ***Pneumon 2010, 23(1):41-47.***

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INTRODUCTION

Fiberoptic bronchoscopy (FB) as a research tool has contributed considerably to the understanding of the pathogenesis of asthma[1-4] and other respiratory diseases[5,6]. Research bronchoscopy has provided the means of collecting biological data which lead to vital information on the contribution of various types of inflammatory cells and their mediators to the disease

processes. The acquisition of bronchial and trans-bronchial biopsies and bronchoalveolar fluid provided the basis of many of the current concepts in the pathogenesis, diagnosis and treatment of pulmonary diseases.

Bronchoscopy is routinely carried out, with a good safety profile, in respiratory patients presenting with symptoms or radiological abnormalities requiring bronchoscopic investigation. In a recent retrospective review of 23,862 patients who underwent bronchoscopic examination or treatment, the reported rate of severe complications was only 0.637%[7]. Despite initial concerns regarding the safety of bronchoscopy in patients with asthma[8-11], it has been reported to be safe and has been used extensively in the investigation of people with asthma over the last few years[12-16]. Nevertheless, there are still concerns regarding the safety of the use of bronchoscopy for research purposes in patients with asthma, and especially patients with severe disease[17].

The authors have used FB for research purposes for about 15 years. The aim of this report is to present the safety data on FB and the sampling techniques used in asthma research. Data are presented on bronchoscopies performed during three studies on a total of 61 patients with asthma (25 severe and 36 mild-moderate) and 14 healthy control subjects.

MATERIAL AND METHODS

Study subjects

A total of 75 subjects (61 patients with asthma and 14 healthy control subjects) participated in three studies. The subjects were recruited from the Athens Chest Hospital Asthma Centre and Outpatient Clinic. The study protocols were approved by the Research Ethics Committee of the Hospital and written informed consent was obtained from all participating subjects. Patients considered eligible for participation were males and females, aged 18-75 years with a clear clinical history of asthma, reversible airflow obstruction with FEV_1 increase >15% following β2-agonists or a positive methacholine challenge (PD_{20} <1mg). Asthma severity was assessed according to the GINA classification[18]. Entry criteria depended on the individual study. The clinical characteristics of the subjects in the three studies are summarized in table 1.

Study 1 was a single centre study investigating the relationship between the inflammatory processes characterizing allergic asthma and rhinitis. A total of 19 patients with mild-moderate asthma (8 atopic and 11 non-atopic) were recruited and underwent bronchoscopy with endobronchial biopsy (EBB) and nasal biopsy. Data on the non-atopic subjects have been published elsewhere[19].

Study 2 was part of the ENFUMOSA study, a multicentre European cross-sectional observational study of severe asthma, as part of which 8 patients with severe asthma and 3 with mild-moderate asthma underwent bronchoscopy and EBB[20].

Study 3 is an ongoing single centre study that focuses on the contribution of specific mediators to Th_2-driven airway inflammation and remodeling processes in patients with asthma[21,22]. So far, 45 subjects (14 healthy controls, 14 with mild-moderate and 17 with severe asthma) have been recruited and have undergone bronchoscopy with brochioalveolar lavage (BAL), EBB and bronchial brushing.

Spirometry

Pulmonary function tests were performed prior to and 2 hours after the bronchoscopy procedure. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using a dry spirometer (Sensor Medics, Vmax22, CA, USA) and the best value of the three maneouvres was expressed as a percentage of the predicted value.

Pre-bronchoscopy patient preparation

Following an overnight fast, subjects were admitted to the day-care unit, where a detailed medical history was taken and baseline observations were performed. These included physical examination, heart rate, blood pressure and respiratory rate measurement, spirometry, and pulse oximetry. All patients had previously undergone coagulation studies (PT, PTT, INR, platelet count) and blood count. A peripheral intravenous catheter was then inserted. Subjects were premedicated with 500 μg atropine *i.m.* and 5-10 mg nebulised salbutamol, and the nose and oropharynx were anaesthetised with lignocaine spray. Immediately before bronchoscopy, 8-10 mg midazolam was administered *i.v.* via the catheter, which remained *in situ* until the patient recovered fully.

Bronchoscopy

FB was performed on an outpatient basis at the Athens Chest Hospital "Sotiria" according to established guidelines[23]. All bronchoscopies were performed in the morning using a flexible bronchoscope (either an Olympus BFP20 or WM-N60 Mobile Workstation). During the

TABLE 1. Characteristics of participants in study of bronchoscopy in patients with asthma

	Mild - moderate asthma	Severe asthma	Healthy control subjects
Study 1	19	-	-
Sex (M/F)	8/11	-	-
Age (range) in years	45 (22-64)	-	-
Atopic	8	-	-
FEV_1 % pred (range) [before bronchoscopy]	86.5 (58-98)	-	-
FEV_1 % pred (range) [after bronchoscopy]	88.3 (68-102)		
Study 2	3	8	-
Sex (M/F)	2/1	3/5	-
Age (range) in years	47 (33-58)	51 (44-62)	-
Atopic	2	4	-
FEV_1 % pred (range) [before bronchoscopy]	81.7 (65-97)	52.5 (34-65)	-
FEV_1 % pred (range) [after bronchoscopy]	84.3 (60-97)	54.6 (33-68)	
Study 3	14	17	14
Sex (M/F)	4/10	4/13	8/6
Age (range) in years	47 (32-63)	56 (29-75)	46 (29-70)
Atopic	7	4	2
FEV_1 % pred (range) [before bronchoscopy]	81.5 (59.2-103.7)	57.8 (27.9-74.9)	92.3 (84-110.8)
FEV_1 % pred (range) [after bronchoscopy]	81.4 (62.1-99.2)	57.1 (29.2-76.2)	90.6 (79.3-103.2)
All Studies	36	25	14
Sex (M/F)	14/22	7/18	8/6
Age (range) yr	46 (22-64)	54 (29-75)	46 (29-70)
Atopic	17	8	2
FEV_1 (% pred + SEM) [before bronchoscopy]	$84.1 \pm 2.1^{£}$	$57.5 \pm 2.8^{¥, €}$	92.3 ± 2.2
FEV_1 (% pred + SEM) [after bronchoscopy]	85.3 ± 2	57.8 ± 2.9	90.6 ± 2.1

FEV1: Forced Expiratory Volume in one second, SEM: standard error of the mean, ¥ $p < 0.05$ compared to healthy controls, ¥ $p < 0.001$ compared to healthy controls, € $p < 0.001$ compared to mild-moderate asthmatics

procedure, the subjects underwent continuous monitoring of pulse oximetry and received oxygen via a nasal cannula as required to maintain oxygen saturations >92%[24]. The flexible bronchoscope was inserted nasally where possible, and the oral route was used only when nasal insertion was impossible (once). The vocal cords and the tracheobrochial tree were anaesthetised with 2% aqueous lignocaine (400 mg maximum) delivered via the bronchoscope.

Sample Collection

After inspection of the bronchial tree, BAL was performed. A mini lavage with 80–100 mL of prewarmed 0.9% saline was instilled into the right middle lobe in 20mL aliquots and then gently aspirated, with a 50-60% recovery rate. The BAL fluid (BALF) was quickly placed on ice and further processed according to the established protocol. Bronchial biopsies were then obtained under direct vision from various sites of the subsegmental carinae of the right lower lobes or right middle lobe. A minimum of 6-7 bronchial biopsies were taken and were either snap-frozen or placed in formalin, depending on the individual study. Airway brushing was performed after collection of EBB in patients participating in the third study. A minimum of five brushings per bronchoscopy were performed on the opposite lung from where the EBB was collected. Each brushing consisted of approximately ten rapid up and down movements of the brush on the airway wall. Nasal biopsies were collected at the end of bronchoscopy. The inferior nasal recess, opposite to the side where the bronchoscope was inserted, was first treated for ten minutes with 2% lignocaine and 0.025% epinephrine, following which nasal biopsy was performed using a Gerritsma forceps.

Post-bronchoscopy patient care

Following bronchoscopy, the subjects remained under observation for two hours, being monitored for pulse oximetry and vital signs. Two hours after bronchoscopy, all subjects underwent spirometry. Once safe swallowing had returned and observations were satisfactory they were discharged, having been given an emergency contact telephone number, and telephone follow-up was made on the following days. Medical re-assessment was performed 7 days after bronchoscopy and the patients were asked about any increase in asthma symptoms and rescue medication use and asthma exacerbations. Adverse events were documented both at the time of bronchoscopy and at follow-up. In the first two studies, the patients recorded peak expiratory flow (PEF) values daily 5 days before and 5 days after bronchoscopy.

Statistics

Data were analysed with GraphPad Prism (v5, San Diego, CA) and p values of less than 0.05 were regarded as significant. The data were checked for normal distribution with the D'Agostino & Pearson omnibus normality test. Comparison between FEV_1 values before and after bronchoscopy was done by using the paired T test. Daily PEFR values recorded before and after bronchoscopy were analysed by repeated measures 1-way ANOVA, accompanied by Bonferroni's multiple comparison test, to detect significantly different time points for the patients with asthma participating in the first two studies.

RESULTS

All patients were clinically stable at the time of bronchoscopy. FB was well tolerated, none of the subjects developed severe adverse reactions such as severe sustained bronchospasm or desaturation during or after bronchoscopy, and no significant bleeding or pneumothorax observed. There was no significant difference in FEV_1 measurements before and after bronchoscopy in either the patients with asthma (p=0.24) or the healthy control subjects (p=0.13), and subgroup analysis demonstrated no significant difference between pre- and post-bronchoscopy FEV_1 levels in either mild-moderate or severe asthma (Figure 1). In addition, no change in PEFR measurements was noted after bronchoscopy in the 30 patients who recorded their values daily (Figure 2). None of the patients with asthma developed an asthma exacerbation or lost asthma control (increase in the symptoms or in rescue medication use), in the week of follow up after the bronchoscopy.

The healthy control subjects experienced no adverse events during or after bronchoscopy. None of the patients with mild-moderate asthma experienced adverse effects during or after bronchoscopy, but two of the patients with severe asthma experienced adverse events during the procedure. One female patient with severe asthma developed mild desaturation (SO_2 91%), which required oxygen administration for 3 hours after bronchoscopy, but she did not develop bronchospasm and her spirometry 3 hours after bronchoscopy remained stable. This was

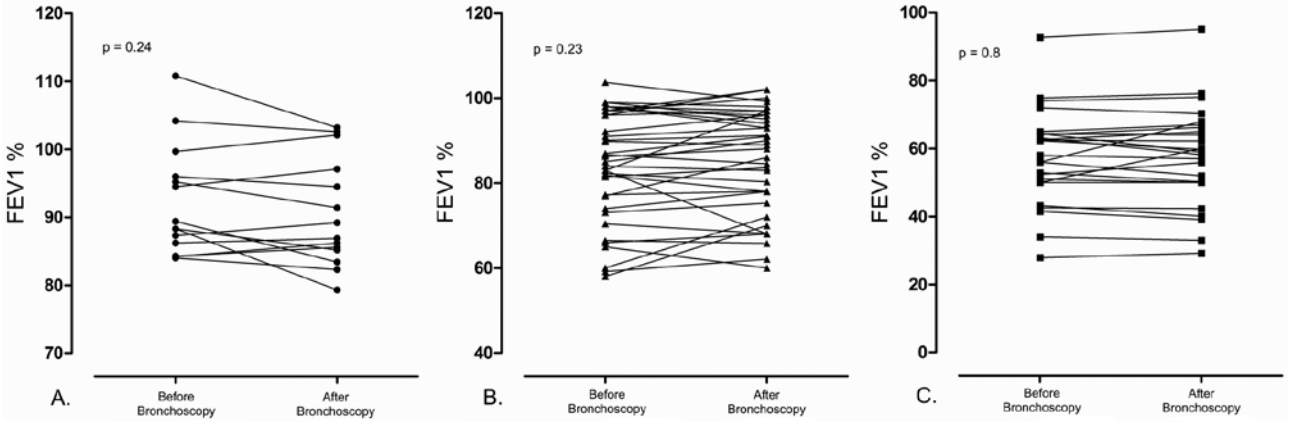

FIGURE 1. FEV_1 (percentage of predicted) values before and 2 hours after research fiberoptic bronchoscopy in healthy control subjects (A) and in patients with mild/moderate (B) and severe asthma (C). No significant change was observed in any of the groups.

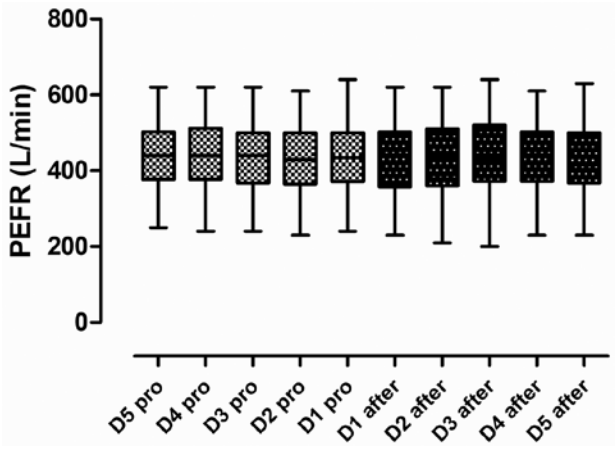

FIGURE 2. PEFR values measured in 31 patients with asthma, 5 days before and 5 days after bronchoscopy. No significant differences were observed between any of the time points. Data are presented as means ± range.

an obese patient who slept very soundly and was snoring after midazolam use. A diagnosis of sleep-apnoea syndrome was suspected and the patient underwent a sleep study that confirmed the presence of obstructive sleep apnoea syndrome. The second patient, also female, showed immediate and complete occlusion of the middle lobe segmental bronchi lumen after instillation of saline from the first lavage syringe (20ml). This effect was only local and the patient did not experience breathlessness or develop desaturation. She was however treated with 2mg of instilled salbutamol solution and an *i.v.* dose of 200mg hydrocortisone and no further intervention was necessary.

DISCUSSION

A total of 75 subjects (61 patients with asthma and 14 healthy control volunteers), participating in three studies, underwent research FB without significant perioperative complications. The healthy volunteers did not demonstrate complications. No adverse events were observed in the first two studies, where bronchoscopy with EBB was performed. In the third study, involving EBB and BAL, two patients with severe asthma demonstrated mild adverse events; one exhibited mild desaturation during bronchoscopy (SaO_2 91%) and the other showed local occlusion of the middle lobe segmental bronchi lumen after instillation of the first lavage syringe. No patient required hospital admission.

Initial reports on the use of bronchoscopy for research purposes in volunteer patients with asthma raised concerns regarding safety issues; arterial hypoxaemia[9], pneumonia[10] and bronchospasm[11] have been described. Later reports demonstrated that FB is quite a safe method for investigating asthmatic inflammation, although a significant fall in immediate post-bronchoscopy FEV_1 has been reported in both patients with asthma and healthy subjects[25]. In the studies reported here, no significant drop in mean FEV_1 was observed after bronchoscopy, regardless of disease severity. This can be explained by the fact that the patients were pre-treated with 5-10 mg nebulized salbutamol, and post-bronchoscopy spirometry was performed 2 hours after the end of the procedure, while in previous studies it was performed earlier. Reports about the effect of bronchoscopy on PEFR vary. Although a fall was observed in mean PEFR after bronchoscopy in the 30 patients with asthma who recorded PEF values daily 5 days before and 5 days after bronchoscopy, the decrease was not statistically significant. A recent study concerning the safety and tolerability of even three consecutive bronchoscopies after allergen challenge inpatients with mild asthma showed no complications during the procedure, and no patient demonstrated clinical deterioration of asthma control in the weeks after the study[16].

Although the findings of earlier studies suggest that bronchoscopy involving EBB and BAL may induce transient changes in airway function and gas exchange in both patients with asthma and healthy subjects[25], this appears to have no significant effect on asthma control, as determined by PEFR, symptom score and medication use[15]. In this study, none of the patients with asthma patients who underwent FB with EBB and BALF collection exhibited an asthma exacerbation or lost asthma control in the week of follow up after the bronchoscopy. A recent study reported a high incidence (37.5%) of post-BAL fever in children who underwent FB and BALF collection[26]. Post-BAL fever was not observed in any of the subjects in this, either healthy or asthmatics, which could be explained by the difference in the study populations and the absence of factors associated with fever (i.e., age <2 years and presence of infection).

Data on research bronchoscopy on severe asthmatics are limited[27;28] and there are even less data available on the safety of the procedure. Bush et all showed that bronchoscopy and EBB under general anaesthesia can be performed safely in children with difficult asthma, when the bronchoscopist and anaesthetist are suitably

trained[29]. In addition, acquisition of 2-6 transbronchial biopsy specimens and BAL suggests no major side effects during even fairly aggressive procedures[30]. On the other hand, a recently introduced form of bronchoscopic treatment, bronchial thermoplasty, is associated with a short-term increase in asthma-related morbidity, probably due to the temperature rise within the bronchi and the longer duration of the procedure[31]. In this study bronchoscopy with EBB and BAL was performed in 25 severe asthmatic patients, many of them exhibiting FEV_1 much less than 50% of predicted, with practically no severe adverse events.

This study has certain limitations. Firstly, documentation of the safety of the bronchoscopy was not the primary objective in any of the 3 studies, and the data for the first 2 studies were collected retrospectively. Secondly, not all of the patients underwent the same bronchoscopic procedures – BAL was done only in the third study. Thirdly, post-bronchoscopy PEFR measurements were performed in only 31 of the patients with asthma. The patients were asked about symptoms deterioration, rescue medication use and asthma exacerbations, but a quantitative tool of asthma control (such as the Asthma Control Questionnaire) was not used. Finally, the relatively small number of patients with severe asthma (25) does not permit definitive conclusions regarding the safety of research FB in this population.

In conclusion, the safety data from the three studies confirm the findings of previous reports on the safety of research bronchoscopy in asthma and support the view that FB is well tolerated even in patients with severe asthma and low pre-bronchoscopy FEV_1 values, provided that the procedure is performed by an experienced bronchoscopist and in a specialized centre where possible adverse reactions may be treated promptly.

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