Published in final edited form as:
J Allergy Clin Immunol. 2011 August ; 128(2): 328–336.e3. doi:10.1016/j.jaci.2011.02.042.

Safety of Investigative Bronchoscopy in the Severe Asthma Research Program

Wendy C. Moore, MD[1,2,5], **Michael D. Evans, MS**[3], **Eugene R. Bleecker, MD**[1,2,5], **William W. Busse, MD**[4,5], **William J. Calhoun, MD**[5], **Mario Castro, MD**[5], **Kian Fan Chung, MD**[5], **Serpil C. Erzurum, MD**[5], **Douglas Curran-Everett, PhD**[5], **Raed A. Dweik, MD**[5], **Benjamin Gaston, MD**[5], **Mark Hew, MD**[5], **Elliot Israel, MD**[5], **Martin L. Mayse, MD**[5], **Rodolfo M. Pascual, MD**[1,2,5], **Stephen P. Peters, MD, PhD**[1,2,5], **Lori Silveira, MS**[5], **Sally E. Wenzel, MD**[5], and **Nizar N. Jarjour, MD**[4,5] **for the National Heart Lung Blood Institute's Severe Asthma Research Program**[5]

[1]Center for Human Genomics and Personalized Medicine Research, Wake Forest University School of Medicine

[2]Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Wake Forest University School of Medicine

[3]Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health

[4]Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health

[5]Severe Asthma Research Program (SARP)

Abstract

Background—Investigative bronchoscopy was performed in a subset of participants in the Severe Asthma Research Program (SARP) to gain insights into the pathobiology of severe disease. We evaluated the safety aspects of this procedure in this cohort with specific focus on patients with severe asthma.

Correspondence and reprint requests: Wendy C. Moore, M.D., Center for Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, Tel: (336) 713-7500, Fax: (336) 713-7566, wmoore@wfubmc.edu.

[5]The Severe Asthma Research Program (SARP) is a multicenter asthma research group funded by the NHLBI and consisting of the following contributors (Principal Investigators are marked with an asterisk):
Brigham & Women's Hospital - Elliot Israel*, Bruce D. Levy, Gautham Marigowda, Michael E.Wechsler; *Cleveland Clinic* - Serpil C. Erzurum*, Raed A. Dweik, Suzy A.A. Comhair, Emmea Cleggett-Mattox, Deepa George, Marcelle Baaklini, Daniel Laskowski; *Emory University* - Anne M. Fitzpatrick, Denise Whitlock, Shanae Wakefield; *Imperial College School of Medicine* - Kian F. Chung*, Mark Hew, Patricia Macedo, Sally Meah, Florence Chow; *University of Iowa* – Eric Hoffman; *University of Pittsburgh* - Sally E. Wenzel*, Fernando Holgion, Jen Chamberlin; *University of Texas-Medical Branch* - William J. Calhoun*, Bill T. Ameredes; *University of Virginia* - Benjamin Gaston*, W. Gerald Teague*, Denise Thompson-Batt; *University of Wisconsin* - William W. Busse*, Nizar Jarjour, Ronald Sorkness, Sean Fain, Erin Billmeyer, Cheri Swenson, Gina Crisafi, Laura Frisque, Dan Polk; *Wake Forest University* - Eugene R. Bleecker*, Deborah Meyers, Wendy Moore, Stephen Peters, Rodolfo M. Pascual, Annette Hastie, Gregory Hawkins, Jeffrey Krings, Regina Smith; *Washington University in St Louis* - Mario Castro*, Leonard Bacharier, Jaime Tarsi; *Data Coordinating Center* - Douglas Curran-Everett*, Ruthie Knowles, Maura Robinson, Lori Silveira; *NHLBI* - Patricia Noel, Robert Smith

Objective—To prospectively evaluate changes in lung function and the frequency of adverse events related to investigative bronchoscopy.

Methods—Bronchoscopy was performed using a common Manual of Procedures. A subset of very severe asthma was defined by severe airflow obstruction, chronic oral corticosteroid use and recent asthma exacerbations. Subjects were monitored for changes in lung function and contacted by telephone for 3 days after the procedure.

Results—436 subjects underwent bronchoscopy (97 normal, 196 not severe, 102 severe and 41 very severe asthma). Nine subjects were evaluated in hospital settings after bronchoscopy; seven of these were respiratory related events. Recent Emergency Department visits, chronic oral corticosteroid use and a history of pneumonia were more frequent in subjects who had asthma exacerbations after bronchoscopy. The fall in FEV1 following bronchoscopy was similar in the severe compared to milder asthma group. Pre-bronchodilator FEV1 was the strongest predictor of change in FEV1 after bronchoscopy with larger decreases observed in subjects with better lung function.

Conclusions—Bronchoscopy in severe asthma subjects was well tolerated. Asthma exacerbations were rare and reduction in pulmonary function after the procedure was similar to subjects with less severe asthma. With proper precautions, investigative bronchoscopy can be performed safely in severe asthma.

Keywords

investigative bronchoscopy; safety; severe asthma; exacerbation

Introduction

Airway inflammation is a central component of asthma [1, 2]. Bronchoscopy has provided an investigative approach to obtain airway fluids and mucosal biopsies, which has been critical to demonstrate the pattern and persistence of inflammation in asthma and begin to identify the link between these features and altered pathophysiology. Investigative bronchoscopy has provided a major step forward to more fully understand airway mechanisms of asthma as these studies focus on the target organ of disease, the lung [3,4]. To date, the majority of bronchoscopy studies have been performed in patients with mild to moderate disease. Severe asthma remains poorly understood and is a phenotype of asthma with greater morbidity. Extending investigative bronchoscopy to patients with more severe disease promises to provide a critical opportunity to gain novel insight into what is anticipated to be unique histopathology, clues to what causes greater severity in this population, and as a stimulus to the development of more effective therapeutic interventions.

The lack of data assessing the safety of investigative bronchoscopy in patients with more severe asthma has been a limitation in the use of this research technique to better understand the pathophysiology of severe disease [5]. There are few published studies evaluating the safety of investigative bronchoscopy in asthma and the effects of this procedure on physiologic changes, and even fewer on the effects of the procedure on short-term asthma control [6-11]. Collectively, only a small number of asthma subjects with severe airflow obstruction have been included in prior studies, and most patients were not being treated with high doses of inhaled or oral corticosteroids at the time of the bronchoscopy.

In 2001, the National Heart Lung Blood Institute established the Severe Asthma Research Program (SARP) at nine sites in the United States and one in the United Kingdom. A major goal of the SARP was to identify and characterize a large number of subjects with severe asthma to establish the clinical characteristics of severe disease and understand

pathobiologic mechanisms important in severe asthma compared to milder disease. To accomplish these goals, asthma subjects of all levels of disease severity were recruited and underwent a comprehensive characterization to identify clinical phenotypes through which severe asthma might be defined [12]. To explore and define the pathobiology of severe asthma in these well characterized patients, it was necessary to obtain samples from the airways to describe patterns of inflammation and what processes may be dysregulated in severe asthma. While many subjects underwent sputum induction for evaluation of airway inflammatory cells and soluble mediators [13], this procedure preferentially samples the large proximal airways and does not allow assessment of inflammation more peripherally or unique features of airways remodeling. To explore differences in submucosal inflammation and architectural changes in the airway, investigative bronchoscopy was incorporated as a key component of the SARP.

Because subjects with increasingly severe asthma would undergo bronchoscopy, a subcommittee of investigators was appointed to develop common procedures for study and to maximize safety of subjects. The bronchoscopy section of the SARP Manual of Procedures (MoP) provides a detailed uniform approach to pre-procedure assessment of underlying severity of asthma, ongoing evaluation for disease stability before, during and after bronchoscopy and consistent post-procedure follow-up to assess the occurrence of adverse effects. The aim of this study was to prospectively evaluate changes in pulmonary function and the frequency of respiratory related events, including hospital based health care utilization and need for oral corticosteroids, in subjects with not severe and severe asthma undergoing investigative bronchoscopy in SARP.

Methods

The Severe Asthma Research Program (SARP)

After establishing standard operating procedures, including a review by an independent Data Safety Monitoring Board and approval by the Institutional Review Boards at each site, subjects underwent a comprehensive phenotypic characterization as previously described [12]. Briefly, after subjects provided written informed consent, clinical staff administered questionnaires (asthma symptoms, medication use, medical history and health care utilization), performed allergen skin prick testing and a comprehensive pulmonary function evaluation on several days including “baseline” pre-bronchodilator spirometry, response to short-acting beta-agonists (2-8 puffs albuterol) and methacholine challenge. Following review of clinical data by investigators, a subset of severe and not severe asthma subjects and normal healthy subjects were recruited for investigative bronchoscopy studies (see inclusion criteria in Table I).

Bronchoscopy Manual of Procedures (MoP)

Prior to initiation of bronchoscopy studies a subcommittee of investigators was appointed to develop a MoP for investigative bronchoscopy. An independent Data Safety Monitoring Board (DSMB) reviewed the MoP with ongoing oversight by this committee through review of clinical site experience and adverse events. The Institutional Review Board at each clinical site also reviewed and approved the bronchoscopy MoP. The entire SARP Bronchoscopy MoP is provided as an attachment in an online data supplement (see Table E1 for Table of Contents of MoP). Clinical sites were required to complete several “phases” wherein investigators requested permission to perform bronchoscopy on subjects with increasingly severe airflow obstruction using a step-wise algorithm. A subset of the severe asthma group was defined *a priori* as “very severe asthma” (VSA) based on baseline severe airflow obstruction (FEV1< 60 % predicted after bronchodilators), a therapeutic requirement of chronic oral corticosteroids and recent or intensive health care utilization in the past year

(see criteria in Table II). Individual centers were required to demonstrate bronchoscopy experience with severe asthma subjects prior to progressing to VSA and their request was reviewed and approved by the bronchoscopy subcommittee prior to being sent to the DSMB for further review. Only after the formal approval by the DSMB, did any site proceed to the next level of asthma severity.

Bronchoscopy procedures

All subjects received albuterol before the bronchoscopy and spirometry was performed before (pre-albuterol FEV1 % predicted) and after (post-albuterol FEV1 % predicted) administration. Each center was then allowed to follow their standard operating procedures and institutional rules with regard to conscious sedation (choice of drug and route of administration), local anesthesia (nebulized, atomized or topical lidocaine) and the use of supplemental oxygen. Bronchoscopic procedures were performed in accordance with the specific aims of the investigative site and could include bronchoalveolar lavage (BAL), endobronchial brushing, mucosal biopsy and, at one site, transbronchial biopsies. The investigator determined the order of procedures and choice of forceps at each clinical site. Initial BAL was performed with 100 ml of prewarmed saline with aspiration of BAL fluid by hand suction for shared samples, but investigators were permitted to instill additional volume at their discretion. Subjects who underwent transbronchial biopsies did not have BAL. Following the removal of the bronchoscope, healthy controls and not severe asthma subjects were observed for at least one hour post-procedure and were eligible for discharge when their FEV1 on post-bronchoscopy spirometry returned to within 85% of the initial FEV1 prior to bronchoscopy. Subjects who failed to achieve this benchmark or who required more than three albuterol treatments post-procedure were admitted to the hospital for overnight observation. Severe and VSA subjects underwent spirometry prior to transfer to a hospital setting for scheduled precautionary overnight observation. These subjects were discharged in the morning following assessment of asthma stability by the investigator. The % change in FEV1 % predicted was calculated as the difference in FEV1 % predicted from pre-bronchodilator spirometry (before albuterol prior to the bronchoscopy) and the lowest FEV1 recorded by spirometry in the hours after bronchoscopy was performed.

Surveillance for Adverse Events

Study coordinators contacted subjects by telephone for three days following bronchoscopy and administered a standardized questionnaire to ascertain the frequency of fever, cough, chest pain, shortness of breath and hemoptysis. Subjects were asked to return to the clinical site for further evaluation whenever needed. Investigators prescribed oral corticosteroids or antibiotics at their discretion. Subjects who went to the Emergency Department (ED) or required an unscheduled or extension of a planned hospitalization (> 24 hours) for asthma exacerbation or asthma related symptoms were reported to the DSMB within 24 hours of the investigator becoming aware of the event.

Statistical Analysis

Results are presented as percentages or means (standard deviations). Continuous variables were compared among groups using ANOVA models; categorical variables using chi-square tests for association. Analyses were carried out both among the four groups (normal and three asthma groups) and among the three asthma groups only. Comparisons of the frequency of cough, chest pain and shortness of breath post-bronchoscopy were adjusted for frequency of reported baseline symptoms prior to the procedure using logistic regression models. Associations between continuous variables are summarized using the Spearman rank correlation coefficient. A p-value < 0.05 was considered statistically significant for these comparisons.

A multivariate model was constructed to identify potential predictors of the change in % predicted FEV1 post-procedure. Thirty-three covariates were initially selected for this analysis, including clinical center, subject data (age, gender, race, HCU, medication use, disease severity), physiologic measures (lung function, PC20, skin test positivity), inflammatory markers (IgE, blood eosinophils, exhaled nitric oxide (eNO), BAL cell counts) and procedural variables from bronchoscopy (procedures performed, medications used, BAL recovery, procedure time). To account for missing data, a multiple imputation approach was used to produce ten simulated datasets and perform model selections. Fourteen covariates were chosen by more than two models (baseline FEV1 % predicted, FEV % reversibility, BAL performed, brushing performed, fentanyl given, procedure time, BAL % recovery, PC20, eNO, number of positive skin tests, BAL eosinophils, age, BMI, race) and were included in the final covariate list, which was then applied to each dataset. These models were combined to get estimates of effect size of a given covariate on change in FEV1 after bronchoscopy. A p-value < 0.05 was considered statistically significant.

Results

Characteristics of subjects enrolled in Bronchoscopy Procedures

Between May 2003 and September 2009, 436 subjects underwent investigative bronchoscopy at nine clinical sites as part of the Severe Asthma Research Program (see Table E2 in an online data supplement). In general, the demographics of this subset of asthma subjects (Table III) reflect those of the entire SARP cohort as previously reported [11]. Asthma subjects in the bronchoscopy cohort were divided into three groups for purposes of this safety analysis: not severe, severe and very severe asthma (VSA), the latter as defined *a priori* based on baseline airflow obstruction, medication requirements and recent frequent health care utilization (Table II). Compared to bronchoscopy subjects with severe asthma, individuals in the not severe group were younger, had a lower BMI and had higher baseline lung function (mean FEV1 = 88 ± 15 % predicted). The not severe asthma group was treated with diverse medication regimes but as a group, had few reported asthma exacerbations and overall lower health care utilization (HCU) during the prior 12 month period. In contrast, subjects in the severe asthma group were older, nearly half were obese with a BMI > 30 kg/m^2, reported higher recent health care utilization and had lower pulmonary function (mean FEV1 = 73 ± 16 % predicted) despite treatment with high doses of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA). The very severe asthma (VSA) group had the lowest mean FEV1 (55 ± 21% predicted) and the greatest frequency of recent HCU despite the requirement for treatment with chronic oral corticosteroids (> 20 mg prednisone daily) in 80% of these subjects.

Bronchoscopy procedures

Medication use and procedural details are shown in Table IV. FEV1 measurements pre-procedure were highly correlated with baseline FEV1 % predicted previously measured during the study ($r = 0.86$, $p < 0.0001$) indicating stable lung function at the time of bronchoscopy. Benzodiazepines were the most common sedative used in all groups [midazolam, median dose = 4 mg (interquartile range 2-6 mg)]. Midazolam doses increased with procedure time ($r = 0.39$, $p < 0.0001$) and both were highest in the VSA group ($p < 0.0001$). Opiates, specifically fentanyl and alfentanyl, were used more commonly in the severe groups ($p < 0.0001$). Topical lidocaine doses were greatest in the VSA group and this correlated weakly with procedure time ($r = 0.10$, $p = 0.04$). Fewer VSA subjects underwent bronchoalveolar lavage (73% v. 89-97%, $p = 0.003$) and BAL recovery was lowest in this group ($p < 0.0001$). All three procedures (BAL, endobronchial brushings and biopsies) were performed in the majority of subjects (72%). Forty-six subjects with asthma underwent transbronchial biopsies at one site; BAL was not performed in these subjects.

Health Care Utilization after investigative bronchoscopy

A total of nine subjects were evaluated or monitored in hospital settings following bronchoscopy (Table V), all but one had severe or very severe asthma. Three subjects developed worsening of asthma during their protocol mandated overnight in hospital observation period (subjects 1-3). These subjects remained in the hospital for additional intravenous or oral corticosteroids and continued inpatient observation at the discretion of the investigator (2-4 days). One severe asthma subject who was not scheduled for overnight observation, failed to recover lung function to 85% pre-procedural values (FEV1 = 79% predicted pre-procedure decreased to 57% predicted post-procedure) and, according to SARP protocol, was observed overnight before being discharged on oral corticosteroids the next morning (subject 4). One subject went to the Emergency Department (ED) for an exacerbation of her asthma several days after bronchoscopy had been attempted, but was unsuccessful due to inability to pass the vocal cords. She was treated with oral corticosteroids then discharged from the ED (subject 5). There was no long-term loss of asthma control in any of these subjects. Of the remaining four subjects who went to the ED following bronchoscopy, two reported pleuritic chest pain (subjects 6-7), one complained of a rash (subject 8) and one subject was experiencing a panic attack (subject 9). None of these subjects developed an asthma exacerbation.

Changes in FEV1 after bronchoscopy among subject groups

A comparison of the post-bronchoscopy % change in % predicted FEV1 among the subject groups showed no statistically significant difference in the distribution of % fall in FEV1 ($p = 0.30$, see Figure 1). In the asthma groups, half of the subjects had a ≤ 5 % fall in FEV1 and there was no difference between the not severe and severe asthma subgroups. All not severe asthma subjects had improvement in their FEV1 to 85% of the pre-procedure value either spontaneously over time or after bronchodilator treatment and were discharged 1-2 hours after bronchoscopy, including those whose FEV1 decreased more than 20% (n = 24). While precautionary overnight observation was mandated by the SARP protocol for VSA subjects, it was also recommended for subjects in the severe asthma group and investigators chose to observe most subjects in this group overnight also (75% subjects). Ninety seven percent of the subjects scheduled for overnight observation were discharged the following morning, including 22 of the 24 severe asthma subjects who had a > 20% decrease in FEV1 % predicted on the day of the procedure.

Effect of baseline lung function on change in FEV1

A correlation of baseline pulmonary function measures (on a different day then bronchoscopy) with % change in FEV1 after bronchoscopy revealed weak relationships between baseline % predicted FEV1 [with withholding of beta-agonists ($r = -0.13$, $p = 0.02$)] and reversibility after 6-8 puffs of albuterol ($r = 0.20$, $p = 0.0003$). Thus, asthma subjects with higher baseline FEV1 had greater decreases in FEV1 after bronchoscopy and those with greater reversibility had smaller decreases in FEV1 following the procedure. There was no relationship between PC20 and % change in FEV1 after bronchoscopy ($r = -0.01$, $p = 0.91$), although subjects with an FEV1 < 55% predicted did not undergo methacholine challenge and thus, are not included in this analysis (33% of the severe and 90% of the VSA groups). On the day of the bronchoscopy an inverse relationship between pre-procedure pre-albuterol % predicted FEV1 and the change in FEV1 after bronchoscopy was still observed ($r = -0.21$, $p < 0.0001$, see Figure 2) with larger decreases in FEV1 observed in those subjects with better lung function. Following administration of albuterol prior to bronchoscopy, however, there was an improvement in FEV1 % predicted in most subjects and the relationship between FEV1 and % change in FEV1 was no longer present ($r = -0.08$, $p = 0.18$). The change in FEV1 for the nine subjects who were evaluated or monitored in

hospital settings after bronchoscopy is shown in Figure 2 (closed triangles and circles, respectively).

In a multivariate analysis to identify predictors of change in FEV1, baseline FEV1 % predicted was the most statistically significant predictor of a change in FEV1 after bronchoscopy, with a -3.6% (CI -4.7, -2.5) decrease in FEV1 % predicted for every 10% increase in baseline FEV1 ($p < 0.0001$). The strongest other predictors in this analysis were covariates related to BAL, with an effect of -11.6% (CI -19.4, -3.8) decrease in post-procedure FEV1 if BAL was performed ($p = 0.003$) and a -1.6% (CI -2.9, -0.3) decrease in FEV1 for every 10% less BAL recovered ($p = 0.02$).

Symptoms after bronchoscopy

In the 3 days following bronchoscopy, the most commonly reported symptoms in the not severe, severe and VSA groups were cough (50%, 47% and 78% of subjects respectively), shortness of breath (14%, 23% and 53%), chest pain (11%, 17% and 35%) and blood streaked sputum (17%, 23% and 38%) (Table VI). While these symptoms were more frequently reported in the VSA group, only cough and blood streaked sputum were statistically significantly different among the groups after the frequency of baseline symptoms was used as a covariate ($p = 0.002$ and $p = 0.02$ respectively). Fever was infrequently reported (2-11%) and was similar in the four groups ($p = 0.06$).

Treatments after bronchoscopy

Oral corticosteroids were prescribed more frequently in the post-procedure period in the severe asthma (25%) and VSA groups (63%) when compared to the not severe group (4%, $p < 0.001$) (Table VI). Specifically, severe asthma subjects with the greatest baseline airflow obstruction (FEV1 < 60% predicted) and those who reported an ED visit in the past year were more likely to be treated with systemic corticosteroids after bronchoscopy (both $p < 0.0001$). Antibiotics were prescribed in only seven subjects, but all were in the severe and VSA groups ($p = 0.003$) and all of them had reported an ED visit in the past year ($p = 0.002$). All five subjects who had an asthma exacerbation after bronchoscopy also reported an ED visit within the past 12 months (100% vs 48%, $p = 0.03$) and a prior history of pneumonia (100% vs 54%, $p = 0.05$) compared to the severe asthma subjects who did not require additional evaluation and treatment post-procedure. There were no differences in bronchoscopic techniques or procedures between the severe asthma subjects who did or did not develop exacerbations, nor those who did or did not receive oral corticosteroids or antibiotics after bronchoscopy.

Discussion

The current study reports our experience with investigative bronchoscopy in a large subset of subjects from the Severe Asthma Research Program, including 143 severe asthma subjects who met the ATS workshop definition of severe asthma, 196 not severe asthma subjects and 97 normal controls. The aim of our study was to prospectively evaluate changes in pulmonary function and the frequency of respiratory related events in subjects with not severe and severe asthma undergoing investigative bronchoscopy in SARP. Our results support the safety of investigative bronchoscopy in subjects with severe asthma and extend previous reports of the safety of this procedure in subjects with mild to moderate disease [6-10].

Investigative bronchoscopy was well tolerated by severe and very severe asthma subjects with only five asthma exacerbations experienced (< 1.5% of the asthma subjects) that resolved quickly (2-4 days). Identification of clinical markers that might have predicted loss

of asthma control after bronchoscopy was difficult because of the scarcity of these events. While all five of the subjects who had asthma exacerbations after bronchoscopy had severe airflow obstruction at baseline (FEV1 40-63% predicted), reported an ED visit in the past year and had a prior episode of pneumonia, these clinical characteristics were common in the severe asthma groups in general and not specific to these subjects. Likewise, while a > 20% decrease in FEV1 was observed in three of these five subjects, there were 21 other severe asthma subjects who sustained similar falls in their FEV1, but were discharged the following morning after planned precautionary overnight observation. Importantly, of the five subjects who had asthma exacerbations, four were being observed in a hospital setting according to SARP protocol and none of these required a higher level of care than a traditional inpatient medical bed. All of these events occurred early in the SARP program and may have resulted from more cautious care of worsening asthma in this research setting. The only asthma exacerbation resulting in an ED visit occurred in a subject with a history of many previous and recent ED visits and in whom the bronchoscope never passed the vocal cords.

Although severe asthma subjects had lower baseline lung function, there was a < 10% decrease in % predicted FEV1 observed following bronchoscopy in the majority of these subjects, similar to that seen in the not severe asthma and normal control groups. This finding is in agreement with a smaller previous study by Van Vyne and colleagues, in which there were ten subjects with an pre-procedure FEV1 < 60% predicted and an elevated severity score, but no observed difference in % change in FEV1 despite the severity of their asthma [8].

Subjects with lower baseline lung function (FEV1 % predicted) had smaller (not larger) decreases in FEV1 after bronchoscopy. Likewise, subjects with greater baseline reversibility to short-acting beta-agonists (6-8 puffs) were less likely to sustain large decreases in FEV1 after the procedure even when adjusting for baseline % predicted FEV1. Taken together, these associations suggest that subjects with severe airflow obstruction, many of whom respond well to bronchodilator administration [12], are not at greater risk for large falls in FEV1 after bronchoscopy. This may be partially due to the protocol required pretreatment of all SARP subjects with albuterol with subsequent improvement in FEV1 prior to bronchoscopy.

Conversely, some asthma subjects with preserved lung function (and thus mathematically less reversibility) had large decreases in their FEV1 % predicted after bronchoscopy. At least two studies have reported an inverse relationship between the degree of baseline airway hyperresponsiveness (PC20 methacholine) and % change in FEV1 or peak expiratory flow rates after bronchoscopy suggesting that the presence of greater bronchial hyperresponsiveness might lead to exaggerated changes in FEV1 with airway instrumentation in subjects with preserved baseline lung function [6, 9]. A similar analysis of our subjects with a baseline FEV1 % predicted > 55% who underwent methacholine challenge, however, did not show any association between the level of bronchial hyperresponsiveness and the decrease in FEV1 after bronchoscopy.

Of the 33 covariates used in the multivariate analysis, the only statistically significant procedural predictor of a greater fall in FEV1 after bronchoscopy was the performance of a bronchoalveolar lavage. Furthermore, there was an additional although smaller in magnitude, effect seen with lower BAL fluid recovery. While these results should be interpreted with care given the need to impute data for the subjects who did not have BAL performed, these findings do suggest that investigators should be cautious when performing bronchoalveolar lavage in subjects with asthma, especially if initial fluid recovery is modest.

Cough was the most frequently reported symptom after bronchoscopy, especially in the severe asthma groups. These groups were more likely to receive oral corticosteroids after the procedure, perhaps due to complaints of persistent cough. Likewise, subjects who reported a recent ED visit or who had a baseline FEV1 < 60% predicted were more frequently treated with oral corticosteroids regardless of a minimal change in FEV1 after bronchoscopy. Since investigators had the discretion to treat subjects after bronchoscopy based on their clinical judgment, this finding suggests that they preferred to treat this group of severe asthma patients based on their baseline clinical data, not events surrounding the bronchoscopic procedure.

There are some limitations to this study. First, despite the commitment and effort to a common Bronchoscopy MoP to monitor pulmonary function and respiratory related events, the nature of the SARP network (eight independent investigator initiated grants) required flexibility of the actual bronchoscopy procedures to allow investigators to meet the specific aims of their independent grants. Second, the goal of some sites was to study the most severe patients, while others focused on a broader range of disease severity. Thus, inherent variability among the sites confounds interpretation of some of the data and may impact our ability to generalize our findings to other investigators. Finally, the low incidence of adverse events in SARP may be a “best case scenario” that reflects the years of experience of many of our investigators.

The current study used a standardized approach to investigative bronchoscopy in a large cohort of severe and not severe asthma subjects to prospectively examine changes in lung function and respiratory related events associated with this research procedure. We confirmed prior reports describing safety aspects of investigative bronchoscopy in patients with mild to moderate asthma, but more importantly, our results support the safety of this procedure in subjects with severe asthma. Despite severe airflow obstruction, complex medication regimens and recent high health care utilization in the severe asthma groups, there were very few asthma exacerbations after the procedure and, when they occurred, they typically resolved within days following the bronchoscopy. Our results confirm that bronchoscopy with appropriate precautions is well tolerated in patients with mild-moderate as well as severe asthma and can continue to be a valuable investigative procedure to define airway inflammation in asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The investigators wish to thank all of the subjects who agreed to participate in the bronchoscopy portion of SARP as well as the physicians, bronchoscopy technicians, nurses and coordinators who ensured their safety during the procedure.

Grant support: HL69116, HL69130, HL69155, HL69167, HL69170, HL69174, HL69349, HL091762, M01 RR03186, M01 RR007122-14, 1UL1RR024992, 1UL1RR024989, 1UL1RR025011.

References

1. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007; 120(5 Suppl):S94–138. [PubMed: 17983880]
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008; 31:143–178. [PubMed: 18166595]

3. National Institutes of Health workshop summary. Summary and recommendations of a workshop on the investigative use of fiberoptic bronchoscopy and bronchoalveolar lavage in individuals with asthma. J Allergy Clin Immunol. 1985; 76(2 Pt 1):145–147. [PubMed: 4019947]
4. Workshop summary and guidelines: investigative use of bronchoscopy, lavage, and bronchial biopsies in asthma and other airway diseases. J Allergy Clin Immunol. 1991; 88:808–814. [PubMed: 1955640]
5. Busse WW, Wanner A, Adams K, Reynolds HY, Castro M, Chowdhury B, et al. Investigative bronchoprovocation and bronchoscopy in airway diseases. Am J Respir Crit Care Med. 2005; 172:807–816. [PubMed: 16020805]
6. Djukanovic R, Wilson JW, Lai CK, Holgate ST, Howarth PH. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. Am Rev Respir Dis. 1991; 143:772–777. [PubMed: 2008989]
7. Chetta A, Foresi A, Bertorelli G, Pesci A, Olivieri D. Lung function and bronchial responsiveness after bronchoalveolar lavage and bronchial biopsy performed without premedication in stable asthmatic subjects. Chest. 1992; 101:1563–1568. [PubMed: 1600774]
8. Van Vyve T, Chanez P, Bousquet J, Lacoste JY, Michel FB, Godard P. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. Am Rev Respir Dis. 1992; 146:116–121. [PubMed: 1626794]
9. Humbert M, Robinson DS, Assoufi B, Kay AB, Durham SR. Safety of fibreoptic bronchoscopy in asthmatic and control subjects and effect on asthma control over two weeks. Thorax. 1996; 51:664–669. [PubMed: 8882070]
10. Elston WJ, Whittaker AJ, Khan LN, Flood-Page P, Ramsay C, Jeffery PK, et al. Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma. Eur Respir J. 2004; 24:375–377. [PubMed: 15358694]
11. Julius P, Lommatzsch M, Kuepper M, Bratke K, Faehndrich S, Luttmann W, et al. Safety of segmental allergen challenge in human allergic asthma. J Allergy Clin Immunol. 2008; 121:712–717. [PubMed: 18028992]
12. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007; 119:405–413. [PubMed: 17291857]
13. Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, Bleecker ER. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. J Allergy Clin Immunol. 2010; 125:1028–1036. [PubMed: 20398920]
14. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis. 1987; 136:225. [PubMed: 3605835]
15. Am J Respir Crit Care Med. Vol. 162. American Thoracic Society; 2000. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions; p. 2341-2351.

Abbreviations

ATS	American Thoracic Society
BMI	Body Mass Index
DSMB	Data Safety Monitoring Board
ED	Emergency Department
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
HCU	Health Care Utilization

ICS	Inhaled corticosteroids
LABA	Long-acting beta-agonist
MoP	Manual of Procedures
OCS	Oral corticosteroids
PC_{20}	Provocative dose (of methacholine) required to drop FEV_1 by ≥20%
SARP	Severe Asthma Research Program
VSA	Very Severe Asthma

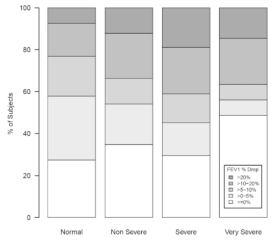

FIGURE 1.

Change in FEV1 after bronchoscopy in the four groups of subjects. Shown is the % change in % predicted FEV1 from the first FEV1 before albuterol administration to the lowest FEV1 following bronchoscopy. There was no statistically significant difference in the distribution of % change in % predicted FEV1 among the groups (p = 0.30)

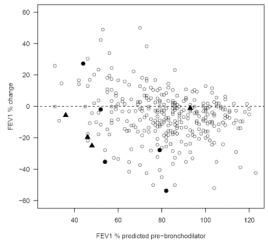

FIGURE 2.

Change in FEV1 after bronchoscopy for individual subjects. There is a mild relationship ($r = -0.21$, $p < 0.0001$) between better baseline lung function and greater % decrease in FEV1. The closed circles represent the subjects who had asthma exacerbations, the closed triangles are subjects who went to the emergency department with other complaints.

TABLE I

INCLUSION CRITERIA FOR SARP BRONCHOSCOPY SUBJECTS

All Subjects
Age ≥ 18 years and ≤ 60 years*
Nonsmoking (< 5 pack year tobacco exposure)
No history of co-existing lung disease
No uncontrolled co-morbidities
Able to provide written informed consent
Normal Healthy Controls
No history of asthma or respiratory symptoms
Normal pulmonary function tests (FEV1 > 75% predicted, FEV1/FVC > 70%)
Negative methacholine bronchoprovocation (PC20 ≥ 25 mg/ml)
All Asthma Subjects
Clinical history consistent with asthma
Meet ATS criteria for diagnosis of asthma[14] with EITHER/OR
• Bronchodilator response to albuterol (≥ 12% change in FEV1)
• Positive methacholine bronchoprovocation (PC20 < 25 mg/ml)†
Clinically stable asthma as determined by the bronchoscopist
Not Severe Asthma Subjects
Treatment with no or low dose inhaled corticosteroids
Severe Asthma Subjects
Meet ATS workshop criteria for the definition of severe/refractory asthma[15] with
ONE Major Characteristic
• Treatment with oral corticosteroids (≥ 20 mg/d) for ≥ 50% of year AND/OR
• Treatment with high-dose inhaled corticosteroids††
AND AT LEAST TWO Minor Characteristics
• Treatment with additional daily second controller medication
• Short-acting beta-agonist use on a daily or near-daily basis
• Persistent airway obstruction (FEV_1 < 80% predicted)
• One or more urgent care visits for asthma per year
• Three or more oral steroid “bursts” per year
• Prompt deterioration with ≤ 25% reduction in corticosteroid dose
• Near-fatal asthma event in the past

*Upper age limit imposed based on concerns for increasing incidence of significant co-morbidities (such as heart disease, diabetes, hypertension, renal failure) in subjects > 60 years of age. Investigators were allowed to request approval for older subjects from the steering committee after review of medical records.

†Subjects with FEV1 < 55% predicted did not undergo methacholine bronchoprovocation.

††High dose inhaled corticosteroid defined as a dose equivalent to ≥ 880 mcg fluticasone propionate.

TABLE II

IDENTIFICATION OF SUBJECTS WITH VERY SEVERE ASTHMA FOR INHOSPITAL OVERNIGHT OBSERVATION

Subjects with Very Severe Asthma (VSA) meet any *ONE* of the following criteria:

- Treatment with chronic oral corticosteroid ≥ 20 mg prednisone daily
- Evidence for worsening asthma control/clinical instability in the past two weeks manifest by any *ONE* of the following*:
  - Increase in short-acting beta-agonist use (≥ 8 puffs over baseline in past 48 hours)
  - Change in oral corticosteroid dose or escalation of inhaler therapy
  - Exacerbation of asthma requiring corticosteroids and/or physician evaluation
- Evidence for chronic clinical asthma instability
  - ≥ 6 asthma exacerbations in past 180 days
- Recent hospital based health care utilization
  - Hospitalization for asthma within the past 6 months†
  - Endotracheal Intubation for asthma symptoms within the past 1 year††
- Severe airflow obstruction with post-bronchodilator FEV1 < 60% predicted

Bronchoscopy was postponed for:

*14 days if any of these criteria were present,

†at least 6 weeks after a hospitalization for asthma and

††more than 6 months after endotracheal intubation.

TABLE III

CLINICAL CHARACTERISTICS OF SUBJECTS

Number of Subjects	Normal 97	Not severe 196	Severe 102	Very severe 41	p-value all	p-value asthma only†
Age at Enrollment (yrs)	31 (10)	34 (11)	39 (12)	43 (11)	<0.0001	<0.0001
Gender (% female)	60	63	61	59	0.94	0.86
Race (% Caucasian)	73	71	65	71	0.57	0.48
Body Mass Index (BMI)	27 (7)	28 (7)	30 (6)	30 (6)	0.009	0.04
% with BMI > 30	26%	26%	47%	53%	<0.0001	<0.0001
Baseline Lung Function*						
FEV1 % predicted	100 (11)	88 (15)	73 (16)	55 (21)	<0.0001	<0.0001
FVC % predicted	102 (11)	96 (13)	85 (17)	74 (17)	<0.0001	<0.0001
FEV1/FVC (%)	0.82 (0.1)	0.75 (0.1)	0.67 (0.1)	0.56 (0.1)	<0.0001	<0.0001
Methacholine challenge (n)	97	190	68	4		
PC20 (mg/ml)**	49.0 (0.03)	1.51 (0.67)	0.72 (0.68)	0.56 (0.82)	<0.0001	0.003
Subjects with ≥1 positive skin prick test (%)	39%	85%	76%	68%	<0.0001	0.03
Asthma Medications (%)						
Inhaled Corticosteroids		60%	99%	90%		<0.0001
Long-acting beta-agonists		43%	90%	83%		<0.0001
Oral Corticosteroids		1%	21%	80%		<0.0001
Health Care Utilization for Asthma (%)						
Emergency Room, past yr		11%	40%	78%		<0.0001
Hospitalization, past yr		1%	20%	59%		<0.0001
Intensive Care Unit, ever		9%	35%	51%		<0.0001

Numeric data presented as mean (SD) or

** geometric mean (log10 SD).

* Pre-bronchodilator spirometry measurements after an appropriate medication withhold.

† Three way comparison of asthma groups only.

TABLE IV

PROCEDURAL DETAILS DURING BRONCHOSCOPY

Number of Subjects	Normal 97	Not severe 196	Severe 102	Very severe 41	p-value all	p-value asthma only†
% predicted FEV1 pre-albuterol	99 (12)	90 (15)	75 (18)	58 (21)	<0.0001	<0.0001
% predicted FEV1 post-albuterol	102 (13)	96 (14)	81 (16)	68 (21)	<0.0001	<0.0001
Sedative Use (% subjects)*						
midazolam	95%	93%	97%	100%	0.18	0.08
fentanyl/alfentanyl	44%	58%	81%	90%	<0.0001	<0.0001
Scope time (min)	24 (10)	24 (10)	27 (11)	32 (8)	<0.0001	<0.0001
Total Lidocaine Used (mg)	355 (194)	347 (151)	312 (165)	425 (117)	0.003	0.0005
Procedures done (% subjects)						
Bronchoalveolar Lavage	97%	89%	92%	73%	0.003	0.005
BAL % recovery	60 (14)	55 (14)	49 (15)	36 (17)	<0.0001	<0.0001
Bronchial Brushings	79%	79%	72%	83%	0.35	.21
Endobronchial Biopsies	95%	93%	98%	98%	0.30	.16
Transbronchial Biopsies, n	0	22	11	13		
% Subjects with 3 procedures**	76%	71%	69%	66%	0.28	0.70

Numeric data presented as mean (SD).

* The most common sedatives used are listed. Alternative sedatives used less commonly included demerol (10% subjects) and morphine (8% subjects).

** Subjects who had transbronchial biopsies did not undergo BAL.

† Three way comparison of asthma groups only.

TABLE V

SUBJECTS WITH HEALTH CARE UTILIZATION AFTER BRONCHOSCOPY

			Baseline Clinical Data			Day of Bronchoscopy		
Subj #	**Age (yrs)/ Sex**	**Asthma Severity**	**Chronic OCS†**	**ED Past yr**	**Baseline FEV1***	**Pre Bronch FEV1***	**Scheduled overnight?**	**Description of Event and Treatment Given†**
1	38y BF	Severe	N	Y	60%	82%	Y	Continued hosp for 4 days for asthma exacerbation; treated with IV/OCS, antibiotics On review of event pt had asthma exacerbation 6 weeks prior to procedure and remote h/o breast cancer with chest irradiation (but normal current CXR)
2	58y WF	Severe	Y	Y	63%	54%	Y	Continued hosp observation for 1 extra day for asthma exacerbation; treated with OCS, antibiotics
3	42y BF	VSA	Y	Y	59%	52%	Y	Continued hosp observation for 1 extra day for asthma exacerbation, chest pain; treated with IV/OCS
4	18y BF	Severe	N	Y	81%	79%	N	Unplanned overnight hosp due to failure to meet FEV1 discharge criteria; treated with OCS On review of event pt had asthma exacerbation 12 weeks prior to procedure
5	22y WF	VSA	Y	Y	40%	44%	N	Bronchoscopy was not completed due to inability to pass vocal cords ED visit 3 days after bronchoscopy for asthma exacerbation with syncope; CTA showed no PE; treated with OCS, antibiotics
6	35y WF	VSA	Y	Y	37%	36%	Y	Discharged in stable condition after overnight stay. Returned to ED that evening with pleuritic chest pain; treated with analgesics only
7	24y BM	Severe	N	Y	41%	46%	N	ED visit (then hosp) 6 days after bronchoscopy for chest pain; CT showed pneumatocoele in area where transbronchial biopsies were done, supportive care only Discharged in stable condition after overnight stay.
8	49y BF	VSA	Y	Y	35%	48%	Y	Returned to ED 2 days after bronchoscopy for lower extremity rash; treated with OCS, anti-histamines for allergic reaction. Not clearly related to procedure.
9	43y BF	Not severe	N	N	92%	93%	N	ED visit 3 days after bronchoscopy for sudden SOB due to panic attack; No treatment given. Not related to procedure.

* FEV1 presented as % predicted FEV1.

† Abbreviations: IV CS = intravenous corticosteroids, CS = oral corticosteroids, CXR – chest radiograph, CT or CTA = chest CT with angiogram (PE protocol), PE = pulmonary embolism.

TABLE VI

SYMPTOMS AND TREATMENTS 1-3 DAYS AFTER BRONCHOSCOPY

Number of Subjects	Normal 97	Not severe 196	Severe 102	Very severe 41	p-value all	p-value† asthma only
Cough*	54%	50%	47%	78%	0.002	0.01
Chest Pain*	2%	11%	17%	35%	0.15	0.12
Shortness of Breath*	3%	14%	23%	53%	0.14	0.07
Blood streaked Sputum	15%	17%	23%	38%	0.02	0.02
Nausea	6%	4%	7%	8%	0.53	0.35
Fever	7%	4%	11%	2%	0.06	0.02
Medications Used						
Post-procedure						
Antipyretic	15%	12%	23%	20%	0.12	0.06
Antibiotic	0%	0%	4%	8%	0.0007	0.003
Prednisone		4%	25%	63%		<0.0001

Data presented as % of subjects.

*p value adjusted for baseline symptom frequency reported on clinical characterization questionnaire.

†Three way comparison of asthma groups only.