

Effects of bronchoscopy on lung function in asthmatics

Christina Bellinger MD*

Eugene R. Bleecker MD

Center for Genomics and Personalized Medicine Research, Wake Forest University School of
Medicine, Winston-Salem, NC

Stephen P. Peters MD PhD

Center for Genomics and Personalized Medicine Research, Wake Forest University School of
Medicine, Winston-Salem, NC

Rodolfo M. Pascual MD

Wake Forest Baptist Health, Department of Pulmonary/Critical Care, Winston-Salem, NC

Jeffrey Krings BSN

Wake Forest Baptist Health, Department of Pulmonary/Critical Care, Winston-Salem, NC

Regina V. Smith BS

Center for Genomics and Personalized Medicine Research, Wake Forest University School of
Medicine, Winston-Salem, NC

Annette Hasties PhD

Center for Genomics and Personalized Medicine Research, Wake Forest University School of
Medicine, Winston-Salem, NC

Wendy C. Moore MD

Center for Genomics and Personalized Medicine Research, Wake Forest University School of
Medicine, Winston-Salem, NC

***Corresponding Author**

Wake Forest Baptist Health

Department of Pulmonary/Critical Care

Medical Center Blvd

Winston Salem, NC 27157

cbelling@wakehealth.edu

phone: 336-713-5780

fax: 336-716-7277

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Background: To better understand changes in pulmonary physiology related to asthma severity following bronchoscopy, we performed scheduled pre- and post-procedure spirometry on all subjects undergoing bronchoscopy in our research program.

Methods: Control subjects and asthma subjects of all severity were recruited for bronchoscopy. On the day of bronchoscopy, subjects underwent spirometry when they arrived, after pre-bronchoscopy treatment with albuterol and then up to three sets within two hours following completion of the bronchoscopy. A subset of patients had a second bronchoscopy after two weeks of treatment with oral prednisolone (40 mg daily).

Results: A total of 92 subjects had at least one bronchoscopy [12 control subjects, 56 nonsevere asthma (NSA), 24 severe asthma (SA)]. The SA and NSA groups had similar decreases in FEV1 ($-20 \pm 13\%$ vs $-19 \pm 16\%$, $p=0.92$) and FVC ($-20 \pm 12\%$ vs $-20 \pm 14\%$, $p=0.80$), but no change in FEV1/FVC ratio. The control and NSA group had more rapid recovery of both FEV1 and FVC by 2 hours compared to the SA group ($p=0.01$). In the subset of 36 subjects (22 NSA, 14 SA) who underwent a second bronchoscopy following administration of oral prednisolone for 14 days, steroids resulted in more rapid recovery of lung function ($p=0.05$) compared to nonsevere asthmatics.⁶ We found no published studies demonstrating lung function recovery over time in asthmatics following bronchoscopy.

Due to the discrepant physiologic findings of previous studies, we planned a comprehensive evaluation of lung function in patients undergoing bronchoscopy (with bronchoalveolar lavage [BAL], biopsies and brushings) immediately following and up to twenty-four hours post procedure in patients with severe and nonsevere asthma and non-asthmatic patients with normal lung function.

Methods

Selection of Bronchoscopy Subjects. Subjects were enrolled as part of the severe asthma research program (SARP). We did a retrospective review of the prospectively collected database. After Institutional Review Board approval, subjects provided written informed consent. All subjects underwent baseline spirometry followed by methacholine challenge to confirm bronchial hyper-reactivity ($PC_{20} 16 \leq \text{mg/mL}$) except for those patients with an FEV1 $< 50\%$ predicted. Asthma subjects were classified as nonsevere (NSA) or severe (SA) based on whether they met the American Thoracic Society (ATS) workshop definition of severe asthma.⁷ A group

of normal subjects without asthma also underwent bronchoscopy. This group was required to have a negative methacholine challenge and no respiratory symptoms.

Inclusion criteria required an age of 18-60, a diagnosis of asthma as confirmed with methacholine challenge (unless FEV1 <50% predicted), and deemed clinically appropriate for bronchoscopy prior to the procedure. Exclusion criteria included FEV1 < 35% predicted before bronchodilator therapy or < 40% predicted after bronchodilator therapy, unstable asthma (defined as increased oral corticosteroids in the past fourteen days or change in medication in the last month), unstable comorbidities, recent respiratory illness, hospitalization within the last six weeks, intubation within the last six months or diffusing capacity less than 70% predicted.

Spirometry. All patients underwent baseline pulmonary function testing (PFTs) to a goal of three acceptable maneuvers according to ATS standards and performed by certified technicians. Subsequently, on the day of the bronchoscopy, they had two pre-bronchoscopy PFTs, before and after bronchodilators (two puffs of albuterol). Patients were monitored for one to three hour following bronchoscopy. During the post-bronchoscopy period, they underwent three to six sets of spirometry. A subset of severe asthma patients deemed high risk for post-procedural respiratory complications due to poor lung function (n=13) were observed overnight for twenty-four hours and had spirometry before discharge.

Bronchoscopy Procedures. All patients underwent fiberoptic bronchoscopy with an Olympus PF 240 bronchoscope (Olympus Corporation, Tokyo, Japan). All three investigators followed a detailed manual of operations for bronchoscopy. Sedatives and/or anxiolytic medication and local anesthesia with lidocaine were administered per standard operating procedures. All subjects were monitored with continuous electrocardiograph, blood pressure measurements and pulse

oximetry. The procedure was performed by a small pool of operators. Procedures performed included the following: BAL, endobronchial brushings and mucosal biopsies. Bronchoalveolar lavage was performed using saline at 37deg F in 50mL aliquots up to 200mL volume followed by manual suction retrieval. If the recovered volume was less than 15mL after the first 100mL instillation then no further saline was instilled. Brushings (3 to 4 times depending on the bronchoscopist's sense of sample adequacy) then followed and were performed in a lower lobe. Finally, endobronchial biopsies (5 to 7 biopsies depending on the bronchoscopist's sense of sample adequacy) were done under direct visualization of a site chosen by the operator. The majority had all procedures performed during bronchoscopy (n=85, 92%).

Oral Steroids. A subgroup of patients (n=36) received oral corticosteroids, prednisolone 40 mg per day for 14 days prior to their second bronchoscopy. These patients were undergoing sample collection for a study examining the effects of steroid on endobronchial mucosa and lavage fluid.

Statistical Analysis. Analyses were performed comparing the control group, nonsevere asthma group and severe asthma group. Results are presented as percentages and means (standard deviations). Continuous variables were compared among groups using ANOVA models and, where a signal was present, groups were compared with Wilcoxon analysis. Nominal variables were analyzed using chi-square tests for association followed by nominal logistic evaluation when applicable. Results were considered significant for p value <0.05.

Results

Subject Characteristics. Between April 2004 and November 2010, 92 subjects underwent 143 bronchoscopies. There were 56 nonsevere asthmatics who underwent a total of 86 bronchoscopies, 24 severe asthmatics who underwent a total of 45 bronchoscopies, and 12

control subjects who each had one bronchoscopy. Baseline characteristics are displayed in Table 1. The majority of subjects were female (58-75%). The severe asthmatic group was older (mean age 45 ± 9 , $p < 0.01$). The severe asthmatics were more likely to be on inhaled corticosteroids (100% vs 63%, $p < 0.01$) and long-acting beta agonists (96% vs 58%, $p < 0.01$) compared to nonsevere asthmatics.

Bronchoscopy Characteristics. Table 2 displays bronchoscopy characteristics between all three groups (controls, NSA and SA). Bronchoscopy was no different among groups. There was no difference in fentanyl dosing between asthmatic groups (NSA, mean 128 ± 45 mcg vs SA, 116 ± 40 mcg, $p = 0.07$) though less was used in the control group (90 ± 52 mcg). Less BAL fluid was recovered in the severe group compared to the nonsevere group and controls (recovery: $41 \pm 18\%$ vs $54 \pm 16\%$ vs $67 \pm 11\%$, $p = 0.03$ versus NSA and $p < 0.01$ versus control). Post-procedure albuterol was administered if the patient experienced shortness of breath. Only 17% of control subjects ($n = 2$) received post-bronchoscopy albuterol while 30% of nonsevere subjects and 42% of severe subjects received albuterol; however, this did not reach significance.

Spirometry Characteristics. Baseline FEV1 % predicted and FVC % predicted on the day of bronchoscopy were statistically lower in the asthmatic groups compared to each other and the severe group compared to the control group (FEV1 % predicted mean 74 ± 22 [SA] vs 89 ± 13 [NSA] vs 99 ± 12 [control], $p < 0.04$; FVC % predicted mean 81 ± 16 [SA] vs 97 ± 13 [NSA] vs 100 ± 15 [control], $p < 0.01$). The FEV/FVC at baseline was significantly lower in the severe asthma group and nonsevere group compared to controls and compared to each other (0.72 [SA] vs 0.76 [NSA] vs 0.85 [control], $p < 0.01$). Following albuterol, FEV1 increased more in asthmatic patients (11% SA, 8%, NSA, 4% Controls, $p = 0.04$).

As demonstrated in Figure 1, post-bronchoscopy spirometry was divided into twenty-minute intervals. In the first twenty minutes following bronchoscopy, all subjects had a decline in FEV1 (12-20%) and FVC (10-20%) with no significant difference between groups. From forty to sixty minutes, the NSA group recovered their FEV1 and FVC sooner compared to the SA group ($p=0.02$, $p=0.03$). Subsequently by 100-120 minute post-bronchoscopy, the NSA group maintained a higher FEV1 compared to the SA group ($p<0.01$). The control group and the NSA group nearly normalized their FVC while the SA group remained lower ($p<0.01$ for SA versus NSA). Due to concurrent falls in FEV1 and FVC, there was no change in the FEV1/FVC ratio, also displayed in Figure 1. For those patients who had twenty-four hour observation after bronchoscopy (n=13) their FEV1 and FVC was still declined from baseline (FEV1 $-14\pm14\%$ and FVC $-14\pm9\%$).

A subset of 36 patients (14 SA and 22 NSA) received oral corticosteroids (OCS) with pre- and post-bronchoscopy. Bronchoscopy characteristics are shown in Table 3. There were no differences in pre-bronchoscopy spirometry nor bronchoscopy characteristics, including duration, total lidocaine, sedation dosing, or lowest oxygen saturation. Baseline spirometry on the day of bronchoscopy was not significantly different: FEV1 % predicted 82 ± 18 vs 80 ± 18 mean, FVC % predicted 90 ± 16 vs 88 ± 16 mean, and FEV1/FVC 0.74 ± 8 vs 0.73 ± 9 mean. There was no difference in mean % drop in FEV1 or FVC initially in the pre- and post-OCS groups (FEV1 $-21\pm11\%$ vs. $-18\pm22\%$; FVC $19\pm19\%$ vs. $15\pm9\%$, respectively). Prior to discharge, the post-OCS group displayed faster recovery in their FEV1 ($-6\pm10\%$) compared to those pre-OCS values ($-13\pm11\%$), $p=0.01$. Figure 2 demonstrates that the severe asthmatics had a more rapid two hour recovery if they were on oral steroids at the time of bronchoscopy. Of these 36 patients,

15 had 3 bronchoscopies, two prior to oral steroids and one after steroids. There were no spirometric differences between the two bronchoscopies prior to oral steroids.

Safety. Patients were contacted sequentially for three days after bronchoscopy to monitor for any adverse events post-procedure. One patient in the NSA group returned the day after bronchoscopy for follow-up spirometry and evaluation due to coughing post-procedure. Otherwise there were no emergency room visits or unanticipated hospitalizations following bronchoscopy.

Discussion

Our study is the first to demonstrate detailed pulmonary function tests reflecting differences in respiratory physiology following bronchoscopy in asthmatics based on disease severity. Prior studies have shown steeper decline or no difference, but all had a single spirometric post-bronchoscopy value or used only peak flow (1-6). Following BAL, brushing and mucosal biopsies, all groups demonstrated a post-procedure fall in FEV1 and FVC despite pre-procedure bronchodilation. Control subjects recovered their FVC and more quickly compared to severe asthmatics while nonsevere asthmatics recovered both their FEV1 and FVC more quickly compared to severe asthmatics. In the subgroup that received oral corticosteroids for two weeks between an initial bronchoscopy and second bronchoscopy, severe asthmatics recovered more quickly toward their spirometric baseline by the two hour post-bronchoscopy spirometry.

Certain baseline characteristics were different among groups. Severe asthmatics were on average older than nonsevere asthmatics and control groups with higher body mass index as

well. As expected, the severe asthma patients were taking more long-acting beta agonists and inhaled corticosteroids compared to the nonsevere asthmatics. Amongst asthmatics, there was no difference in prior emergency room visits or prior hospitalizations but the severe asthmatics were more likely to have been intubated for respiratory failure in the past (OR 5.5, 95% CI 1.7-20.4). Bronchoscopy duration was marginally longer in the severe asthma group compared to the nonsevere asthma group, and fentanyl dosing was slightly higher in asthma patients versus controls. Change in oxygen delivery also did not differ significantly among all groups nor did post-procedure albuterol administration. Bronchoalveolar lavage fluid recovered was highest in controls and declined with asthma severity. Eosinophil and neutrophil content of BAL fluid among asthma severity was not different.

This is the largest and most comprehensive post-bronchoscopy lung function evaluation in asthmatics to date. However, an even larger size including more control and more severe asthmatic may uncover other physiological findings in post-bronchoscopy spirometry. Larger studies examining the protective effects of steroids on lung function may also be revealing.

With concurrent falls in and recovery of FEV1 and FVC, we believe these changes reflect a change in lung compliance. Instrumentation and lavage fluid likely induce small airway narrowing and meniscus closure following bronchoscopy much like an acute asthma exacerbation. During an asthma exacerbation small airway closure occurs as a meniscus forms over a narrowing lumen. Subsequent early closure of airways results in reduced FEV1 and FVC with a rise in residual volume.⁸ Delayed recovery of lung function may suggest that while bronchoscopy is safe in patients with severe asthma⁹, a longer post-recovery observation or use

of prophylactic steroids may be helpful. This is particularly noteworthy in the era of bronchial thermoplasty.

Conclusion

Overall, we have demonstrated a significant difference in respiratory physiology following bronchoscopy in asthmatics, severe and nonsevere, and controls. Spirometry post-bronchoscopy demonstrates more rapid recovery of FEV1 and FVC in controls and nonsevere asthmatics compared to severe asthmatics. Oral steroids may offer a protective advantage in severe asthmatics undergoing bronchoscopy as it enabled them to more quickly recover lung function after the procedure.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgments

Christina Bellinger MD*

Contribution: data compilation, paper composition, statistics

Eugene R. Bleecker MD

Contribution: lab facility, oversight

Stephen P. Peters MD PhD

Contribution: lab facility, oversight

Rodolfo M. Pascual MD

Contribution: performed bronchoscopy

Jeffrey Krings BSN

Contribution: patient enrollment, performed spirometry

Regina V. Smith BS

Contribution: patient enrollment, performed spirometry

Annette Hasties PhD

Contribution: processed BAL samples, paper editing

Wendy C. Moore MD

Contribution: performed bronchoscopy, paper development and editing

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Figure 1. Changes in lung function following bronchoscopy. Spirometry post-bronchoscopy was compared to the post-bronchodilator, pre-procedure spirometry (baseline). Lung function was grouped in twenty minute intervals. A) Percent drop in FEV1 among controls, non severe asthma (NSA) and severe asthma (SA) patients in twenty minute intervals. At the 41-60 and 101-120 minute times post-procedure the SA were significantly slower to recover lung function compared to the NSA group. Only areas of significance are noted by brackets. B) Percent drop in FVC among controls, NSA, and SA patients in twenty minute intervals. At the 21-40 minute time post-procedure the SA group was significantly slower to recover lung function compared to the NSA. At the 101-120 minute time post-procedure the SA group was significantly slower to recover lung function compared to the control group and NSA group. At the 41-60 minute interval SA were significantly lower than the control group. Only areas of significance are noted by brackets. C) Change in FEV1/FVC ratio after bronchoscopy with no significant difference in any group at any time point.

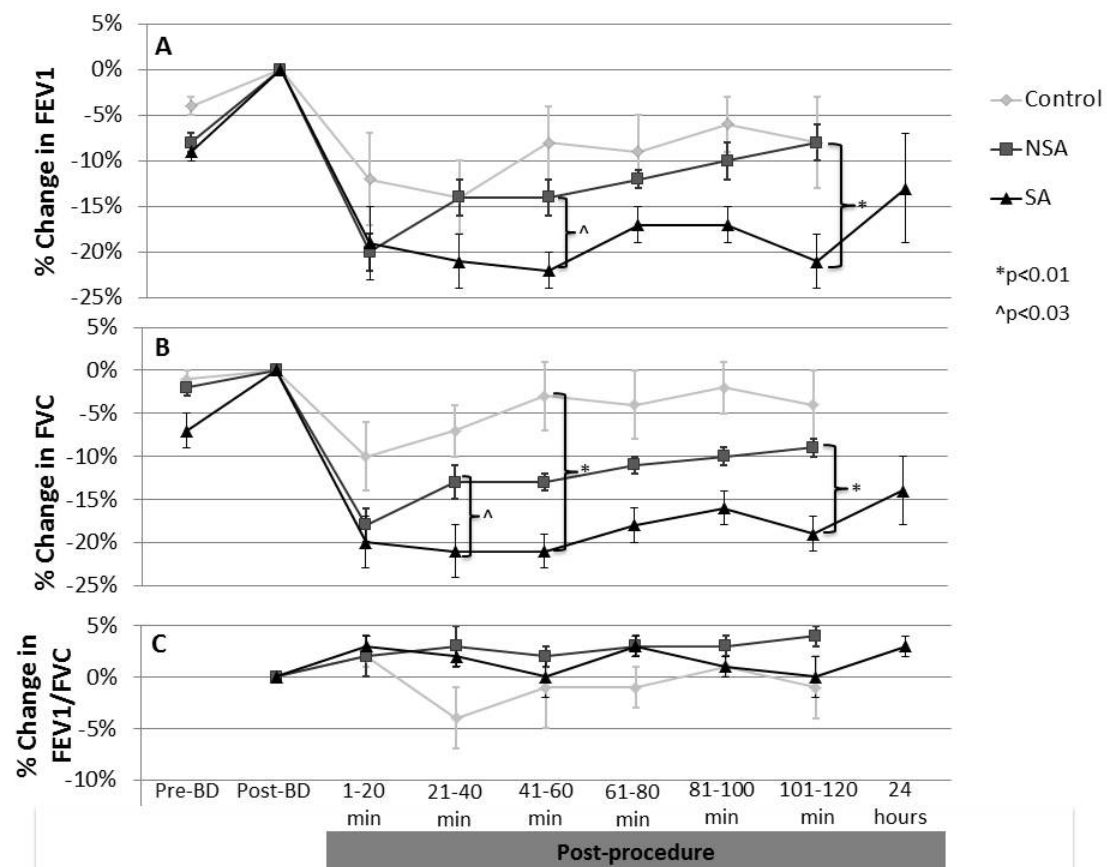
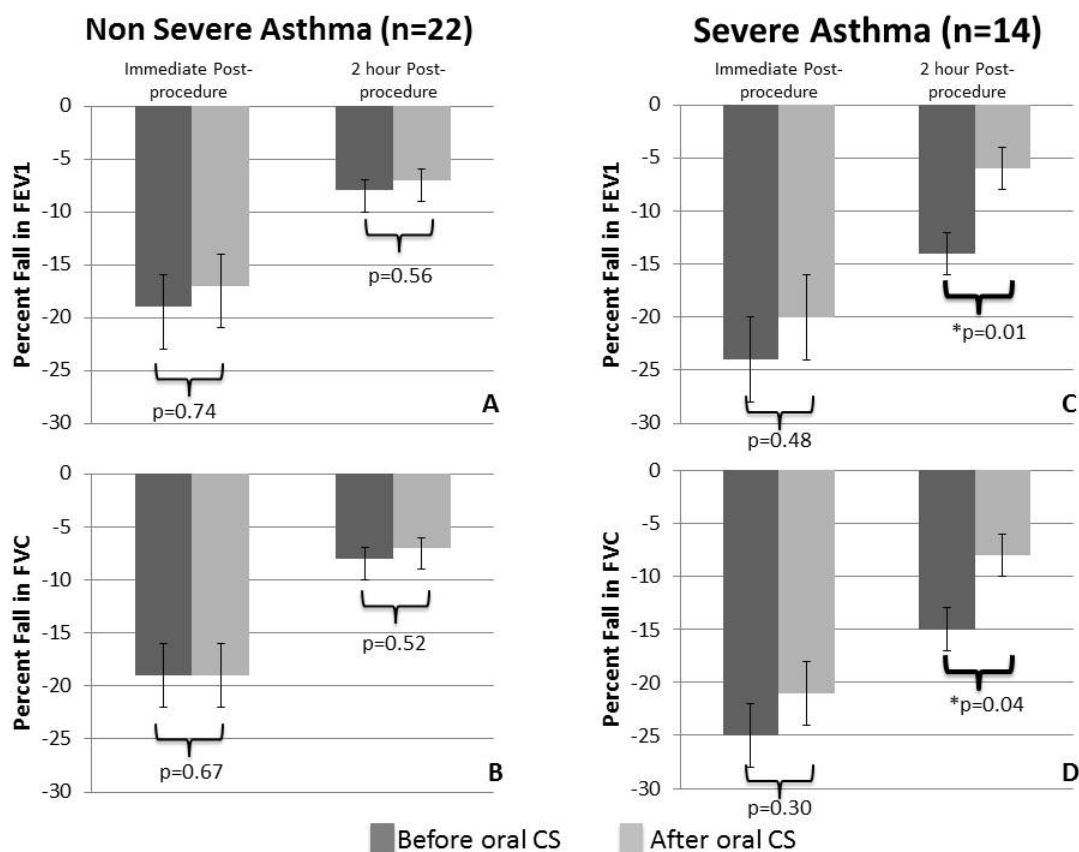


Figure 2. Changes in lung function in asthma patients undergoing two bronchoscopies: one without oral steroids pre-treatment and one later with steroid pre-treatment. Immediate post-procedure lung function is shown next to two-hour post-procedure lung function. A and B) Percent fall in FEV1 and FVC in non severe asthmatics before and after oral corticosteroids (CS). There was no statistically significant difference in the decline immediately post-procedure or two hours post-procedure. C and D) Percent fall in FEV1 and FVC in severe asthmatics before and after steroids. At the two-hour post-procedure time, patients on oral steroids had improved recovery in lung function.



	Control (n=12)	Nonsevere Asthma (n=56)	Severe Asthma (n=24)	Control vs Asthmatics p value	NSA vs SA p value
Age, mean (SD)	25 (5)	37 (10)	45 (9)	<0.01	<0.01
Female	8 (75%)	41 (73%)	14 (58%)	0.39	0.45
BMI, mean (SD)	26 (6)	32 (7)	32 (6)	<0.01	0.94
Ethnicity, % Caucasian	8 (75%)	28 (50%)	8 (33%)	0.12	0.22
Age Asthma Onset, mean (SD)	NA	15 (12)	22 (15)	NA	0.09
History of ER visits	NA	30 (59%)	18 (75%)	NA	0.15
History of Hospitalization	NA	18 (35%)	13 (54%)	NA	0.03
History of Intubation	NA	5 (10%)	9 (38%)	NA	0.03
Methacholine Challenge, PC20 (SD)	25 (7)	1 (5)	1 (2)	<0.01	NS
Medication Use at Enrollment*					
Short-acting beta agonist	0	55 (98%)	24 (100%)	NA	0.99
Inhaled corticosteroids	0	35 (63%)	24 (100%)	NA	<0.01
Long-acting beta agonist	0	32 (58%)	23 (96%)	NA	<0.01
Oral corticosteroids	0	0	1 (5%)	NA	0.13
Theophylline	0	0	1 (5%)	NA	0.11
Leukotriene receptor antagonist	0	9 (16%)	8 (33%)	NA	0.36
Anti-histamine	0	16 (29%)	6 (25%)	NA	0.71
Nasal steroids	0	2 (4%)	2 (17%)	NA	0.04
Proton pump inhibitor	0	2 (4%)	5 (21%)	NA	0.01
Opioids	0	1 (3%)	4 (15%)	NA	0.06

Table 1, Baseline Characteristics

NS, not significant, NA, not applicable, SD, standard deviation, BMI, body mass index, ER, emergency room, PC20, percent concentration causing a 20% decline in FEV1, NSA, nonsevere asthma, SA, severe asthma; *no patients were taking macrolides, benzodiazepines or inhaled anticholinergics

Table 2, Bronchoscopy Characteristics

	Control (n=12)	Nonsevere Asthma (n=56)	Severe Asthma (n=45)	Control vs Asthmatics p value	NSA vs SA p value
Duration in minutes, mean (SD)	25 (4)	23 (5)	25 (5)	0.46	0.28
Total lidocaine in mg, mean (SD)	402 (102)	442 (75)	422 (67)	0.37	0.87
Sedation					
Fentanyl (mcg)	90 (52)	128 (45)	116 (40)	<0.01	0.25
Versed (mg)	1.3 (1.1)	1.4 (1.1)	1.7 (1.5)	0.14	0.07
Change in LPM, mean (SD)	1 (1)	2 (2)	2 (2)	0.25	0.36
Decrease in SPO2, mean (SD)	4 (2)	5 (1)	5 (1)	0.95	0.81
Albuterol needed post-procedure	17%	30%	42%	0.18	0.23
BAL % Recovery (SD)	67% (11)	54% (16)	41% (18)	<0.01	0.03
BAL Eosinophils (SD)	0.1% (0.2)	0.8% (2.5%)	0.2% (0.5%)	0.34	0.68
BAL Neutrophils (SD)	1.6 % (0.9)	1.4% (1.6%)	2.7% (4.5%)	0.17	0.26
Baseline Spirometry on Day of Bronchoscopy					
FEV1% predicted, mean (SD)	99 (12)	89 (13)	74 (22)	<0.01	0.06
FVC % predicted, mean (SD)	100 (15)	97 (13)	81 (16)	<0.01	<0.01
FEV1/FVC, mean (SD)	0.85 (0.07)	0.76 (0.07)	0.72 (0.10)	<0.01	0.46
Post-Bronchodilator Spirometry					
Mean % Increase FEV1	4%	8%	11%	0.04	0.81
Mean % Increase FVC	0%	3%	6%	0.08	0.23

NS, not significant, SD, standard deviation, mcg, micrograms, mg, milligrams, vs, versus, SA,

severe asthma, NSA, nonsevere asthma, NA, not applicable

Table 3, Bronchoscopy Characteristics of Patients with Bronchoscopy Before and After Steroids

	Non Severe Asthma (n=22)			Severe Asthma (n=14)		
	1 st Bronchoscopy (before oral CS)	2 nd Bronchoscopy (after oral CS)	p value	1 st Bronchoscopy (before oral CS)	2 nd Bronchoscopy (after oral CS)	p value
Baseline Spirometry on Day of Bronchoscopy						
FEV1% predicted, mean (SD)	86 (13)	85 (13)	0.79	74 (23)	72 (23)	0.83
FVC % predicted, mean (SD)	95 (12)	93 (13)	0.50	82 (17)	80 (16)	0.74
FEV1/FVC, mean (SD)	0.74 (0.08)	0.75 (0.07)	0.72	0.72 (0.10)	0.72 (0.10)	0.97
Bronchoscopy Characteristics						
Duration in minutes, mean (SD)	254 (4)	22 (4)	0.72	25 (6)	26 (5)	0.75
Total lidocaine in mg, mean (SD)	432 (85)	473 (72)	0.18	419 (55)	414 (84)	0.87
Sedation						
Fentanyl (mcg)	126 (47)	123 (36)	0.82	112 (39)	116 (47)	0.78
Versed (mg)	1.1 (0.9)	1.3 (1.2)	0.72	1.8 (1.5)	1.7 (1.3)	0.84
Albuterol needed post- procedure	7 (32%)	6 (27%)	0.74	6 (50%)	6 (50%)	1.00
BAL % Recovery (SD)	56% (17)	60% (13)	0.43	37% (18)	43% (20)	0.43

Abbreviations: CS, corticosteroids, SD, standard deviation, mcg, micrograms, mg, milligrams,

BAL bronchoalveolar lavage