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Safety and Tolerability of Comprehensive Research Bronchoscopy in Chronic Obstructive Pulmonary Disease

Results from the SPIROMICS Bronchoscopy Substudy

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Abstract

Rationale: There is an unmet need to investigate the lower airways in chronic obstructive pulmonary disease (COPD) to define pathogenesis and to identify potential markers to accelerate therapeutic development. Although bronchoscopy is well established to sample airways in various conditions, a comprehensive COPD research protocol has yet to be published.

Objectives: To evaluate the safety and tolerability of a comprehensive research bronchoscopy procedure suitable for multicenter trials and to identify factors associated with adverse events.

Methods: We report the detailed methodology used to conduct the bronchoscopy used in SPIROMICS (the Subpopulations and Intermediate Outcome Measures in COPD Study). The protocol entailed collection of tongue scrapings and oral rinses as well as bronchoscopy with airway inspection, bronchoalveolar lavage (BAL), protected brushings, and endobronchial biopsies. Visual airway characteristics were graded on a scale of 0 (normal appearance) to 3 (severe abnormality) in four domains: erythema, edema, secretions, and friability. Adverse events were defined as events requiring intervention. Logistic regression modeling assessed associations between adverse event occurrence and key variables.

Results: We enrolled 215 participants. They were 61 ± 9 years old, 71% were white, 53% were male, and post-bronchodilator forced

expiratory volume in 1 second was 89 ± 19% predicted. Self-reported asthma was present in 22% of bronchoscopy participants. Oral samples were obtained in greater than or equal to 99% of participants. Airway characteristics were recorded in 99% and were most often characterized as free of edema (61.9%). Less than 50% reported secretions, friability, or erythema. BAL yielded 111 ± 57 ml (50%) of the 223 ± 65 ml of infusate, brushes were completed in 98%, and endobronchial biopsies were performed in 82% of procedures. Adverse events requiring intervention occurred in 14 (6.7%) of 208 bronchoscopies. In logistic regression models, female sex (risk ratio [RR], 1.10; 95% confidence interval [CI], 1.02–1.19), self-reported asthma (RR, 1.17; 95% CI, 1.02–1.34), bronchodilator reversibility (RR, 1.17; 95% CI, 1.04–1.32), COPD (RR, 1.10; 95% CI, 1.02–1.20), forced expiratory volume in 1 second (RR, 0.97; 95% CI, 0.95–0.99), and secretions (RR, 1.85; 1.08–3.16) or friability (RR, 1.64; 95% CI, 1.04–2.57) observed during bronchoscopy were associated with adverse events.

Conclusions: A research bronchoscopy procedure that includes oral sampling, BAL, endobronchial biopsy, and brushing can be safely performed. Airway characteristics during bronchoscopy, demographics, asthma or COPD, and lung function may convey increased risk for procedure-related events necessitating intervention.

Keywords: chronic obstructive pulmonary disease; bronchoscopy; methodology/protocol; safety

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Chronic obstructive pulmonary disease (COPD) is a chronic, heterogeneous disease characterized by progressive airflow limitation and altered inflammation. Previous estimates of worldwide COPD prevalence exceeded 174 million adults (1), although a recent nationally representative study estimated 100 million cases (mostly undiagnosed) in 2015 in China alone (2). In the absence of medical therapies proven to arrest disease progression, morbidity and mortality from COPD continue to increase (3). Thus, there is a critical unmet need to investigate the lower airways in COPD safely and accurately, both to improve understanding of pathogenesis and to identify potential surrogate biomarkers to accelerate therapeutic development.

Bronchoscopy is a well-established technique to sample airway disease (4–8). However, although clinically indicated bronchoscopy is performed routinely in individuals with COPD and research bronchoscopies are widely performed, a comprehensive research bronchoscopy protocol has not been published. We hypothesized that a comprehensive bronchoscopy procedure that entails tongue scraping, oral rinse, bronchoalveolar lavage (BAL), bronchial brushings, and endobronchial biopsies would be safe and well tolerated among individuals with COPD. We also hypothesized that findings present during bronchoscopy would be associated with developing an adverse event. We tested these hypotheses using the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) bronchoscopy substudy.

Methods

Bronchoscopy Substudy Design

The study design of SPIROMICS has been published (9). SPIROMICS and its bronchoscopy substudy were approved by the institutional review boards at all participating medical centers. Enrolled SPIROMICS subjects were eligible if they provided additional informed consent to undergo research bronchoscopy and met local site requirements for a bronchoscopy (e.g., any laboratory tests that were required by institutional policy to be administered before a bronchoscopy). Participants were excluded for any of the following conditions: age older than 80 years old, history of cardiac disease or other comorbid condition severe enough to increase risks significantly based on investigator discretion (including known allergies or intolerance to medications required to conduct the procedure), arterial oxygen pressure less than 60 mm Hg or arterial oxygen saturation less than 88% on room air that qualified them for supplementary oxygen at rest, post-bronchodilator forced expiratory volume in 1 second (FEV₁) less than 30% predicted, or the use of warfarin or clopidogrel. Participants with self-reported cardiovascular disease were allowed to participate; however, acute cardiac events (acute myocardial infarction, angina, coronary artery bypass surgery, balloon angioplasty, percutaneous coronary intervention, carotid revascularization, uncontrolled hypertension, or stroke/transient ischemic attack) within the previous 6 months would be typical

causes for exclusion. To ensure sufficient sizes of control groups for analysis, our enrollment strategy oversampled nonsmoking healthy control individuals and smokers with preserved lung function. Anticipated enrollment goals were 60 nonsmokers (<1 pack-year of tobacco; prebronchodilator FEV₁/forced vital capacity [FVC], >0.70; and FVC greater than the lower limit of normal), 100 smokers with normal lung function (≥20 pack-years of tobacco; post-bronchodilator FEV₁/FVC, >0.70; and FVC greater than the lower limit of normal), 120 individuals with mild/moderate COPD (≥20 pack-years of tobacco; post-bronchodilator FEV₁/FVC, <0.70; FEV₁, ≥50% predicted), and 20 individuals with severe COPD (≥20 pack-years of tobacco; post-bronchodilator FEV₁/FVC, <0.70; FEV₁, <50% predicted but >30% predicted).

Bronchoscopy Setup

All participating study centers underwent a training and oversight meeting. Bronchoscopists and technicians attended an in-person training session that reviewed the study protocol, outlined safety procedures, and instructed the research team on all aspects of specimen collection as well as sample handling. Technicians were certified in specimen processing. The first five bronchoscopies completed at each site were performed in subjects with a post-bronchodilator FEV₁ greater than 50% predicted. The data from these were reviewed by an oversight committee before the site was granted authorization to continue to recruit participants for

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Author Contributions: J.M.W.: had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the analysis; P.G.W.: chaired the bronchoscopy committee that developed the original protocol, together with committee members (R.J.K., E.K., W.C.M., J.L.C.); J.M.W. and J.L.C.: contributed to the conception and design of the statistical analysis; J.M.W., D.A.A., I.B., R.P.B., D.J.C., E.K., R.J.K., W.C.M., and P.G.W.: contributed to the acquisition of the data; and J.M.W. and J.L.C.: contributed to the drafting of the manuscript. All authors contributed to revisions of the manuscript for critically important intellectual content and approved the version of the manuscript to be published.

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additional bronchoscopies. The oversight committee reviewed all adverse events during the study.

At an initial visit before bronchoscopy, we confirmed eligibility, discussed the rationale and risks of the procedure, obtained informed consent, and performed a targeted history and physical examination by a physician. That visit also included a blood draw for safety laboratory testing as required by the individual medical centers, as well as collection of an induced sputum specimen, which was processed entirely for flow cytometric analysis (10).

For the bronchoscopy visit, approximately 2–4 weeks later, participants were instructed to fast for at least 8 hours before the procedure and to have an adult available to accompany them home. For sample collection, we prepared upper airway anesthesia solutions containing 1%, 2%, or 4% lidocaine using center-specific protocols. Total lidocaine dosing for the procedure was limited to 600 mg or 9 mg/kg, whichever was less (11, 12). For use as a BAL solution, a 500-ml bag of 0.9% sodium chloride was prewarmed to 37°C in a distilled water bath and subsequently administered using 60-ml syringes. Specimen traps were placed on ice. Endobronchial biopsies were performed using Olympus FB-231D.A forceps. Disposable microbiology brushes (catalog no. 130; ConMed) and cytological brushings (catalog no. 149; ConMed) were used for sample collection for microbiome and cytological analysis, respectively.

Oral and Tongue Specimen Collection

Vital signs were performed, followed by optional FEV₁ measurement before and 15 minutes after delivering four puffs of albuterol to confirm FEV₁ greater than 30% predicted. Before upper airway anesthesia, the tongue was scraped six times to accumulate debris on the curette and then swirled in a specimen container as part of a sample for microbiome analysis. This process was repeated two additional times. The oral rinse procedure consisted of having the participant gargle 10 ml of sterile 0.9% sodium chloride for 20 seconds, followed by swishing in the mouth for 5 seconds and then spitting into the same specimen container used to collect tongue scrapings.

Bronchoscopy Procedure

After collection of oral samples, we initiated upper airway anesthesia using lidocaine.

Sedatives/anxiolytics, including fentanyl and midazolam, were given intravenously in small incremental doses as needed to achieve moderate sedation according to local policies and procedures. The use of supplemental oxygen and selection of the route of nasal versus oral entry were done in accordance to local policies and procedures. After the bronchoscope was introduced into the airways and passed the vocal cords, we performed a full airway inspection while providing lower airway topical anesthesia using lidocaine before any sample collection. During the airway inspection, we graded overall airway appearance using a prespecified scoring system (Table 1) based on bronchitis scoring (13).

After airway inspection, we collected three protected brush specimens in a lower lobe bronchus. We then performed two separate washes/BALs in adjacent lung segments (with preference for the right middle lobe or lingula) using the same sequence of instillations of 0.9% sodium chloride and gentle manual (hand) suction by syringe to obtain lavage fluid. Wall suction was not used. The first 20-ml aliquot (which could be repeated once if no return) was considered the bronchial washing. It was followed by BAL performed in the same location using 40-ml aliquots twice, then a single 50-ml aliquot. However, the 50-ml lavage was not performed if the combined volume from the 20-ml wash and the two 40-ml BALs were less than 15 ml. A second wash/BAL was performed in an adjacent lung segment in the same lobe using the same protocol for all participants, independent of BAL return from the initial lavage. Thus, the targeted total instilled volume of saline was 300 ml (with a theoretical maximum of 340 ml if both 20-ml wash maneuvers needed to be repeated), a larger amount than most commonly used in subjects with COPD (14). The two separate bronchial washes were pooled into a single aliquot, and the two BAL specimens were pooled into specifically designated lidocaine-free specimen traps on ice.

Next, three cytological brushes were deployed serially in the ipsilateral lower lobe bronchi at the segmental or subsegmental carina. These brushes were processed immediately by a technician in the bronchoscopy suite. Finally, eight endobronchial biopsies were performed from the second- through fifth-order

Table 1. Observations during airway inspection

Characteristic	Score
Erythema	
Normal	0
Light red	1
Red	2
Beefy red	3
Edema	
Normal airway	0
Blunting of bifurcations	1
Airway narrowing	2
Airway occluded	3
Secretions	
Normal	0
Strands of clear mucus	1
Globules of mucus	2
Airway occluded	3
Friability	
Normal	0
Punctate submucosal hemorrhages	1
Linear submucosal hemorrhages	2
Frank bleeding	3

carinae in the contralateral lung, beginning in the lower lobe and proceeding proximally. Sample collection could be stopped at any point at the discretion of the bronchoscopist, based on the research participant's tolerance of the procedure.

Sample Processing

A schematic for the entire procedure, including sample processing, is shown in Figure E1 in the online supplement. For microbiome analysis, we first reserved a 4.5-ml aliquot of the neat wash and BAL specimens, which were frozen and shipped to the SPIROMICS Genomics and Informatics Core (GIC) at the University of North Carolina. Next, a trained technician performed a hemocytometric cell count, which was used to adjust the sample volumes for further processing. Aliquots of BAL and washings were reserved for cytocentrifugation to prepare differential cells counts (15). Portions of the BAL sample were reserved for isolation of alveolar macrophages by adherence, which were shipped to the GIC for RNA isolation and for immunophenotyping as previously reported (10). Airway brushes were frozen and shipped to the GIC for RNA isolation and for microbiome analysis. Each brush tip was placed into a tube containing RNase-free phosphate-buffered saline on ice. To free cells from the brush, these tubes were vortexed on a low setting, followed by

pooling of the cells from all three brushes and measurement of total and differential cell counts using 200 μ l of sample. The remainder of the pooled sample was centrifuged, and the cell lysates were prepared for RNA isolation using QIAzol lysis reagent (QIAGEN). Biopsies were allotted as follows: 1, snap frozen; 2–5, formalin; 6, snap frozen; and 7–8, formalin. The snap-frozen samples were placed immediately into liquid nitrogen in the bronchoscopy suite and were later homogenized using QIAzol lysis reagent. The fixed samples were subsequently processed for formalin fixation and paraffin embedding and used in histologic evaluation.

Assessment for Adverse Events

All participants were monitored for at least 2 hours after administration of sedation. Vital sign measurement was performed every 15 minutes for the first hour and every 30 minutes thereafter until discharge. We measured FEV₁ between 1.5 and 2 hours after bronchoscopy. If post-procedure FEV₁ was less than 90% of the preprocedure, prebronchodilator FEV₁, then two to four puffs of albuterol were administered, and spirometry was repeated. If the FEV₁ remained more than 10% lower than the preprocedure FEV₁, this was considered a significant FEV₁ decline, and the investigator was alerted to consider therapy. In addition, the following discharge criteria were assessed during the 2-hour post-procedure recovery period: 1) able to sip water without coughing, 2) heart rate less than 100 beats/minute, 3) FEV₁ greater than 90% of preprocedure FEV₁, 4) able to ambulate without difficulty, and 5) no apparent distress. If the participant fulfilled all of these criteria, they were discharged. At the time of discharge, all participants were given instructions to contact the on-call providers for rigors, purulent sputum production, hemoptysis, or dyspnea not promptly relieved by albuterol. All participants were contacted via telephone the day after bronchoscopy. We prospectively defined clinically relevant adverse events as adverse events that required the following interventions: pharmacologic treatment (i.e., administration of bronchodilators, antibiotics, and/or corticosteroids), a new supplemental oxygen therapy requirement after bronchoscopy, or hospitalization for any reason.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation or the number of observations and relative frequency (percent) for continuous or categorical variables, respectively. Bivariate analyses were conducted by using unpaired *t* tests for continuous variables and chi-square test for categorical variables for adverse events. To determine associations between factors and development of an adverse event requiring intervention, we performed logistic regression modeling to calculate risk ratios representing the risk of an adverse event related to exposure variables. A *P* value less than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics version 23 software (IBM).

Results

Participants

We enrolled 215 participants (72% of goal of *N* = 300) in the bronchoscopy substudy, including 27 nonsmokers, 91 smokers with normal lung function, 89 individuals with mild/moderate COPD, and 8 individuals with severe COPD. Participants were 61 $\pm$ 9 years old, 71% were white, and 53% were male, and post-bronchodilator FEV₁ was 89 $\pm$ 19% predicted. As compared with the SPIROMICS cohort as a whole (15), participants in the bronchoscopy substudy were younger and had higher FEV₁ percent predicted. Race- and sex-based demographics were similar. Any history of asthma was self-reported in 22% of the cohort; other comorbidities and clinical features are detailed in Tables 2 and E1.

Bronchoscopy Findings

Samples for microbiome analysis were obtained from the tongue in 212 of 213 subjects (>99%) and from oral rinse in 212 of 214 subjects (99%). Data were missing for tongue sampling in two participants and for oral rinse in one participant. Participants received an average 289 $\pm$ 224 mg of lidocaine, corresponding to 2.7 $\pm$ 2.8 mg/kg lidocaine for the procedure. Airways were fully inspected and characteristics were recorded in all but three participants (owing to missing data). Airways were typically characterized as free of edema (61.9%) and of secretions (43.7%); they were frequently nonfriable (47.4%) but frequently had light red erythema (49.3%) (Table 3). Of the most

severe classifications of the four reported airway features, airway edema causing airway narrowing (7%) and friability characterized by frank bleeding (7.4%) were the most often reported.

As per the protocol recommendations, bronchial washing and BAL were performed in the right middle lobe or lingula in 91% of the cases, with the remaining 9% occurring in the upper or lower lobe. For the bronchial washings, an average of 47.9 $\pm$ 20.7 ml was infused with an average return of 13.8 $\pm$ 10.3 ml. For the BAL, bronchoscopists delivered a mean 223 $\pm$ 65 ml of saline and withdrew 111 $\pm$ 57 ml (50%) BAL return. The resultant cell counts for the washes and BALs are shown in Table 3. Protected brushes were completed in 211 of 215 (98%) bronchoscopies. Of the 204 individuals who underwent endobronchial biopsy, 168 (82%) successfully had the requisite eight biopsies performed.

Adverse Events

The research bronchoscopy was generally well tolerated (Table 4). Approximately 13% of participants had a decline in FEV₁ to less than 90% of the preprocedure value, but such spirometric changes were predominantly self-limited or asymptomatic. As compared with participants with a post-procedure FEV₁ greater than 90% of baseline, those with a fall in FEV₁ to less than 90% had similar rates of intervention (13% vs. 6%; *P* = 0.22). Nearly one-third (31.8%) of participants initially failed to meet at least one prespecified discharge criterion, although there was no increased frequency of intervention in this group compared with the individuals who fulfilled all discharge criteria (9.3% vs. 6.0%; *P* = 0.45).

Adverse events requiring intervention occurred in 14 of 208 (6.7%) of bronchoscopies. These included wheezing, dyspnea, cough, bronchospasm, epistaxis, reduced FEV₁, dizziness, bleeding postbiopsy, and nausea. Three of these events required hospitalization, including one for pneumothorax and two for decline in respiratory status. No participants in this study developed signs and symptoms concerning for lidocaine toxicity, needed reversal agents for anesthesia, or required intravenous fluid boluses for hypotension. Not surprisingly, adverse events were more common in participants with COPD (defined as FEV₁/FVC <0.7) than in those without COPD (11.8% vs. 2.6%; *P* = 0.008).

Table 2. Baseline characteristics

	Cohort (N = 215)
Age, yr	61 ± 9
White race	152/220 (71%)
Male sex	114 (53%)
Height, cm	170 ± 9
Weight, kg	83 ± 17
BMI, kg/m ²	28.4 ± 4.8
Pre-BD FEV ₁ , L	2.22 ± 0.75
Post-BD FEV ₁ , L	2.33 ± 0.75
Post-BD FEV ₁ , % predicted	89 ± 19
Post-BD FVC, % predicted	99 ± 14
Post-BD FEV ₁ /FVC	0.88 ± 0.16
Bronchodilator reversibility	62/215 (29%)
Chronic bronchitis (SGRQ)	69/200 (35%)
LAA ₋₉₅₀ , %	3.5 ± 4.8
Asthma	47 (22%)
Current smoker	73/190 (38%)
Pack-year history	42 ± 31
Cardiovascular condition	115/209 (55%)
Gastrointestinal condition	94/211 (45%)
Pulmonary vascular condition	28/209 (13%)
Psychiatric condition	77/211 (36%)
Sleep apnea	30/203 (14%)
Stratum	
1	27 (12.6%)
2	91 (42.3%)
3	89 (41.4%)
4	8 (3.7%)
GOLD stage	
N/A	27 (12.6%)
0	90 (41.9%)
1	39 (18.1%)
2	50 (23.3%)
3	9 (4.2%)
4	0 (0%)
Oxygen saturation, %	97 ± 2

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA = low-attenuation area; N/A = not applicable (non-COPD); SGRQ = St. George's Respiratory Questionnaire; Stratum 1 = <1 pack-year of tobacco, prebronchodilator FEV₁/FVC >0.70, and FVC greater than the lower limit of normal; Stratum 2 = ≥20 pack-years of tobacco, post-bronchodilator FEV₁/FVC >0.70, and FVC greater than the lower limit of normal; Stratum 3 = ≥20 pack-years of tobacco, post-bronchodilator FEV₁/FVC <0.70, and FEV₁ ≥50% predicted; Stratum 4 = ≥20 pack-years of tobacco, post-bronchodilator FEV₁/FVC <0.70, and FEV₁ <50% predicted but >30% predicted. Data are expressed as mean ± standard deviation or number (percent).

We used logistic regression models to identify demographic, clinical, physiologic, and bronchoscopic features that were associated with developing an adverse event requiring intervention. In logistic regression models, seven variables were significantly associated with that outcome: female sex, preprocedure FEV₁ percent predicted, COPD, self-reported asthma, bronchodilator reversibility, and observed lower respiratory tract secretions and friability as shown in Table 5. Tables E2 and E3 include data specific to the subgroup of participants with COPD.

Discussion

The results of this bronchoscopy substudy, one of the largest (N = 215) multicenter trials of research bronchoscopy reported to date in smokers and control individuals, confirm the feasibility and safety of comprehensive investigational bronchoscopy in participants with mild to moderate COPD. Nearly all participants in our study were able to undergo all components of our detailed protocol. The rate of complications requiring intervention was similar to that previously reported, and

hospitalization after this procedure was very infrequent (<1%). In logistic regression models, we found that female sex, self-reported asthma history, COPD, preprocedure FEV₁, bronchodilator reversibility, and bronchial secretions and friability observed during bronchoscopy were associated with clinically significant adverse events that required intervention. These findings support the use of investigational bronchoscopy as one component of a multipronged approach to defining COPD pathogenesis through acquiring samples used to identify intermediate biomarkers of disease progression and activity.

Bronchoscopy performed solely for investigation, and not for clinically indicated reasons, is an invasive procedure that provides unique information unavailable by other means. For many years, BAL has been the procedure of choice to evaluate immunologic and inflammatory processes, oxidative stress, and infectious processes in the lower respiratory tract (16–22). More recently, it has become widely used for proteomic, genomic, and metabolomic analyses (15, 23–26), and its reliability as a sample for microbiome analysis was recently validated by comparison with protected specimen brushings (27). The initial paper describing results of immunophenotyping from the SPIROMICS bronchoscopy substudy disclosed alveolar space eosinophilia in active smokers with airflow obstruction that was not detectable by analysis of peripheral blood or induced sputum (28), an example of the importance of compartmentalization of pulmonary inflammatory and immune responses. Airway brushings and endobronchial biopsies extend the information available from bronchoscopy by sampling epithelial and parenchymal cells in addition to leukocytes (29, 30). Because endobronchial biopsies maintain the architecture of the airways, these modalities permit evaluation of the structural changes occurring in COPD. An important advantage of the SPIROMICS bronchoscopy substudy is the ability to integrate its findings with a wealth of data collected on the entire cohort (25, 31), potentially paving the way for eventual substitution of less invasive biomarkers.

In this regard, the SPIROMICS bronchoscopy substudy complements other initiatives of the National Heart, Lung, and Blood Institute to provide lower airway samples for multi-omics analysis as an

Table 3. Bronchoscopy procedures and findings

	Cohort (N = 215)
Erythema	
Normal	81 (37.7%)
Light red	106 (49.3%)
Red	20 (9.3%)
Beefy red	5 (2.3%)
Edema	
Normal	133 (61.9%)
Blunting of airways	64 (29.8%)
Airway narrowing	15 (7.0%)
Secretions	
Normal	94 (43.7%)
Strands of clear mucus	89 (41.4%)
Globules of mucus	24 (11.2%)
Airways occluded	5 (2.3%)
Friability	
Normal	102 (47.4%)
Punctate submucosal hemorrhages	73 (34.0%)
Linear submucosal hemorrhages	21 (9.8%)
Frank bleeding	16 (7.4%)
Diagnostic Characteristics	
BAL cell count, $\times 10^4$ cells/ml	4,530 $\pm$ 10,596
Brush cell count, $\times 10^4$ cells/ml	237 $\pm$ 258
Biopsied participants	(n = 204)
Endobronchial biopsy number	
0	5 (2.5%)
3	4 (2.0%)
4	3 (1.5%)
5	7 (3.4%)
6	6 (2.9%)
7	11 (5.4%)
8	168 (82.4%)

Definition of abbreviation: BAL = bronchoalveolar lavage.

Data expressed as mean $\pm$ standard deviation or number (percent).

efficient means to bridge gaps to development of personalized therapies. SPIROMICS recently completed its first phase and is now preparing for return study visits at 5–7 years of follow-up, including state-of-the-art microbiome analysis that

was informed by the earlier Lung HIV Microbiome Project (32). Compared with the Lung HIV Microbiome Project, the availability of inspiratory–expiratory computed tomographic imaging of the chest at several lung volumes provides very

considerable opportunities to link molecular and lung structural outcomes (33–35). Integration of lung microbiome results, derived in part from research bronchoscopies, with multiple other data types, including thoracic computed tomography, is also a central goal of the recently completed GRADS (Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis Study) cohorts (7, 8).

Although others have reported adverse event outcomes related to procedural components included in our approach (14), none have evaluated the association between adverse outcomes and the comprehensive techniques included in a single research bronchoscopy. As understanding of the complex nature of molecular pathways implicated in COPD pathogenesis and progression increases, having a proven method to acquire a diverse array of samples using a single procedure is of paramount importance.

Adverse outcomes after bronchoscopy in patients with COPD for clinical indications occur in 4–10% of cases, depending on the study methodology and definitions of complications used (14, 36–39). For example, a Swiss study evaluating the use of moderate sedation in 1,092 patients observed complication rates of 9.2% (insertion of an oropharyngeal or nasal airway), 5.9% (minor bleeding), and less than 1% for intubation, pneumothorax, and transfer to an intensive care unit (38), respectively, similar to our observed frequency of clinically significant adverse events. Bellinger and colleagues conducted a single-center study of 258 individuals with and without a diagnosis of COPD (37). They found that 13% of patients developed a minor complication (bronchospasm, minor desaturation, early procedure termination, minor hemoptysis, hypotension, and medication reactions) and 5% experienced a major complication (bronchospasm, respiratory failure, pneumothorax, or hospitalization), higher than our current experience. Compared with our study, Bellinger and colleagues observed a lower frequency of bronchial brushings (~30%) and endobronchial biopsies (~9%) based on the clinical nature of their study. Finally, in a study of patients with COPD and severe airflow obstruction undergoing navigational bronchoscopy for clinical indications, 8.3% developed complications (39). One striking finding of these studies that contrasted with ours is that lung function was not predictive

Table 4. Adverse events

	Cohort (N = 215)
FEV ₁ <90% baseline	23/172 (13.4%)
Failed to meet at least one prespecified discharge criterion	54/215 (25.1%)
Chest discomfort	52/204 (25.5%)
Not alert and responsive	3/205 (1.5%)
Not oriented to person, place, and time	3/204 (1.5%)
Tachycardia (pulse >100 beats/min)	3/204 (1.5%)
Difficulty ambulating	4/204 (2.0%)
Cough/difficulty with sipping water	8/191 (4.2%)
Adverse event that required intervention	14/208 (6.7%)
Admission overnight for observation post-bronchoscopy	3/204 (1.5%)

Definition of abbreviation: FEV₁ = forced expiratory volume in 1 second.

Data expressed as number (percent).

Table 5. Factors associated with adverse event development during bronchoscopy that required intervention

	RR*	95% CI	P Value
Age, yr	0.99	0.93–1.05	0.7
White race	1.08	1.02–1.15	0.01
Female sex	1.10	1.02–1.19	0.02
BMI, kg/m ²	1.05	0.96–1.17	0.3
Obesity (BMI, ≥30 kg/m ²)	1.05	0.97–1.14	0.2
Preprocedure post-BD FEV ₁ , % predicted	0.97	0.95–0.99	0.03
Bronchodilator reversibility	1.17	1.04–1.32	0.009
Oxygen saturation, %	0.91	0.75–1.11	0.4
Chronic bronchitis (SGRQ)	1.00	0.93–1.08	0.9
COPD	1.10	1.02–1.20	0.02
Asthma	1.17	1.02–1.34	0.03
Current smoker	1.02	0.93–1.11	0.7
Pack-year history	1.00	0.99–1.02	0.6
CV condition	0.97	0.89–1.04	0.4
GI condition	1.04	0.96–1.13	0.3
Pulmonary vascular condition	1.01	0.90–1.14	0.8
Sleep apnea	1.00	0.90–1.11	0.9
LAA ₋₉₅₀ , %	1.02	0.92–1.12	0.7
Erythema	1.79	0.91–3.53	0.09
Edema	1.87	0.94–3.71	0.08
Secretions	1.85	1.08–3.16	0.02
Friability	1.64	1.04–2.57	0.03

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease defined as post-bronchodilator FEV₁/FVC <0.70; CV = cardiovascular; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GI = gastrointestinal; LAA = low-attenuation area; RR = risk ratio; SGRQ = St. George's Respiratory Questionnaire.

*Univariate logistic regression analysis.

of adverse outcomes (40). This observation may be biased by study design because we did not include individuals with COPD with an FEV₁ less than 30% predicted or those with comorbid chronic hypoxemic or hypercapnic respiratory failure, and thus our study was prone to including participants that were healthy enough to undergo the procedure.

By contrast, the frequency of adverse events after investigational BAL and endobronchial biopsy in an asthmatic population was 12.5% (41), higher than what we observed. In the Severe Asthma Research Program, individuals with asthma underwent a comprehensive bronchoscopy procedure that entailed BAL, endobronchial biopsy, and brushings (4). Although the rate of events requiring hospitalization (~2%) in

the Severe Asthma Research Program was similar to that in our study, events requiring interventions (prescription of antibiotics and/or corticosteroids) occurred in approximately 14%, a much higher rate than in our COPD population. Importantly, both self-reported asthma and bronchodilator reversibility were associated with developing a clinically relevant complication in our cohort. Somewhat surprisingly, we observed an association between female sex and adverse events. Although not previously reported for COPD (37, 39), this link has been described for research bronchoscopies in critically ill patients (42) and warrants further investigation.

Strengths of our study include the novel procedural design that includes upper and lower airway sample collection and the

multicenter nature of SPIROMICS. These features allow for the application of the protocol to future studies and in other centers investigating COPD and other respiratory disorders. Our study is limited by several factors. First, we did not achieve our enrollment goal. However, we were able to recruit a substantial proportion of the target for each category (never smoker, smoker, and mild/moderate COPD) and to collect adequate specimens in more than 95% of attempts, minimizing the effects of incomplete enrollment. For reasons of safety, we deliberately had minimal representation of participants with severe COPD. However, sample collection in control and mild to moderate COPD allowed for analysis of processes that may play a role in the development of COPD but that also could be targeted before patients develop very severe airflow limitation.

Another important limitation was the lack of data on doses or types of medication used for sedation or the use of anesthesiologists in the procedure. Despite this limitation, no participants in our study required reversal agents indicative of sedation-related complications. In addition, we did not capture data on the route of bronchoscopy use (oral vs. nasal) and thus cannot comment on that technical aspect and outcomes. Finally, our analysis of risks for complications was also limited by the overall low rate of adverse events that required treatment, which reduces the power of our regression analyses and increases the risk for errors related to multiple testing.

In summary, we describe a research bronchoscopy procedure that provides multiple samples for diverse analyses. The presence of bronchial secretions or friability observed during the procedure, in addition to FEV₁, COPD, self-reported asthma, bronchodilator reversibility, or female sex, predicted outcomes necessitating treatment. Our protocol was generally well tolerated and could safely be performed in the outpatient setting. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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