Assessment of Continuous Positive Airway Pressure Therapy in OSA and ILD

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BACKGROUND

Study Purpose and Rationale

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease of the peripheral lung parenchyma that affects 0.5% of older adults in the U.S. and confers a median survival of only 3.8 years.[1-3] While pirfenidone and nintedanib slow disease progression, neither drug reverses fibrosis nor prevents ongoing subclinical alveolar epithelial cell (AEC) injury, the antecedent cause of fibrosis in IPF.[4,5] We and others have shown that subclinical AEC injury as well as extracellular matrix (ECM) remodeling are also detectable using serum biomarkers, including increases in surfactant protein-D (SP-D), Krebs von den Lungen-6 (KL-6), and MMP-7 (a marker of AEC injury and ECM remodeling). Each of these biomarkers is also elevated in IPF and other fibrotic ILDs.[6-11] We and others have found that obstructive sleep apnea (OSA), a condition that is highly prevalent in adults with fibrotic interstitial lung diseases, including IPF, is also associated with increases in serum KL-6, SP-A and MMP-7, and with angiopoietin-2 (Ang-2; an endothelial marker), and that OSA is associated with subclinical ILD on CT.[12-15] These data support (1) the use of serum biomarkers to detect subclinical AEC injury and ECM remodeling, and (2) the hypothesis that OSA may contribute to subclinical AEC injury. Based on these data, our central hypothesis is that moderate-to-severe obstructive sleep apnea causes subclinical AEC injury and, in susceptible individuals, peripheral lung fibrosis and fibrotic ILD.[16] OSA might lead to AEC injury and ECM remodeling by exerting peripheral stretch of the lung, which has been hypothesized to be an underlying cause of IPF and other fibrotic ILDs.[12,13] Obstructive apneas and hypopneas are characterized by repetitive forceful inspiratory efforts against a completely or partially closed airway.[17] This causes wide swings in pleural pressure exerting peripheral tractional stress on the lung, potentially causing stretch and injury to AECs analogous to that which occurs during positive pressure ventilation.[18-20] Other mechanisms linking OSA and subclinical AEC injury are possible, including promotion of oxidative injury by intermittent hypoxia and microaspiration from gastroesophageal reflux disease (GERD).[21,22] We propose to leverage the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep Study, a community-based cross-sectional study, the HeartBEAT and BestAIR randomized clinical trials of CPAP for OSA, and an inception cohort of ILD patients diagnosed with OSA. We propose to establish OSA as a modifiable contributor to AEC and endothelial injury and thereby provide

sufficient evidence to support a large-scale clinical trial testing whether CPAP improves clinical outcomes in IPF. This will be achieved through three Specific Aims:

Specific Aim 1: Determine whether greater OSA severity is associated with higher levels of serum biomarkers of AEC and endothelial injury and ECM remodeling in community dwelling adults.

Specific Aim 2: Determine whether CPAP use is associated with reductions in AEC and endothelial injury and ECM remodeling biomarkers in adults with moderate-to-severe OSA. Using stored serum samples from the HeartBEAT and BestAIR trials, we will assess serum MMP-7, SP-D, SP-A, and Ang-2 levels in adults with moderate-to-severe OSA after randomly allocated CPAP or no-CPAP. We hypothesized that CPAP use will be associated with reductions in these biomarkers. This hypothesis has been proven incorrect. Contrary to our hypothesis, the levels of four biomarkers of lung inflammation and extracellular remodeling were not reduced by CPAP in patients with OSA. Indeed, CPAP therapy was associated with an increased circulating level of Ang-2, an endothelial growth factor that is released from pulmonary endothelial cells in the setting of acute lung injury. This finding raises the possibility that CPAP, by increasing alveolar distension, may exacerbate processes that contribute to lung inflammation in OSA.

Original Specific Aim 3: 1) Determine whether untreated OSA promotes AEC and endothelial injury and ECM remodeling biomarkers in adults with ILD and OSA compared with those without OSA; 2) Determine prospectively whether clinically-initiated 4-week PAP therapy increases markers of alveolar endothelial lung injury in OSA.

The results of **Aim 2** analysis indicating potential harm associated with CPAP therapy in OSA necessitated revision of the original aim 3. The **revised Aim 3** is: a) to determine prospectively whether clinically-initiated 4-week PAP therapy increases markers of alveolar endothelial lung injury in OSA; b) to determine whether untreated OSA promotes AEC and endothelial injury and ECM remodeling biomarkers in adults with ILD and OSA compared with those without OSA. Rationale behind revision of Aim 3: Considering that CPAP unexpectedly increased a marker of alveolar endothelial injury in OSA patients without known ILD, we think it is essential to

validate these findings in a prospective cohort and to document prospectively whether untreated OSA worsens existing lung injury in patients with concomitant ILD. We will use a two-pronged approach to address this question: 1) We plan to recruit prospectively additional 78 patients with untreated moderate-to-severe OSA and assess the above biomarkers of alveolar endothelial injury before and after 4 weeks of clinically-initiated PAP therapy (not randomly allocated owing to the well-recognized societal hazard posed by untreated OSA patients with daytime somnolence). Using the effect size and SD estimates from the HeartBEAT and BestAir samples, a sample of 78 patients will provide 80% power to detect an effect of the size that we observed in **Aim 2** with a(2) = 0.05; 2) We will recruit all participants as planned for **Aim 3** (anticipated 100 patients with ILD and concomitant OSA and 65 patients with ILD who do not have OSA) and compare their baseline levels of alveolar epithelial and endothelial injury biomarkers. This approach is crucial to establish whether patients with concomitant ILD and OSA have a greater degree of alveolar endothelial injury compared with ILD patients without OSA. If OSA turns out not to contribute independently to alveolar endothelial injury, this information would also be valuable considering that PAP may worsen existing alveolar endothelial injury in ILD patients, which suggest that alternative treatments for OSA that do not increase alveolar distension (for example, oral appliances) may be particularly suitable for patients with concomitant ILD and OSA. After validating our findings from Aim 2 as described above, we will explore in future studies whether oral appliances lower markers of AEC and endothelial injury in ILD patients with OSA.

Study Design

Aim 1: Determine whether the greater OSA severity is associated with higher levels of serum biomarkers of AEC and endothelial injury and ECM remodeling in community dwelling adults. We will perform cross-sectional analyses in this Aim.

Sampling frame and participants: We will sample participants from the MESA Sleep Study. We will sample the 1,830 MESA Sleep study participants who have available polysomnography data and no self-reported lung disease. We realize that a small proportion of participants will have missing or low-quality samples.

Measurement of exposures: The primary exposure of interest will be the obstructive AHI, defined as the number of all obstructive apneas and hypopneas with >4% desaturation during sleep divided by the # of hours of sleep. We will also examine the number of obstructive apneas and hypopneas regardless of desaturation observed per hour of sleep, the proportion of sleep time with obstructive apneas and hypopneas, nadir and average oxyhemoglobin saturation (SpO2), the percentage of sleep time with an SpO2 3% desaturation or arousal. We also will explore indices specific to sleep state (REM/NREM), and oxygen desaturation events occurring without prior apneas/hypopneas.

Measurement of outcomes: Our outcomes of interest are 4 serum protein biomarkers. Laboratory analyses using MESA Exam 5 morning fasting serum will be performed using quantitative sandwich ELISA assays from R&D Systems (MMP-7, SP-D, Ang-2) and Biovendor (SP-A) at the MESA Core Laboratory at the University of Vermont where these samples are stored.

Aim 2: Determine whether CPAP use is associated with reductions in AEC and endothelial injury and ECM remodeling biomarkers in adults with moderate-to-severe OSA.

Study Design: Retrospective cohort study using data and biosamples from two previously performed studies.

Sampling frames and participants: Participants will be sampled from two completed clinical trials: the HeartBEAT and BestAIR trials. Each trial shares common design features and study eligibility criteria with a few exceptions, notably the timing of the measurement of the primary endpoint. Both were designed to test the hypothesis that active CPAP compared to a control intervention improves 24-hour blood pressure in patients with moderate-to-severe OSA and cardiovascular risk factors. The results of the HeartBEAT trial have been reported in the New England Journal of Medicine[23]. It was a four-site, three-arm, parallel group, randomized trial of 12 weeks of CPAP, oxygen supplementation, or healthy lifestyle and sleep education for adults aged 45 to 75 years with moderate-to-severe OSA (AHI > 15/hr) and either[23] coronary artery disease or[24] three or more cardiovascular risk factors[23]. Those with heart failure, a resting SpO2 < 90%, any current use of supplemental oxygen, or current smoking were excluded. All HeartBEAT participants with available serum who were randomized to the CPAP arm or the healthy lifestyle and sleep education arm (n = 200) will be included in this Aim (those randomized to oxygen will not be included in this Aim). The BestAIR trial is a two-site,

randomized trial comparing active CPAP (with or without behavioral support for CPAP use) to control interventions (education with or without sham CPAP) over 6 to 12 months of follow-up[24]. For the purpose of this analysis, all individuals receiving active CPAP will be compared to all individuals in the control arms. Inclusion criteria were similar to the HeartBEAT trial: age 45 to 75 years with moderate-to-severe OSA (AHI > 15/hr) with clinical heart disease, diabetes or >3 cardiovascular risk factors. All BestAIR participants will be included (n = 169).

Exposure measurement: We will use the original randomized allocation assigned in the two trials as our primary exposure. In both trials, participants were randomly assigned with equal probability to treatment arms using a stratified permuted block design with stratification by recruitment site and presence of coronary artery disease.

Outcomes: We will measure MMP-7, SP-D, SP-A, and Ang-2 in baseline and follow-up (3 months in HeartBEAT; 6 months in BestAIR) morning fasting sera using commercially available ELISA kits as described in Aim 1. These samples are already stored at the University of Vermont.

This Aim 2 has been completed. We focused on BestAIR and HeartBEAT trials participants with moderate to severe OSA (AHI 15) who adhered with CPAP for 4 h daily. As this adherence level is averaged over all days, it is higher than the conventional clinical target of 4 hours/night for at least 5 nights/week, and was chosen because we expected the effect to be most pronounced in these patients. In addition, this planned “per protocol” analysis, restricting to individuals randomized to CPAP who used it for at least 4 hours/night based on objective monitoring, corresponds with our current Aim 3 study design. However, contrary to our hypothesis, the levels of four biomarkers of lung inflammation and extracellular remodeling were not reduced by effective PAP therapy in OSA patients. In fact, effective PAP therapy was associated with an increased circulating level of Ang-2, an endothelial growth factor considered a marker of acute lung injury.

Given the limited biospecimen resource, we re-evaluated the markers planned for analysis and decided to substitute osteopontin for SP-A, as a putative marker of fibrogenesis and ECM remodeling, and therefore likely to provide more valuable information than SP-A. SP-A had been identified as a marker of AEC injury; however, it was felt that SP-D is a better marker of the same domain, and the redundancy was not needed, especially considering limited biospecimen resources.

Revised Specific Aim 3: a) to determine prospectively whether clinically-initiated 4-week PAP therapy increases markers of alveolar endothelial lung injury in OSA. b) to determine whether untreated OSA promotes AEC and endothelial injury and ECM remodeling biomarkers in adults with ILD and OSA compared with those without OSA.

Study Design & Sampling Frame: We will perform a prospective study. We will sample participants from the New York Presbyterian/Columbia Pulmonary Fibrosis Foundation Care Center and from The Columbia University Center for Sleep Medicine.

Selection Criteria, Expected Enrollment, and Screening: This study plans to enroll approximately 165 subjects with interstitial lung disease. We anticipate that 100 of those will have concomitant OSA and 65 will not have concomitant OSA. We will enroll 78 OSA patients from The Columbia University Center for Sleep Medicine and assess the above biomarkers of alveolar endothelial injury before and after 4 weeks of clinically-initiated PAP therapy (not randomly allocated owing to the well-recognized societal hazard posed by untreated OSA patients with daytime somnolence).

Inclusion Criteria for Patients with ILD:

1. Informed consent
2. Age 18 years or greater
3. Diagnosis of any of the following fibrotic interstitial lung diseases as defined by ATS/ERS/JRS/ALAT guidelines and research statements and Delphi surveys[3, 4, 5]: Idiopathic pulmonary fibrosis - Idiopathic non-specific interstitial pneumonia (NSIP) with fibrosis - Chronic hypersensitivity pneumonitis with fibrosis - Connective tissue disease related interstitial lung disease (CTD-ILD) - Unclassifiable idiopathic interstitial pneumonia with fibrosis

Exclusion criteria for Patients with ILD:

1. Clinically significant lung disease other than fibrotic interstitial lung disease
2. Planned change to the IPF treatment during the study period
3. Current cigarette smoking (past 4 weeks)

4. Lower respiratory tract infection in past 60 days. (Upper respiratory tract infection is not a contraindication)
5. History of life threatening cardiac arrhythmias
6. Known chronic heart failure (LVEF < 45% or echo evidence of RV dysfunction or PH)
7. Chronic opiate analgesic use
8. History of sleepiness-related automobile accident within past year of enrollment
9. Expected survival time in the opinion of the investigator of less than 6 months
10. History of stroke or spinal cord injury

Study Overview: After informed consent and review of inclusion/exclusion criteria, study participants will undergo full-night polysomnography at their baseline visit (see below). Phlebotomy, spirometry, 6-minute walk test, diffusing capacity, and questionnaires completed at the research visit.

Inclusion criteria for OSA patients:

1. Age >18 years
2. Clinical diagnosis of untreated OSA documented by nocturnal polysomnography.

Exclusion criteria for OSA patients:

1. Current treatment with CPAP or oral appliance
2. Identical exclusion criteria as for ILD patients

STATISTICAL PROCEDURES

Polysomnography: Participants with ILD will undergo home polysomnography (PSG) after they have consented to the study. We will use the Nox A1 sleep recorder manufactured by Nox Medical (Reykavik, Iceland) for the home PSG recordings. This will strictly be a research study and not meant for clinical purposes. PSG devices will be returned to Columbia and recordings uploaded by the research team. PSG exams will be transferred to and scored by the Brigham and Women's Sleep Reading Center (Boston, MA, USA) in accordance with the American Academy of Sleep Medicine Manual[28]. Patients without ILD will be recruited from The Columbia University Center for Sleep Medicine after clinically indicated polysomnography.

Supplemental oxygen: If participants use supplemental oxygen while sleeping at baseline, they will use their supplemental oxygen as prescribed by their healthcare provider during the home PSG.

Phlebotomy and urine will be performed using methods previously used in MESA. Morning fasting blood with tourniquet time < 2 min. will be drawn. Mid-stream urine will be collected. The samples will be processed within 30 minutes and stored at -80°C.

Spirometry and DLCO will be performed by trained technicians in accordance with ATS/ERS guidelines in the MESA PFT lab in the CTSA and PFT lab in Herbert Irving Pavilion 3rd Floor.[30, 31]

Questionnaires will be completed by participants. Questionnaires include Epworth Sleepiness Scale (ESS).[32,37]

Demographic and clinical data (age, gender, race/ethnicity, smoking status, cigarette packyears, and medical history) will be ascertained using standardized questionnaires. Height and weight will be measured using a calibrated stadiometer scale. A board-certified pulmonologist will perform a standardized physical exam and record her or his findings in a pre-formatted form.

Clinical Data & Events: We will record clinical data, including, hospitalizations, exacerbations, and deaths.

Outcome measures: 1) Determine whether untreated OSA promotes AEC and endothelial injury and ECM remodeling biomarkers serum (MMP-7, SP-D, osteopontin and Ang-2) in adults with ILD and OSA compared with those without OSA; 2) Determine prospectively whether clinically-initiated 4-week PAP therapy increases markers of alveolar endothelial lung injury (MMP-7, SP-D, osteopontin and Ang-2) in OSA. All assays will be performed in Dr. Tracy's lab as described in Aim 1. Secondary outcomes will include changes in FVC, DLCO, 6-minute walk distance, dyspnea, and HRQOL.

Data Management: We will use a REDCap database for data entry and management as we have previously done in the Lung Transplant Body Composition Study.

STUDY PROCEDURES

For patients with ILD, after informed consent and review of inclusion/exclusion criteria, study participants will undergo home polysomnography (see below). Phlebotomy, spirometry, diffusing capacity and questionnaires will be measured at the research visit.

Participants with ILD will undergo home polysomnography (PSG) after they have consented to the study. We will use the Nox A1 sleep recorder manufactured by Nox Medical (Reykavik, Iceland) for the home PSG recordings. This will strictly be a research study and not meant for clinical purposes. PSG devices will be returned to Columbia and recordings uploaded by the research team. After being uploaded, studies will be exported in standardized format (European Data file; edf) and transferred by secure FTP to the Sleep Reading Center at Brigham & Women's Hospital for scoring by a single research sleep technologist according to well-established protocols. Brigham Sleep Reading Center will perform interpretation using standard AASM scoring criteria.

For patients with OSA only (without ILD), they will undergo clinically indicated polysomnography in the Center for Sleep Medicine. The investigators have no role in determining the need for polysomnography or CPAP therapy in this OSA only cohort. CPAP will be prescribed by their clinician provider and not by the study investigators. Therefore, polysomnography and CPAP are not considered study procedures for OSA only cohort.

Supplemental oxygen: If participants use supplemental oxygen while sleeping at baseline, they will use their supplemental oxygen as prescribed by their healthcare provider during the home PSG.

Phlebotomy will be performed via venipuncture. Morning fasting blood with tourniquet time < 2 min. will be drawn. Samples will be processed within 30 minutes and stored at --80°C. Mid-stream urine will be collected.

Six-minute Walk Test (6MWT), Spirometry, and DLCO will be performed by trained staff in accordance with ATS/ERS guidelines.

Participants will complete Epworth Sleepiness Scale (ESS). These questionnaires will be administered according to the instructions provided in the attached documents.

RECRUITMENT AND CONSENT

Patients with ILD will be recruited from the ILD center. Patients who express interest in the study will be referred to the study team, and study team members will approach interested patients to provide additional information about the study. HIPAA form D is required for study investigators and research team to pre-screen and identify patients from the clinical practice who have met the inclusion criteria. These participants will be approached during their regularly scheduled clinic visits and given information about the study. For "OSA only" cohort, they will be recruited from the Center for Sleep Medicine after their OSA diagnosis had been confirmed clinically by polysomnography. All patients in the Center for Sleep Medicine will be screened for eligibility, and those that are eligible based on inclusion and exclusion criteria will be approached by phone call. Enrollment and consent will occur during the research visit.

RESEARCH AIMS & ABSTRACTS

Research Questions/Hypotheses:

Specific Aim 1: Determine whether greater OSA severity is associated with higher levels of serum biomarkers of AEC and endothelial injury and ECM remodeling in community dwelling adults. We hypothesize that a higher obstructive AHI is associated with greater serum MMP-7, SP-D, SP-A, and Ang-2 levels in 1,830 MESA Sleep Study participants after controlling for potential confounders.

Specific Aim 2: Determine whether CPAP use is associated with reductions in AEC and endothelial injury and ECM remodeling biomarkers in adults with moderate-to-severe OSA. Using stored serum samples from the HeartBEAT and BestAIR trials, we will perform randomized comparisons of serum MMP-7, SP-D, osteopontin, and Ang-2 levels in 369 adults with moderate-to-severe OSA who received CPAP or control interventions. We hypothesize that CPAP use will be associated with reductions in these biomarkers.

Revised Specific Aim 3: a) to determine prospectively whether clinically-initiated 4-week PAP therapy increases markers of alveolar endothelial lung injury in OSA. b) to determine whether untreated OSA promotes AEC and endothelial injury and ECM remodeling biomarkers in adults with ILD and OSA compared with those without OSA..

Scientific Abstract:

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease of the peripheral lung parenchyma that affects ~0.5% of older adults in the US and carries a median survival time of only 3.8 years. While pirfenidone and nintedanib slow the decline of lung function in IPF, neither drug reverses fibrosis or prevents the ongoing alveolar epithelial cell (AEC) injury that leads to fibrosis in IPF. The identification of interventions that prevent AEC injury in IPF would have a paradigmshifting impact. A recent novel hypothesis suggests that "tractional" injury in the periphery of the lung may be responsible for the development of IPF. Our central hypothesis is that obstructive sleep apnea (OSA), which affects 59-88% of adults with IPF, is a prevalent cause of recurrent peripheral tractional stress in the lung that leads to AEC injury and, in susceptible individuals, lung fibrosis. We believe that Müeller maneuvers occurring during obstructive apneas and hypopneas likely stretch and injury alveolar epithelial cells, contributing to fibrosis in susceptible adults over the course of 10-20 years. In mice, inspiratory resistive loading (analogous to an obstructive hypopnea) induces AEC injury and results in increased alveolar-capillary membrane permeability. In humans, we and others have shown that adults with OSA have elevated circulating levels of surfactant protein-A (SP-A) and Krebs von den Lungen-6 (KL-6), markers of AEC injury, and elevated matrix metalloproteinase-7 (MMP-7) levels, a marker of extracellular matrix remodeling, suggesting that subclinical AEC injury and ECM remodeling occurs in OSA in otherwise healthy adults. Alveolar epithelial and endothelial injury is also detectable by measurement of serum surfactant protein-D (SP-D) and angiopoetin-2 (Ang-2), respectively. In IPF, AEC injury is detectable by elevations in some of these markers, and MMP-7 levels are a key diagnostic and prognostic biomarker in IPF. We propose to establish OSA as a contributor to AEC injury in those with and without IPF, and to obtain data that will inform and justify a phase 2 clinical trial of continuous positive airway pressure (CPAP) to improve outcomes in adults with IPF and OSA. We will investigate associations between OSA and evidence of AEC and endothelial injury and ECM remodeling in the MESA Sleep Study, a population-based cohort of adults who underwent home polysomnography in 2010-2012. We will also investigate whether treatment with CPAP is associated with a change in serum markers of AEC and endothelial injury and ECM remodeling in adults with OSA without IPF. Our study will provide strong evidence for or against a pathogenic role of OSA in IPF, and is likely to provide critical data that we will use to design a phase 2 trial asking whether oral appliances lower markers of alveolar epithelial and endothelial injury in ILD patients with OSA.

Lay Abstract:

Interstitial lung diseases are a family of lung diseases characterized by inflammation and scarring of the walls of the air sacs of the lungs. These diseases are not due to infection; nor are they a form of cancer. In most cases, scar tissue builds up over the course of a few years and leads to lung failure and death. Most patients die within 3 to 5 years. Few treatments are available. Some can undergo a lung transplant, but most people are unable to receive one due to contraindications to transplantation and/or due to a shortage of donors. We have developed a research program that investigates the causes of IPF and other interstitial lung diseases, since most cases occur for unknown reasons. Our research has identified sleep apnea as a possible contributor to interstitial lung disease.

We now propose to perform three studies:

1) Perform research blood tests for markers of lung injury and inflammation in people with and without sleep apnea using an existing large study called "MESA." This part of the study will use existing data and existing blood samples that are stored at the University of Vermont. This Aim will not include enrollment of any new study participants. We will test whether these markers are elevated in people with sleep apnea compared to those without sleep apnea.

2) Perform research blood tests for markers of lung injury and inflammation in people with sleep apnea and determine whether treating sleep apnea lowers the levels of these markers in the blood. We will use existing data and existing blood samples from two prior studies. The blood samples are stored in the University of Vermont. The University of Vermont Laboratory will measure these markers and provide the data to us. This Aim will not include enrollment of any new study participants.

3) Perform sleep studies on adults with obstructive sleep apnea and interstitial lung diseases who we prospectively enroll at our center. They will undergo non-invasive studies, including sleep study, breathing tests, blood tests, walking test, and questionnaires. We will also perform blood tests before and after CPAP therapy prescribed clinically in patients with obstructive sleep apnea without known lung disease.

We hope that all of these studies will help us understand whether sleep apnea damages the lungs and whether people with and without ILD, and whether treatment of sleep apnea affects the lungs.

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