Title: Smoking Cessation and Functional CT assessment of Pulmonary Arterial Dysfunction in Smoking associated Emphysema
Version 1

11 September 2017

Overview

For Aim 5 80 (ages 25-65) Gold 0-2 subjects that are current smokers (defined by PFTs, questionnaires and interviews as discussed below) will be recruited. Participants will be equally distributed between males and females and will be representative of the national racial/ethnic populations. Subjects will be recruited using advertisements, email blasts, smoking cessation clinic and physician referrals. Participants that are enrolled into the study will have a total of 4 visits (baseline, 30 day, 60 day and 90 day) over 3-4 months. During the study visits, subject will have vitals, blood tests, urine sample, CT scans, pulmonary function tests, and complete questionnaires. Subjects will also participate in a smoking cessation program. Subjects will be contacted weekly, by phone, for smoking cessation follow up.

Inclusion/exclusion criteria

Inclusion criteria
Between the age of 25 to 65 at baseline
Be willing to participate in a smoking cessation program
Be willing to attend all clinic visits
Must be currently smoking at least ½ pack/day at baseline (confirmed with cotinine level and CO Smokerlyzer
>5 pack-year history of smoking
GOLD 0: FEV1≥0.80 and FEV1/FVC>0.70
GOLD 1: FEV1≥0.80 and FEV1/FVC < 0.70
GOLD 2: 0.50≤FEV1<0.80 and FEV1/FVC < 0.70
Be willing to abstain from using any nicotine patches, e-cigarettes, or marijuana for the duration of the study.
Exclusion criteria
Women only: Cannot be pregnant or nursing at baseline or plan to become pregnant during the course of the study
Body Mass Index (BMI) > 32
Weight > 220 pounds
Allergies to shell fish, seafood, eggs or iodine
Heart disease, kidney disease or diabetes
Diagnosis of asthma
Any metal in or on the body (that cannot be removed) between the nose and the abdomen
Any major organ system disease (by judgement of the study medical team)
A glomerular filtration rate of 60 cc per minute or less.
Nitroglycerin usage or nitrates and use of PDE5 inhibitors

Prior history of hypersensitivity to sildenafil
Currently prescribed a phosphodiesterase (PDE) inhibitors medication (ex: Viagra, Cialis, etc)
Known Pulmonary Hypertension
Has used e-cigarettes and marijuana <1 years

Recruitment

Subjects will be recruited using IRB approved advertisements and subjects will also be referred to our study by physician teams and the UIHC smoking cessation clinics. We will also notify, by phone or letter, subjects enrolled in the COPDGene IRB: 200710717 and Spiromics IRB: 201308719 studies, who have consented to be contacted for other studies they may qualify for.

Pre-Screening

When potential subjects call or are contacted, they will be given information about the study, its procedures and time commitment. If the subject is interested, the subject will be pre-screened using the IRB approved form. If subject appears to qualify, a study visit will be scheduled.

Consent

Subjects will be consented in a private room and given time to read through the Informed Consent document if they have not already done so. They will be given time so that the study team can answer any questions they might have regarding the study privately. The study team member will then go through the consent form to verify that the subject understands what to expect, what is involved with the study, what the risks are, confidentiality and privacy aspects, etc. Once the study team member is confident that the candidate understands and is comfortable with participating in the study and the study team has answered all the subject's questions, the study team member will have the subject sign and date the consent form. The study team member who is preforming the consent will also sign and date the consent form and make sure the subject has a copy of it for their own files before they leave.

Schedule of Study Assessments and Procedures

Activity	Consenting visit	Baseline visit	30 day visit	60 day visit	90 day visit
Written Informed Consent	X	X			
Pre-screen Inclusion/Exclusion form	X	X			
Human Subject Questionnaire		X			
St. George's Respiratory Questionnaire		X			X
Chronic Respiratory Questionnaire		X	X	X	X
Baseline Dyspnea Index Questionnaire		X	X	X	X
Medication review		X	X	X	X
Fagerstrom Questionnaire		X			
Tobacco Interview Form		X			
Six Minute Walk Test w/BORG Scale		X			X
Vitals		X	X	X	X
Height & weight		X			
Exhaled CO Smokerlyzer		X	X	X	X
Pulmonary Function Tests[a]		X			X
IV Catheter placement		X			X
Blood draw for serum creatinine		X			X
Blood draw for serum cotinine		X	X	X	X
Blood draw for C-reactive protein level		X			X
Blood draw for serum and plasma		X			X
Urine pregnancy test in WOCBP		X	X	X	X
Urine sample for bio specimen collection		X			X
Contrast perfused blood volume (PVC) CT scan[b]		X			X
Non-contrast CT scan		X	X	X	X
Smoking cessation enrollment		X			
Smoking cessation in person follow-up**			X	X	X
Review and record any SAE/AE or medication changes			X	X	X
Dispense medication/placebo		X	X	X	

****Subject smoking cessation follow-up phone calls will be done once per week by study coordinator while subject is enrolled in the study.**

a. At baseline visit, DLCO will be repeated after 2nd contrast CT scan
b. At baseline visit, two contrast PVC CT scans will be done. One PVC CT will be done pre-dose and one PVC CT will be obtained 60 minutes post-dose.

Vitals, height & weight, and urine pregnancy test

A properly trained member of the study team or UIHC Clinical Research Unit (CRU) employee will perform pre-study vital statistics which include: Heart rate, respirations, blood pressure, temperature, SaO2, height and weight. Women of child bearing potential (WOCBP) will have a urine pregnancy test.

CO Smokerlyzer

Subject will be instructed on how the CO Smokerlyzer will be done. Subject will be asked to inhale and hold their breath for the pre-set 15 seconds. A beep will sound during the last 3 seconds of the countdown (on the monitor screen) and following the last beep, the subject will be instructed to blow slowly into the mouthpiece, aiming to empty the lungs completely. %COhb and %fCOhb will be recorded. The subject will be asked to repeat the test again and the results will again be reported. If the results are not <3%, a third test should be performed to ensure repeatability and accuracy.

Pulmonary function tests

Complete pulmonary function testing is performed in the PFT lab. All studies conform to American Thoracic Society standards. Both pre- and post- bronchodilator spirometry will be done. Simple spirometry provides FEV1, and FVC and the FEV1/FVC ratio. DLCO will be measured using the single breath carbon monoxide method. Subdivisions of lung volume are measured by body plethysmography. If subjects don't meet the FEV1 and FEV1/FVC GOLD 0-2 criteria, they will be considered screen-fails and will not continue with any other study procedures.

IV Catheter placement

Subjects who meet the PFT criteria will be taken to the CRU and CRU nurse, study physician or a properly trained member of the research team will place an IV catheter in the antecubital vein in the subject's right arm. This will be used for contrast injection during the perfused blood volume scans. Blood will also be drawn from the IV catheter for the creatinine, C - reactive protein, cotinine levels and the additional two blood tubes that will be collected for blood and serum analysis at the baseline visit and 90 day visit. Subjects will not have IV catheter placement at any other visits.

Blood and Urine Collection

Blood samples will be taken to test the subject's creatinine, cotinine and C-reactive protein level. Two additional tubes of blood will be drawn for serum and plasma collection (baseline and 90 day visit). The creatinine level will only be tested prior to the contrast CT (baseline visit and 90 day visit). The cotinine and C-reactive protein level will be tested at baseline, 30 day, 60 day, and 90 day visits. Women of child bearing potential (WOCBP) will have a urine pregnancy test.

CT Scans

A subject may undergo 13 total low-dose scans throughout the study within 3 months:

Baseline Visit: 3 low-dose non-contrast CT volumetric research scans (TLC, FRC, RV) and 2 low-dose dual-energy contrast CT research scans at FRC.

30-day Visit: 2 low-dose non-contrast CT Volumetric research scans (TLC, RV)

60-day Visit: 2 low-dose non-contrast CT Volumetric research scans (TLC, RV)

90-day Visit: 3 low-dose non-contrast CT Volumetric research scans (TLC, FRC, RV) and 1 low-dose dual-energy contrast CT research scan at FRC.

Exposure Output

1. The spiral dual energy contrast scan protocol uses dose modulation with tube A: 120 ref mAs/80kV, tube B: 67 ref mAs/Sn150 kV, with a pitch of 0.55 and rotation time of 0.25sec. The CTDIvol is assumed to be 4.28mGy, with total DLP of 143.2mGy*cm for a 30cm scan.

   Total mrem for three scans: 740 mrem

2. The spiral volumetric scan protocols use dose modulation with 10 reference mAs, 120kV, pitch of 1.0, & rotation time of 0.25sec. The CTDIvol for one scan at 10mAs is 0.67mGy, with total DLP of 22.6mGycm for a 30cm scan.

Total mrem for 10 scans: 1190 mrem

The maximum amount of radiation from the research-related radiation procedures is equivalent to approximately 25% of the annual limit for a radiation worker.

Subjects will wear a pulse oximeter while being scanned.

Smoking Cessation

Subjects will enter a 3-month smoking cessation program overseen by Dr. Jeff Wilson and Jane Greiner, RN who run the hospital-based smoking cessation program. Dr. Hoffman's study coordinator will work full time in cooperation with the University of Iowa Hospitals and Clinics Smoking Cessation Clinic in the Pulmonary Rehabilitation Program to maximize success rate. The clinic operates under the Surgeon General's Clinical Practice Guideline Treating Tobacco Use and Dependence: 2008 Update. The study team will meet with the subject in person at the baseline, 30 day, 60 day and 90 day visits and follow up by phone weekly. At the baseline visit the subject will be asked to taper down their use of tobacco for the first week in the study prior to their commitment to quit smoking for the remainder of the study.

Follow up will seek to identify problems already encountered and potential challenges in the immediate future, assessment of current medication use and problems, and restatement of resources to help support them during their tobacco use cessation such as quit-line support.
If tobacco use has occurred, a review of the circumstances and encouragement to recommit to total abstinence will be done.

Randomization

Subjects will then be randomized to either Sildenafil, 20 mg orally 3x/day, or Placebo in equal numbers after beginning the smoking cessation program above.

Questionnaires

At baseline, four questionnaires will be administered by the study team:

Human Subject Questionnaire
Chronic Respiratory Questionnaire
Baseline Dyspnea Index Questionnaire
St. George's Respiratory Questionnaire

At the 30 and 60 day visits, two questionnaires will be repeated:

Chronic Respiratory Questionnaire
Baseline Dyspnea Index Questionnaire

At the 90 day visit, three questionnaires will be repeated:

Chronic Respiratory Questionnaire
Baseline Dyspnea Index Questionnaire
St. George's Respiratory Questionnaire

As part of the smoking cessation program, two additional questionnaires are administered:

Fagerstrom Questionnaire
Tobacco Interview Form

Six Minute Walk

Subjects will complete a six minute walk test according to the ATS statement (ATS Statement, 2002)

Subjects are encouraged to walk as far as possible for six minutes. Subjects will have heart rate and oxygen saturation (SpO_2) measured as well as having their dyspnea rated using BORG scale, prior to and immediately following, the six minute walk.

Subjects will be instructed that they can stop at any time.

The six minute walk will be done at baseline and 90 day visits.

Safety Monitoring

A DSMB has been set up with Drs. Lakshmi Durairaj and Thomas Gross as members. Members will be provided summary data on a 6-month basis.