Lung Imaging of Apoptosis in Chronic Obstructive Pulmonary Disease (COPD)

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BACKGROUND

Study Purpose and Rationale:

Current imaging modalities in lung disease primarily focus on the evaluation of end organ damage and destruction (1). While molecular imaging approaches have been developed in oncology (2-5) and in the assessment of cardiovascular disease (6, 7), the utility of such an approach in lung disease is not yet established. The development of methods to image cellular processes and targets related to disease pathogenesis will allow an evaluation over the time course of disease and provides information as a potential biomarker of disease activity and response to therapy. Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death worldwide and is a progressive lung condition in which tobacco smoke and other stimuli trigger inflammation, production of destructive enzymes and programmed cellular death within the lung (8). Although inflammation can be seen in smokers without COPD, both apoptosis and MMP production are not seen at an increased rate in smokers without COPD (9-12), with the rate of apoptosis correlating with emphysema severity (12). Collaborative studies have successfully developed an imaging approach specifically targeting apoptosis in a pre-clinical model of emphysema (13). These data provide the first evidence of our ability to visualize in vivo with molecular imaging an ongoing cellular process consistent with lung destruction in an animal model of smoke exposure. Molecular imaging offers the advantage of relatively small molecular size probes that can clear from the blood pool and cross capillaries to access receptors or protein antigenic binding sites within tissue, allowing non-invasive functional measurements of disease. This probe (AxV-128/Tc) has already undergone Phase 1 clinical testing for tracer kinetics and radiodosimetry in Canada (12 healthy volunteers, 6 men and 6 women) and the safety profile has been established (see attachment from Advanced Accelerators). We propose to advance into patients this imaging approach with the goal of detecting alterations in pulmonary apoptosis in various stages of COPD. A correlation of known biomarkers with apoptosis imaging will also be assessed. If successful, these imaging techniques will greatly advance the field of pulmonology with clinical imaging modalities to non-invasively assess response to therapies and to potentially guide in prognostication.

Study Design:

This will be a prospective study examining the use of 99mTc-Annexin V-128 (AxV-128/Tc) SPECT/CT technology in the imaging and functional assessment of the lung of patients with COPD, healthy volunteer smokers without COPD and healthy volunteer subjects without smoking history.

STUDY PROTOCOL

We will study patients with and without lung disease (COPD) and compare AxV-128/Tc SPECT-CT scans. To test the hypothesis that AxV-128/Tc SPECT-CT scanning can detect apoptosis in patients with COPD, we will perform a case control study in patients with varying severity of COPD. There will be four groups of subjects: -Patients with moderate COPD: GOLD Stage II, FEV1/FVC < 0.7 and FEV1 50-79% predicted -Patients with severe COPD: GOLD Stage III-IV, FEV1/FVC < 0.7 and FEV1 < 50% predicted -Healthy controls who are currently smoking (> 10 pack years) with normal spirometry (FEV1 > 80% and FEV1/FVC > 70%) -Healthy controls who never smoked (less than 100 lifetime cigarettes) with normal spirometry (FEV1 > 80% and FEV1/FVC > 70%) The subjects will undergo spirometry (lung function tests) and blood and urine samples will be drawn prior to undergoing SPECT Scan. The spirometry will ascertain the severity of COPD and blood and urine samples will allow us to measure markers of lung injury as well as cotinine to confirm the smoking status of the subject. Blood samples will be also stored for analysis of biomarkers and possible future DNA and RNA analysis.

Study population: We will study 16 patients with COPD (8 patients with GOLD Stage 2 disease, 8 patients with GOLD Stage 3-4 disease) and 8 healthy volunteer smokers without COPD, and 8 healthy volunteer subjects without smoking history or lung disease to compare AxV-128/Tc SPECT-CT scans in smokers, patients with COPD, and normal control patients.

Recruitment: The patient population will be drawn from the Center for LAM and Rare Lung Diseases, Jo-Ann F. LeBuhn Center for Chest Disease and the Price Family Center for Comprehensive Chest Care and will be stratified by severity of disease. Recruitment of healthy volunteers will be performed with advertisements in Columbia University's "recruitme" website, and flyers throughout the medical center. In order to be eligible, patients with COPD must have a

forced expiratory volume in one second (FEV1) less than 80% of predicted for age and height, and bronchodilatory reversibility of less than 15% or 200 ml with airflow obstruction evidenced by an FEV1/Forced Vital Capacity (FVC) ratio of 70% and FEV1 > 80% of predicted for age and height.

Study Procedures: After obtaining informed consent, the subjects will undergo:

Pulmonary Function Testing: pre- and post-bronchodilator spirometry, lung volume and DLCO measurements.

Urine sample: urinalysis and smoking status will be confirmed by urine cotinine level.

Pregnancy Test: If participant is a woman of child-bearing potential, a urine pregnancy test may be performed to ensure study eligibility. Pregnant women may not participate in this research study as risk of technetium to an embryo or unborn fetus may exist. Women of childbearing potential include all women except those whose menstrual periods have not occurred for more than one year after menopause (change of life) or those who have had sterilization surgery (tubes tied) or hysterectomy (removal of uterus or womb).For women whose menstrual period started less than 4 weeks prior to the study date, a urine dip stick pregnancy test will be performed prior to study drug administration.

Blood sample: Serum biomarkers including leukocyte count, fibrinogen and CRP will be obtained for correlation of these serum biomarkers for COPD exacerbation risk with lung apoptosis-targeted imaging. In addition, apoptotic endothelial microparticles (CD42bCD62E+/CD42bCD31+) will be assessed in order to obtain a direct comparison between imaging signal (%ID) and alternate markers of apoptosis that can be obtained non-invasively.

Repeat PFTs after initial imaging in order to determine the ability of AxV-128/Tc imaging to predict later lung function decline.

SPECT/CT imaging: Vials of AxV-128 provided by AAA will be shipped to Nuclear Diagnostics, a satellite pharmacy that serves Columbia University Medical Center Nuclear Medicine. Nuclear Diagnostics will label AxV-128 with 99mTc and deliver pre-calibrated doses by time of injection to the CUMC Nuclear Medicine Department. Each dose will be injected intravenously by a Medical Doctor (i.e., PI, co-investigators) and if unavailable a certified Nuclear Medicine Technologist (NMT) or Registered Nurse (RN). The injected dose is between 8-10mCi and never more than 10mCi as stated in the IND. Radiation is measured before and residual after injection.

Scans will be performed on Siemen's Symbia T hybrid SPECT/CT (16 slice) scanner in the Nuclear Medicine department. A chest CT scan will be performed with breath hold at the clinical dose using a standard diagnostic CT imaging acquisition protocol. Immediately following the CT acquisition, a SPECT will be performed with a FOV set for the chest from lower neck to upper abdomen. Standard CT acquisition protocols will be used.

Vitals: Vitals will be obtained at two time points: before injection of tracer/blood draw and after the SPECT/CT imaging has been performed. Vital signs indicate the status of a person's life-sustaining functions including: Blood pressure, Heart rate and oxygen saturation rate. These measures will be recorded for safety purposes only.

Medical History: Medical history including diagnoses and current medications taken will be collected during the study visit. Participants are encouraged, but not required to provide outside medical documentation confirming COPD or Alpha-1 diagnosis or any recent Pulmonary Function Testing, blood work and imaging done clinically. Study investigators will review any outside medical documentation and determine if any study procedures may be substituted for outside clinical records as to not burden participants repeating exams already done clinically.

Follow up calls: One of the study team members will conduct follow up phone calls at 24-72hours, 1 month and 6 months post imaging. These calls will be done for safety purposes only and will only take 1-2 minutes. Information collected includes any reporting of side effects and any medical diagnosis or medication changes.

Reproducibility (Short and Long Term): In order to document short term reproducibility of the imaging method and give an assessment of a meaningful change of signal in a patient, up to 10 of the subjects with COPD (from either the moderate or severe COPD groups) will undergo repeat AxV-128/Tc SPECT/CT scans within one week of the original scan. Patients will not undergo repeat imaging if there has been a significant change in their clinical status including a COPD exacerbation pulmonary infection, or CHF exacerbation. Repeat imaging will only be performed on patients with COPD as it is anticipated based upon literature documenting that never smokers have negligible levels of apoptosis within the lung. The Phase I data of AxV-128/Tc with normal subjects also demonstrated less than 5% ID lung uptake. Smokers without disease will be excluded from this reproducibility study as smoking may be variable from day to day and may alter signal results.

In addition, long term changes in this imaging method will be assessed on subjects with COPD with an additional AxV-128/Tc SPECT-CT scan and same procedures listed above. The follow up visit may be done without an additional AxV-128/Tc SPECT-CT scan and same procedures listed above. Please note that only a SUBSET of subjects will undergo 1 year or 1 week repeat scan. One year follow up visits are approximate 1 year +/- 8 months. This is to compensate for coordinating contacting participant and scheduling visits around their most convenient time.

Imaging and data analysis: Mean ± SD for values for uptake of AxV-128/Tc for individual lobes and for lungs will be determined for each COPD group and compared using unpaired t-test for values with Gaussian distribution and Mann-Whitney (Wilcoxon rank) test for continuous variables without normal distribution. Gaussian distribution will be determined using the Kolmogorov-Smirnov test. We have included moderate, severe and very severe COPD patients assuming that the signal will increase with the severity of COPD. We could therefore establish an exposure-response relationship between severity of COPD (on a non-linear scale) and signal. This assumption is based upon our work establishing a correlation between COPD severity and apoptotic index in the lung (12). Mean ± SD for values for volumes and Hounsfield units will also be compared among the same groups. We will also assess tracer uptake normalized for lung volumes. In the emphysema patients we are measuring a signal coming from living (and dying) tissue that is interspersed in air. In the more severe cases of COPD, the lung tissue takes up less volume within the lungs and the air forms greater percent of each lobe. We will attempt to account for these changes by normalization for Hounsfield units. In addition values for %ID tracer uptake will be correlated with values for PA:A ratio. For the serial reproducibility studies, the values for whole lungs and lobes from the two studies will be analyzed for agreement using Bland-Altman analysis.

Incidental finding of clinical significance: Potential incidental findings of clinical significance that may be discovered during imaging procedure may include tumors, hematomas, infectious complications such as abscesses and vascular abnormalities among others.. The following procedures pertain to the finding of incidental findings (IF) that may occur during the imaging of the subjects. The images will be read by a radiologist credentialed by the Department of Radiology as soon as possible but no later than two weeks following receipt of the image. Imaging will only take place at Columbia University Medical Center. If the credentialed

radiologist will find an IF with clinical significance this will be recorded in the research record and the subject will notified by the PI who is a critical care physician either in person or by phone followed by a letter or email.

If an IF has been reported we will notify the IRB during the next review about the number of Required Review Images, a list of the subject study numbers, the type of scan, the date of the scan, a description of the IF of Clinical Significance, the date of communication with the subject and the outcome, if known.

Eligibility Criteria

Inclusion Criteria:

1. Males and females age 45-80 years
2. Able and willing to comply with the study procedures
3. Gold class II COPD or greater
4. Healthy Smoker
5. Healthy non-smoker
6. Lie flat for 30 minutes

Exclusion Criteria:

1. Current Malignancy
2. Bronchiectasis
3. Recent COPD exacerbation (less than 1 month)
4. Recent pulmonary infection (less than 1 month)
5. Asthma or other significant lung disease
6. Pregnancy or lactation
7. Claustrophobia or inability to lie still in a supine position

RESEARCH AIMS & ABSTRACTS

Research Question(s)/Hypothesis(es):

We hypothesize that there will be an increased AxV-128/Tc signal in the lungs of patients with COPD as compared to control patients. This signal is hypothesized to be higher in patients with more severe COPD.

Scientific Abstract:

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death and is characterized by clinical symptoms and spirometry. Additional measures for diagnosis can be taken using imaging modalities such as CT. However, the evaluation of lung destruction in COPD is limited by the inability to visualize the activation of pathological processes since imaging modalities are only able to evaluate end-organ damage. In this proposal, we aim to assess a molecular imaging probe targeting apoptosis, a cellular process known to be pathogenic in COPD. Apoptosis, a process of programmed cellular death, correlates with COPD severity and is not seen in the normal adult lung. In the past several years we have demonstrated the successful ability of AxV-128/Tc to detect apoptosis in vivo in a rabbit smoke exposure emphysema model. Additionally, Phase 1 studies have demonstrated safety of this agent in healthy patients. Therefore, we will bring AxV-128/Tc forward as a probe to image the apoptotic disease process of the lung in patients with COPD. We will determine if the imaging signal correlates with serum biomarkers of apoptosis and inflammation. It is our hypothesis that AxV-128/99mTc imaging will show increased uptake in the lungs of patients with COPD, and that this signal intensity will correlate with accepted markers of apoptosis and inflammation. If successful, such an approach will be a powerful tool to potentially predict disease progression after diagnosis, identify patients at risk for disease exacerbation related lung function decline, and monitor response to disease targeted therapy. The total effective dose from the combined SPECT and CT scans is 6.71 mSv. This effective dose is below what a patient receives during a standard 2 dose rest and stress cardiac nuclear imaging study and well within the range of current clinical nuclear imaging tests. The exact long term risk for development of cancer from diagnostic radiological procedures is currently under debate but all imaging procedures in this study are aimed to keep total radiation burden ALARA (As Low As Reasonably Achievable).

STATISTICAL PROCEDURES

Serum biomarkers of inflammation and levels of apoptotic endothelial microparticles will be correlated with % injected dose of radiotracer on SPECT-CT imaging results. Up to ten patients with COPD will undergo a second SPECT-CT scan within 1 week of the first baseline/visit#1 scan in order to determine the short-term reproducibility of the signal and to determine what would be a meaningful change in signal. Patients must be clinically unchanged in the intervening week. A subset of COPD diagnosed subjects will undergo a repeat scan after 1 year of the baseline/visit#1 scan; this will include repeat SPECT-CT, pulmonary function testing, blood and urine testing. The purpose of the repeat imaging to determine (1) the ability of the initial scan to determine later lung function decline and (2) if change in signal over a 1 year time point is associated with meaningful clinical change. In addition, we will compare SPECT-CT signal (percent injected dose, %ID) as a primary endpoint, apoptotic endothelial microparticles and serum biomarkers of inflammation in patients with COPD, smoking history without COPD, and healthy non-smoking control participants. There is no human data of AxV-128/Tc SPECT-CT imaging in lung disease that would allow us to determine an appropriate sample size for this study. We will therefore base this on our rabbit studies (13) which found a %ID of approximately 0.645 +/- 0.427 % in animals without and 2.0 +/- 0.589 % in animals with smoke exposure with a common standard deviation of (0.63+0.589) / 2 = 0.508 %. We will need 5 patients per group to achieve a power of 80% and a confidence level of 99%. We will recruit 8 subjects who never smoked and are without lung disease, 8 patients who were smokers without lung disease, and 16 patients with COPD (8 with GOLD Stage 2 disease and 8 with Gold Stage 3-4 disease). Eight patients per group will give us sufficient power even when compensating for increases in variability in human subjects.

REFERENCES

1. Washko GR. Diagnostic imaging in COPD. Semin Respir Crit Care Med. 2010;31(3):276-85.
2. MacManus M, Everitt S, Hicks RJ. The evolving role of molecular imaging in non-small cell lung cancer radiotherapy. Seminars in radiation oncology. 2015;25(2):133-42.
3. Everitt S, Hicks RJ, Ball D, Kron T, Schneider-Kolsky M, Walter T, Binns D, Mac Manus M. Imaging cellular proliferation during chemo-radiotherapy: a pilot study of serial 18F-FLT positron emission

tomography/computed tomography imaging for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2009;75(4):1098-104.

4. Rischin D, Hicks RJ, Fisher R, Binns D, Corry J, Porceddu S, Peters LJ, Trans-Tasman Radiation Oncology Group S. Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a substudy of Trans-Tasman Radiation Oncology Group Study 98.02. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(13):2098-104.

5. Postema EJ, McEwan AJ, Riauka TA, Kumar P, Richmond DA, Abrams DN, Wiebe LI. Initial results of hypoxia imaging using 1-alpha-D: -(5-deoxy-5- [18F]-fluoroarabinofuranosyl)-2-nitroimidazole (18F-FAZA). European journal of nuclear medicine and molecular imaging. 2009;36(10):1565-73.

6. Nahrendorf M, Frantz S, Swirski FK, Mulder WJ, Randolph G, Ertl G, Ntziachristos V, Piek JJ, Stroes ES, Schwaiger M, Mann DL, Fayad ZA. Imaging Systemic Inflammatory Networks in Ischemic Heart Disease. J Am Coll Cardiol. 2015;65(15):1583-91. PMCID: PMC4401833.

7. Jung KH, Lee KH. Molecular imaging in the era of personalized medicine. Journal of pathology and translational medicine. 2015;49(1):5-12. PMCID: PMC4357402.

8. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256-76.

9. Segura-Valdez L, Pardo A, Gaxiola M, Uhal BD, Becerril C, Selman M. Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD. Chest. 2000;117(3):684-94.

10. Yokohori N, Aoshiba K, Nagai A, Respiratory Failure Research Group in J. Increased levels of cell death and proliferation in alveolar wall cells in patients with pulmonary emphysema. Chest. 2004;125(2):626-32.

11. Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. American journal of respiratory and critical care medicine. 2001;163(3 Pt 1):737-44.

12. Imai K, Mercer BA, Schulman LL, Sonett JR, D'Armiento JM. Correlation of lung surface area to apoptosis and proliferation in human emphysema. The European respiratory journal. 2005;25(2):250-8.

13. Goldklang MP, Tekabe Y, Zelonina T, Trischler J, Xiao R, Stearns K, Romanov A, Muzio V, Shiomi T, Johnson LL, D'Armiento JM. SPECT/CT Imaging in a Rabbit Model of Emphysema Reveals Ongoing Apoptosis In Vivo. Am J Respir Cell Mol Biol. 2016.