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Protocol: AAAR0395
Title: In vivo imaging of peri-operative destructive processes in the lung
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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]. Increased matrix metalloproteinase (MMP) activity and ongoing apoptosis are known to be fundamental processes in the lung destruction seen in COPD [9-16]. Collaborative studies successfully developed an imaging approach specifically targeting apoptosis in a pre-clinical model of emphysema. In the present proposal this imaging modality will be advanced into patients to detect pulmonary apoptosis in various stages of COPD and in lung injury associated with prolonged anesthesia using PET scans technology. 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.

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Study Design
This is a prospective observational study. We will study patients undergoing major surgery, specifically Whipple procedures (pancreatico-duodenectomies) and compare AxV-128/Tc SPECT□CT scans before and after surgery in COPD and non-COPD patients.

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. We will compare as primary endpoint apoptotic endothelial microparticles and serum biomarkers of inflammation pre□and post-operatively on patients undergoing Whipple operations or other major surgery. If we assume that a correlation coefficient of 0.7 is clinically relevant we will require 15 subjects to achieve a power (1 -) = 0.8 with a Type I error () = 0.025. We will recruit 40 subjects total, 20 subjects with COPD and 20 subjects without COPD.

Confidentiality and Privacy
All subject identifiers will be removed after collection of the data and the data will receive a code that will allow us to link this data to the medical record number using a linking code. The linking code will be stored on a locked and secured, encrypted computer of the principal or the investigators. Access to any of the data will be restricted to the principal investigator and the coinvestigators by assignment of a password. The computers storing the data will be stored in a locked up room and will only be accessible to the principal investigator or the coinvestigators. Hard copies of research data such a data collection sheets will also be secured in a locked up room and destroyed at the end of the study. Patient identifiers (including but not restricted to names or Medical record numbers) will be removed once the data have been entered into a computer database. Access to this data will be restricted by assignment of password. Computers that contain these data will be securely locked up to prevent access by unauthorized people.

Patient identifiers (including but not restricted to names or Medical record numbers) will be removed once the data have been entered into a computer database. Access to this database will be restricted by assignment of password. Computers that contain this data will be securely locked up to protect privacy, and to prevent access by unauthorized users. Discussions about research participation will take place in the privacy of the patient's hospital room. Limitations to protection include the disclosure of research notes and mandatory reporting.

Study Procedures

We will study patients undergoing major surgery (e.g., Whipple procedures (pancreatico-duodenectomies), biliary reconstruction or partial hepatectomy) and compare AxV-128/Tc SPECT-CT scans before and after surgery in COPD and non-COPD patients. These procedures such as the Whipple procedure have been chosen because the surgery itself is unlikely to injure the lung, but is a surgery with long enough duration of mechanical ventilation to potentially induce lung injury (80). Other major surgeries may be studied as well. Twenty patients with moderate COPD (Gold stage II: FEV1/FVC<0.70 and FEV1 50-79% normal) and twenty patients with normal lung function undergoing Whipple procedures or other major surgeries will be enrolled in the study. After obtaining informed consent the subjects will undergo spirometry for baseline lung function testing. The subjects will then undergo a baseline AxV-128/Tc SPECT-CT scan at least 2 days prior to surgery. The peri-operative management including the intra-operative ventilatory and anesthetic management will be left to the discretion of the clinical care team. Two to three days after surgery, patients will undergo repeat AxV-128/Tc SPECT-CT scan.

At each scan a blood sample to correlate serum biomarkers and a urine sample to measure cotinine to confirm the smoking status of the subject will be drawn. For the post-operative imaging, we will exclude patients with hemodynamic instability (vasopressor requirement at 36 hours post-operatively), inability to transport due to other clinical instability as determined by clinical care team or withdrawal of consent. Blood samples will be also stored for possible future DNA and RNA analysis.

Pulmonary Function Testing:

Pre- and post-bronchodilator spirometry, lung volume and DLCO measurements will be obtained prior to surgery only. Any clinical chest CT scans or pulmonary function testing performed in the interim at Columbia University for clinical care will be analyzed to assess lung structural and morphometric changes.

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.

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 and may be abstracted from surgical medical records.

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 (if not already found in electronic medical system of NYP/CUMC). 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 after first imaging session (prior to surgery) and again 24-72hrs, 1 month and 6 months after second imaging session (after surgery). 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.

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.
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.

Study drug
Name: Tc-99m rhAnnexin V-128
Dose: 10 mCi
Study phase: Phase 2
Manufacturer Information: Advanced Accelerator Applications, USA
Route of administration: Intravenous

Recruitment/Screening Procedures
All patients scheduled to undergo Whipple surgery or other major surgeries at Columbia University Medical Center (CUMC) will be eligible for enrollment. Eligible patients will be identified and approached by the surgeon or anesthesiologist in charge of their care to ask if they are willing to discuss participation in this study. Flyers will also be placed in waiting room of pancreatic clinic. If the patient agrees to discuss participation, a member of the research team will contact the patient, explain the study including risks and benefits in order to obtain informed consent preoperatively. Patients will be consented in their respective hospital room. The consent will not be sought on the same day of the patient's surgery. At a minimum, the surgeon will provide the consent form to the patient prior to the day of surgery. If participant continues to express interest after the study was thoroughly explained, we then inquire if it is OK to proceed with eligibility questions. We go over the inclusion and exclusion criteria as listed below:

Eligibility Questions: Inclusion Questions: (I) Males and females age 45-80 years (II) Able and willing to comply with the study procedures (III) Will undergo major surgical procedure (IV) Non-Smoker (V) Lie flat for 30 minutes? Exclusion Questions: (I) Current Lung Malignancy (II) Recent COPD exacerbation (less than 1 month) (III) Recent pulmonary infection (less than 1 month) (IV) Asthma or other significant lung disease (V) Pregnancy or lactation (VI) Have high creatinine level (VII) Have smoked within the last 30 days (any type of smoking – cigarettes, marijuana...etc.)

As part of the screening, subjects will self-report their medical history over the phone to the study team (i.e., smoking history, COPD Exacerbation history, medications and medical history relevant to study and Alpha-1 deficient or carrier state if applicable). For subjects whom can provide medical records, these will not be accessed until the subject has signed the informed consent form. Please note that the eligibility screener form serves as the source document for patent's self-reported medical history.

After Screening Procedures:
If they seem to meet the criteria, we then ask if it is OK to maintain their contact information (including: name, phone number, address and DOB) to give them a call back once an investigator has agreed upon their eligibility status to participate in the study (and signed the eligibility/screener internal document). Please note, the investigator, CRC and surgical clinical staff have pre-screened the potential participant and provided access for the CRC to introduce study after clinic appointment with surgeon. After thoroughly explaining the study and verifying eligibility, the participant may be consented and study procedures may be scheduled for prior and after to the surgery date.

Research Question(s)/Hypothesis(es)
Investigate the hypothesis that AxV-128/Tc SPECT-CT imaging identifies peri-operative lung injury-
Investigate the hypothesis that AxV-128/Tc SPECT-CT imaging discerns more severe perioperative lung injury in patients with COPD compared to patients without COPD.

Scientific Abstract
Lung injury is commonly not detected unless structural damage has occurred. Single-photon emission computed tomography - SPECT CT scanning using a specific tracer that lights up when it detects apoptosis (programmed cell death) has been used to detect even minor lung injury for example by smoke inhalation in animals and may be more sensitive to detect less. The present study aims to study SPECT-CT scan using a tracer for apoptosis, 99mTc Annexin V-128 (AxV128/Tc), to detect lung injury after major surgery. Prolonged ventilation during surgery can cause minor lung injury but is usually not detected. We are planning to study 40 patients (20 patients with pre-existing lung disease-COPD and 20 patients with normal preoparetiave lung function) who are undergoing Whipple operations or other major surgery. We will obtain SPECT-CT scans before and then 2-3 days after surgery and compare the uptake of a radioactive tracer with plasma markers of lung injury (sRAGE, IL-6, Clara-cell 16 and SP-D among others). We will ask the subjects to undergo spirometry testing, blood draws, urine collection and a SPECT-CT scan that last about one hour before and after surgery. The subjects will receive $250 for each scan as compensation for their time.The total effective dose from each 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).

Lay Abstract
We are testing a new Nuclear Medicine scan that can detect death of cells in the lungs following injury. When patients have major surgery they are intubated (tube placed in their windpipes) and ventilated using a respirator. When the period of time a patient is on the respirator is long such as is needed is extensive surgical procedures such as removal of the pancreas for pancreatic cancer, lung injury can occur. This injury can prolong recovery in some patients and increase risk for a poor outcome. It would be clinically helpful to identify patients who are at increased risk to have this lung injury before surgery to plan better ways to prevent it. Some patients with COPD have been identified to be at higher risk. In this study we plan to inject this new radiotracer and image the lungs on a standard nuclear medicine imaging camera before surgery and see if the results of the scan can help predict patients who will have poorer outcomes due to acute post-operative lung decompensation. If the patient is stable enough we plan to repeat the scan after surgery which will show how much damage the prolonged time on the respirator has caused. We plan to study 40 patients scheduled for Whipple surgery or other major surgery, 20 without history of lung disease and 20 with some known COPD. Each scanning procedure

takes about 40 minutes. The risk from the additional radiation exposure is not different from any other nuclear medicine procedures in current general clinical use.