Noninvasive Assessment of Abdominal Aortic Aneurysm Wall Structural Integrity and Inflammation as Predictors of Expansion and/or Rupture

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I. BACKGROUND AND SIGNIFICANCE

Abdominal aortic aneurysm (AAA) is a significant medical problem, with a high mortality rate, accounting for approximately 150,000 hospital admissions per year. AAA is the 10th leading cause of death in Caucasian men, ages 65 - 74 years, and has accounted for nearly 16,000 deaths overall.[1] Necropsy studies from the United States and Europe suggest an overall prevalence for AAA of 2-4% for men and 1-2% for women.[2,3] Population based screening studies demonstrate a prevalence of approximately 9% in men and 2% in women.[4] It has been demonstrated that the prevalence of AAA increases with increasing age, with an increased prevalence in males compared to females. Noninvasive screening in the elderly population has led to an overall increased incidence of asymptomatic AAA.[2,3,4,5] Currently, 35,000 to 40,000 aneurysms are treated surgically in the United States.[6] Once AAA formation has commenced, aneurysms will continue to grow at a variable rate, until they ultimately rupture. AAA rupture is associated with very high morbidity and mortality. Perioperative mortality rates of approximately 45% have been reported for open AAA repair in the United States since the late 1980s.[7] Approximately 60% of patients with ruptured AAA die before reaching the hospital,[8] and emergency open surgical repair carries a mortality rate of 35-70%.[9] The incidence of AAA rupture continues to increase despite aggressive attempts to screen at-risk populations.[10],[11],[12] Improvements in early aneurysm detection and surveillance are necessary to decrease the incidence of AAA rupture and associated mortality.[13]

It is believed that AAA rupture occurs when the aortic wall stress exceeds the tensile strength of the degenerated AAA wall. Finite element analysis (FEA) may be utilized to implement biomechanical principles in an effort to assess AAA expansion and/or rupture risk.[14,15,16,17] Efforts have been made to include intraluminal thrombus (ILT) and the anisotropic AAA tissue behavior into the computer models of AAAs. AAA rupture occurs when the stress acting on the AAA wall exceeds its strength; therefore, the prediction of AAA rupture must include wall stress and strength distributions. Considering this, rupture potential index (RPI) is defined as the ratio of the acting wall stress to the wall strength, and the maximum RPI for AAA represents its rupture risk. Comparing peak stresses and strains using anisotropic and isotropic constitutive relations, we have demonstrated significant increases in peak stress when using the anisotropic relationship.[18] Considering ruptured AAA patients (N=8) and non-ruptured AAA patients (N=4), we have demonstrated a significant decrease in AAA wall strength of those AAAs that went on to rupture. The differences in RPI values did not reach statistical significance, when comparing ruptured and non-ruptured AAAs; however, our initial data suggests that peak RPI may serve as a better predictor of AAA rupture than maximum diameter or peak wall stress alone.[19]

It is hypothesized that the final event leading to aortic rupture involves the degradation of collagen within the media, extending out through the adventitia. This occurs through a catalytic process induced by inflammatory cells in the aortic wall. Macrophages and neutrophils are a major source

of key enzymes at play, particularly serine proteases and matrix metalloproteinases, and are believed to play a critical role in this tissue degradation.[20] Inflammation of the vascular wall related to phagocytic macrophage activity can be demonstrated by increased uptake of 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) PET in the arterial wall.[21] Accordingly, ^{18}F-FDG PET has been used to assess AAA wall inflammation,[22] and increased ^{18}F-FDG uptake has been identified in symptomatic AAAs (pain on palpation of AAA) and with rapid aortic enlargement.[23] Considering symptomatic AAA patients (N=3), Reeps *et al*. demonstrated significantly increased ^{18}F-FDG AAA uptake that correlated with greater macrophage populations on AAA wall histology, as well as higher MMP9 expression and decreased collagen fiber content, when tissue was taken at the time of repair.[24] In a follow-up manuscript, Reeps *et al*. demonstrated the ability to discriminate between symptomatic (N=5) and asymptomatic (N=18) AAA patients on the basis of ^{18}F-FDG uptake. They then correlated this increased ^{18}F-FDG uptake with aortic wall macrophage infiltration and MMP9 expression.[25] We have reviewed ^{18}F-FDG PET scans for AAA patients at a single institution compared with those of atherosclerotic, non-aneurysmal aortas and demonstrated significantly greater global ^{18}F-FDG uptake by AAAs.[26] Utilizing the porcine pancreatic elastase (PPE) exposure model in rats stimulated to rupture with β-aminopropionitrile (BAPN) exposure, we have demonstrated the ability of ^{18}F-FDG microPET to identify metabolically active sites in a pre-rupture state that ultimately rupture.[27]

Translocator protein (TSPO), formerly referred to as peripheral benzodiazepine receptor, is an 18-kDa outer mitochondrial protein highly expressed in phagocytic inflammatory cells, such as macrophages in the periphery and macrophage-like microglial cells in the central nervous system. It has been demonstrated that other inflammatory cells including neutrophils, B cells, natural killer, as well as CD4- and CD8-positive cells express TSPO to varying degrees.[28] The TSPO radioligand ^{11}C-PBR28 ([methyl-11C]N-acetyl-N-(2-methoxybenzyl)-2-phenoxy-5-pyridinamine) has been used for neuroimaging with primates and humans, as well as imaging lung injury in humans.[29,30] Other TSPO radioligands, including ^{11}C-PK1195, have been utilized to evaluate macrophage presence and behavior in rodent and human carotid plaques.[31,32]

We have previously demonstrated the utility of ^{18}F-FDG and ^{11}C-PBR28 to study inflammation associated with the PPE model of AAA development in rats, thereby verifying similar ^{18}F-FDG imaging characteristics in this model compared to humans.[33] In conjunction with increased TSPO gene expression and protein expression in AAA, this data supports the potential role of ^{18}F-FDG and TSPO radioligands for the assessment of aortic wall inflammation during the development of aortic aneurysms in patients. Based on macrophage uptake and autoradiographic findings, as well as the natural history of AAA rupture, we are seeking to explore the uptake and distribution of TSPO radiotracers compared to ^{18}F-FDG and the potential of ^{11}C-PBR28 for the prediction of AAA expansion and/or rupture. This is the first study to assess the use of ^{11}C-PBR28 to confirm the work we have performed in rat models of AAA expansion and rupture. The goal of this project at this point is not to change current subject management, but we plan to establish the groundwork that will serve as a basis for a larger scale study in the future.

II. SPECIFIC AIMS

The aim of this project is to assess the ability of three different imaging techniques to determine

abdominal aortic aneurysm (AAA) rupture risk individually and in concert. Currently, the primary factor considered for risk of human AAA rupture is aortic diameter; however, it is well documented that small AAAs (<5cm) rupture, while many large AAAs (>8cm) are incidentally discovered. Thus, there is no absolute diameter threshold at which AAAs rupture. Approximately 60% of patients with ruptured AAA die before reaching the hospital, and emergency open surgical repair carries a mortality rate of 35-70%. This suggests that a new diagnostic modality must to be developed to reliably predict AAA rupture risk.

We will image subjects with atherosclerotic, non-aneurismal aortas as a control group. We will also image smaller, surveillance size (3.0-4.5cm) AAAs, AAAs that will undergo treatment (female >5.0cm, male >5.5cm), as well as rapidly expanding AAAs (>0.5cm over 6 months and/or >1.0cm over 12 months). The assessment of AAA wall structural integrity by FEA, generated utilizing CTA, will be studied in the context of increased metabolic activity and inflammation determined by ^{18}F-FDG and ^{11}C-PBR28 PET. We hypothesize that areas of increased ^{18}F-FDG and ^{11}C-PBR28 uptake will correlate; however, areas of more discrete, focal ^{11}C-PBR28 uptake will correlate with areas of greatest RPI and decreased strength in the AAA wall, and this will be most pronounced in rapidly expanding AAAs. However, we also hypothesize that a fraction of smaller AAAs will exhibit a similar pattern, demonstrating areas of increased metabolic activity and inflammation that are at increased risk of expansion and/or rupture, independent of size or diameter.

Aim 1. Perform coregistered, FEA, as well as ^{18}F-FDG and ^{11}C-PBR28 PET of the infrarenal aorta using PET-CTA.

Approach. Consider a rapidly expanding AAA group that will demonstrate changes in the structural integrity and inflammatory cascade within the AAA wall validating a current approach to AAA treatment. Consider a surveillance group of AAA subjects that will demonstrate the ability of FEA as well as ^{18}F-FDG and ^{11}C-PBR28, to identify those subjects that are at increased risk of AAA expansion and/or rupture, independent of size.

Aim 2. Compare patterns of decreased aortic strength with patterns of increased stress and inflammation across three subject groups to determine the appropriateness of expanding these analyses to a larger group of clinically relevant subjects.

Approach. Utilizing evolving software to evaluate the same aortic volume across data sets, we will compare areas under greatest stress and lowest strength determined by FEA. Multiplanar and volumetric analyses of co-registered, FEA as well as ^{18}F-FDG and ^{11}C-PBR28 PET images will also be performed. With direct co-registration of the data sets for each subject, qualitative comparisons will be made regarding areas of ^{18}F-FDG and ^{11}C-PBR28 uptake, as well as stress, strength, and RPI.

III. SUBJECT SELECTION

Twenty-four subjects will be recruited for this study. Six control subjects (three males and three females), will be considered. Control subjects will have known atherosclerosis by standard clinical criteria, without aneurysmal disease. Six subjects (three males and three females) with small AAAs

(diameter 3.0-4.5cm), six subjects (three males, AAA >5.5cm and three females, AAA >5.0cm) with AAAs that are indicated for treatment, and six subjects (three males and three females) with rapidly expanding AAAs (>0.5cm over 6 months and/or >1.0cm over 12 months) will be considered. During a clinical visit, the treating physician will introduce the study to each subject, and the study coordinator will provide a comprehensive description and materials to the subject.

Subjects 45 years of age or older will be considered and subjects from any at-risk populations (e.g.: cognitively impaired persons, prisoners) will not be included. A subject will not be eligible for inclusion if any exclusion criteria for PET-CTA apply. Any woman of childbearing age, who is planning to become pregnant, is breastfeeding, and/or suspects she may be pregnant, will not be enrolled in the study.
A subject will not be eligible for inclusion in this study if any of the following criteria apply:

- less than 45 years of age;
- pregnant or breastfeeding;
- any greater than normal potential for cardiac arrest;
- Renal disease – defined as eGFR < 60mg/ml/1.73m^2
- claustrophobic reactions and/or is unable to lie comfortably on a bed inside the scanner for 60 minutes as assessed by physical examination and medical history (e.g. back pain, arthritis);

A TSPO polymorphism has been previously demonstrated, and quantitative interpretations of signal can be confounded by interindividual variability in binding affinity.[34] To avoid this confounder, we will perform Ala147Thr TSPO polymorphism genotyping as part of the screening process. Those subjects identified as mixed affinity or high affinity from the genetic testing results will continue with PET-CTA imaging. Those subjects who are identified as low affinity will be considered screen failures and will not have PET-CTA scanning performed.

Eligibility will be determined by a screening interview and review of the medical record. All subjects recruited for the study will be able to withdraw from the study at any time.

IV. SUBJECT ENROLLMENT

Subjects scheduled for a vascular surgery clinic visit who fulfill the eligibility criteria will be identified through the patient appointment log.

The clinicians will introduce the study to the subject during a clinic visit and will obtain permission from the potential subject to be approached by study staff. Subjects will then be approached in person (ideally, and whenever possible) by a study coordinator to undergo consent and schedule the study. At this time, subjects will be informed that the PET-CTA scanning session will be performed on the BJH main campus.

The subjects will be informed about the PET-CTA scans, including that these scans will have no benefit or impact on their management as well as the risks associated with receiving Iopamidol, a regularly used CTA contrast agent, as well as ^{18}F-FDG and ^{11}C-PBR28, the two radiotracers being studied.

Informed consent will be obtained from the subjects by a member of the study team prior to obtaining the TSPO polymorphism genotyping blood sample and before the imaging session. The study team member obtaining consent will explain the purpose of the study and its potential benefits to society at large. The protocols for the scans will be explained in detail. Subjects will be informed about potential risks and benefits of PET-CTA and that the scans will have no benefit or impact on their management. Subjects will be informed that they may withdraw from the study at any time, for any reason. They will be informed that their refusal to participate in the study or choosing to terminate participation at any point will have no influence on their future care and treatment. Study subject information will be protected under HIPAA guidelines.

All subjects will receive a one-time $200 remuneration following completion of the study required PET-CTA scans. All subjects will also be offered parking validation for BJH main campus parking.

V. STUDY PROCEDURES

Subjects who have not had an eGFR blood test performed within the previous 90 days will have approximately 10 ml or 2 teaspoons of blood drawn for creatinine testing prior to the scan being performed.

Subject Screening - Subjects will be recommended by their treating physician for the study during a clinic visit. The study team member obtaining consent will reinforce with the subjects that participation is voluntary and any decision not to participate will not in any way affect their care, now or in the future. If the subject chooses to participate, the study team member will obtain written informed consent. Any woman of childbearing age, who is seeking to become pregnant, is breastfeeding, or who suspects she may be pregnant, will not be enrolled in the study.

As part of subject screening a genetic test (Ala147Thr TSPO polymorphism genotyping) will be performed. During enrollment subjects will be informed about the genetic testing for study eligibility. If subjects decide to be part of the study and sign the consent, blood will be drawn by the study coordinator. Only those subjects identified as mixed affinity or high affinity from the genetic testing results will continue with PET-CTA imaging. Those subjects who are identified as low affinity will be notified by the study team and will not have PET-CTA scanning performed. Participation in the study will end for the low affinity subjects following the genetic testing.

Any female subject of child bearing potential will have a serum or urine pregnancy test the day of the PET scans.

Any subject under 45 years-old will not be enrolled in this study. No third parties will assist with recruitment of eligible subjects for this protocol.

Imaging Details:

Positron Emission Tomography (PET)- Computed Tomography Angiography (CTA) – Eligible participants will undergo ^{18}F-FDG and ^{11}C-PBR28 PET-CT and contrast-enhanced CTA imaging performed on the Siemens Biograph 40 PET-CT scanner. All participants will be studied after at least 12-16 hrs of fasting. Subjects will be positioned for maximum comfort on the imaging

table, supine and arms resting above the head or across the chest out of the field of view. PET imaging will begin with ^{11}C-PBR28. A dosage range of 10-20 mCi is planned. A low-dose CT attenuation scan of the abdomen and pelvis will be acquired for subsequent correction of photon attenuation. Each subject will receive a single intravenous bolus injection of the maximum planned dosage of 20 mCi diluted with normal saline up to a total of 20 mL. The imaging acquisition over the aneurysm site will begin immediately with a ~20-minute dynamic imaging scan. At the end of this imaging scan a 20 min static scan will be performed in the adjacent abdominal or pelvic site (to serve as a reference location). Subject will remain in the scanner for the FDG injection and CT angiography. Subjects will receive an intravenous bolus injection of 10 mCi of ^{18}F-FDG followed by a 90-minute period prior to reimaging. Next, subjects will receive a standard dose of the Iopamidol contrast agent (50cc) followed by CTA imaging of the abdomen and pelvis using standard acquisition parameters to identify the arterial region of interest (ROI) to determine the blood input function. At the end of the CTA imaging scan, subjects will be removed from the scanner to rest in an uptake room to allow for the decay of ^{11}C-PBR28. Subjects will be asked to use the restroom to empty their bladder after being removed from the scanner after the CTA imaging and again prior to being repositioned on the imaging table for the FDG scan. A second low-dose CT attenuation will be performed with subsequent ~20-minute dynamic imaging acquisition for FDG. The entire imaging session, including both PET and CT acquisitions, will last up to approximately three hours. The CTA images will be used to identify the arterial region of interest (ROI) for use in determining the blood input function.

Aortic wall ^{11}C-PBR28 and ^{18}F-FDG uptake will be considered in terms of standard uptake values (SUV) considering the infrarenal abdominal aorta from the crossing of the left renal vein to the iliac bifurcation. Voxel-wise SUV values over the AAA will be qualitatively assessed across subjects and groups. Maximum (SUVmax) and mean (SUVmean) values normalized to the blood pool and non-aneurysmal thoracic aorta will also be considered. SUVmax and SUV mean values associated with areas of focal uptake will also be considered and compared across subjects and groups using a Students *t*-test, with $P = 0.05$ indicating significance.

Image Evaluation:
Images will be evaluated by an experienced vascular surgeon, who will only evaluate the infrarenal abdominal aorta. Other organs and anatomic structures in the field of view will be evaluated by a radiologist on the study team for incidental findings.

While there is some subjectivity in the manner by which a region of interest (ROI) is determined for image analysis, this study may not be blinded between control and experimental subjects, as control subjects will have non-aneurysmal aortas. However, the analyzing vascular surgeon will be blinded to whether a subject has a small versus a rapidly expanding AAA.

FEA Interpretation:
FEA will be performed by Dr. David Vorp's group at the University of Pittsburgh. PET-CTA scans performed for the study will be copied onto CD, labeled with a study ID only and mailed by a member of the Washington University Study team. No PHI will be provided to University of Pittsburgh. The PET-CTA scans and FEA performed by Dr. Vorp's laboratory at the University of Pittsburgh will be saved for possible future analysis or data presentation.

VI. BIOSTATISTICAL ANALYSIS

This is an exploratory (hypothesis generating) study. Subject Maximum transverse diameters, mean and peak wall stresses, mean and minimum wall strengths, and mean and peak RPI values will be compared between groups using a Students *t*-test, with $P < 0.05$ indicating significance. Aortic wall ^{11}C-PBR28 and ^{18}F-FDG uptake will be considered in terms of standard uptake values (SUV) considering the infrarenal abdominal aorta from the crossing of the left renal vein to the iliac bifurcation. Voxel-wise SUV values over the AAA will be qualitatively assessed across subjects and groups. Maximum (SUVmax) and mean (SUVmean) values normalized to the blood pool and non-aneurysmal thoracic aorta will also be considered. SUVmax and SUVmean values associated with areas of focal uptake will also be considered and compared across subjects and groups using a Students *t*-test, with $P < 0.05$ indicating significance. Multiplanar and volumetric analyses of coregistered FEA, with ^{11}C-PBR28 and ^{18}F-FDG PET images will also be performed. With direct coregistration of the data sets for each subject, qualitative comparisons will be made regarding areas of ^{11}C-PBR28 and ^{18}F-FDG uptake, stress, strength, and RPI. Quantitatively, correlations of each data set per subject will be determined.

There will be experimental and control group analysis by comparing subject demographics and aortic image measures. ANOVA with post hoc analyses will be performed to compare the groups.

Power Calculation:

From clinical experience, we expect total 24 subjects, approximately six subjects (3 men and 3 women) with small AAA size that will continue to undergo surveillance (3.0-4.5cm), six subjects (3 men and 3 women) with AAAs that will undergo treatment, and six subjects (3 men and 3 women) with rapidly expanding AAAs (>0.5cm over 6 months and/or >1.0cm over 12 months). Control group will be consist of 6 subjects (3 men and 3 women) with known atherosclerosis, by nature of carotid stenosis and no aortic aneurismal dilation. Since this is an exploratory study, there is no definite power calculation for qualitative measures but quantitative analysis for continues variables, to reach a power of 0.80 with confidence level of 95% at alpha level of 0.05, there are approximately 10 subjects are needed per group. This is a small exploratory study, and we will limit the subject enrollment to six subjects per group due to the financial reasons.

Statistical analysis will be performed using the SAS statistical package (SAS Institute Inc., Cary, NC).

Specific Data Variables

- Demographic/Social
    - Age, sex, race, smoking status
- Clinical
    - Height, weight, BMI
    - History of DM, HTN, CAD, COPD, CKD, CHF
    - Medication history (including current medications)
    - Hemodynamic laboratory results
- Procedural
  PET image measures, FEA image measures

VII. RISKS AND DISCOMFORTS

Risks of PET-CT:
Subjects participating in this study who undergo PET-CTA, will be exposed to radiation from PET-CTA scans of the abdomen and pelvis. Please note that this radiation is not necessary for the subject's medical care and is for research purposes only.

This study will expose subjects to radiation from PET-CTA scans of the abdomen and pelvis and from the radiotracers ^{11}C- PBR28 and ^{18}F-FDG. For ^{11}C-PBR28 a dosage range of 10-20 mCi is planned. The Effective Dose for cumulative and maximal radiation dosimetry is 2.42 rem and 2.73 rem, respectively. This includes a single intravenous injection of the maximum planned administered dosage of 20 mCi of ^{11}C-PBR28 and 10 mCi of ^{18}F-fludeoxglucose plus two low-dose CTAC scans with topogram and contrast-enhanced CTA imaging of the abdomen and pelvis. Maximal Radiation Dosimetry includes one additional low-dose CTAC scan with topogram for subjects who undergo a make-up study in the event of technical difficulties due to cyclotron radiopharmaceutical failure or with the PET-CT scanner.

If a subject is pregnant or breastfeeding they may not participate in this research study.

Since the effects of radiation can be cumulative, it is important to know of past research related radiation exposure. If the subject has participated in other research studies in the past 12 months that have involved radiation exposure, they will be asked to inform the investigators or study staff. If it is determined that the subject's prior radiation exposure exceeds our current guidelines, it is possible that they will not be allowed to participate in this study.

Risks of the Radiotracers ^{11}C-PBR28 and ^{18}F-FDG:
There are no known side effects to these radioactive dyes. FDG is approved by the FDA and is used daily across the United States. ^{11}C-PBR28 is an investigational radioactive drug. An investigational drug is one that has not been approved by the U.S. Food and Drug Administration (FDA). This means that PBR28 can only be used in research studies.

There are no known pharmacological risks or side effects of receiving ^{11}C-PBR28 at the dose subjects will receive. However, as with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Subjects will be instructed to notify study staff right away if they think they are having an allergic reaction.

^{18}F-FDG is a type of radiation emitting product that may increase an individual's risk of cancer. We use the smallest dose necessary for imaging and ensure safety during injection.

Risks of the IV:
Placing an IV catheter into the arm may cause some pain, discomfort, bruising, bleeding, swelling, and redness in that area. There is a slight risk of infection which can be treated, temporary loss of pulse at the wrist, and fainting. There may be bruising, pain or discomfort for 2-3 days after the

IV catheter is removed. Rarely, an infection may occur at this site, and if infection does occur, it will be treated appropriately. A urine or serum blood (about 2 teaspoons) of blood may be taken during this study for pregnancy test, if required.

Risks of Iopamidol Dye:
Rare side effects from the contrast dye Iopamidol include:

- Nausea (up to 2 in 100 of people).
- Hives (itchy red bumps on the skin, < 1 in 100 people)
- Severe allergic reaction, which can be life threatening (very rarely happens, < 1 in 100,000 people). If you have any signs of allergic reaction, we will treat you immediately.

Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Subjects who think that they are having an allergic reaction, should notify the study physician immediately. If they are having trouble breathing, they should tell the study physician immediately. If experiencing any swelling of the face and/or throat, and/or experiencing any trouble breathing after leaving the imaging center, they should call 911 immediately and seek medical assistance.

Risks of Unexpected Findings:
We are performing PET-CTA scans in this study to answer research questions, not as part of the medical care. The information created by this study will not become part of the subject's hospital record. The PET-CTA scans are not the same as a scan that another physician would order. It may or may not demonstrate anatomy/pathology that would be found on standard PET or CTA scans.

The imaging studies performed for this study are for research purposes only. We will only evaluate the infrarenal abdominal aorta. Other organs and anatomic structures in the field of view will be evaluated for incidental findings by a radiologist on the study team.

VIII. POTENTIAL BENEFITS

There is no expected direct benefit for subjects taking part in this study. Results of this study may contribute to prevention of AAA rupture in the future.

IX. MONITORING AND QUALITY ASSURANCE

Any unanticipated problems and adverse events involving risk to human subjects will be reviewed by the Principal Investigator and will be reported to the Human Research Committee and the BJH RDRC, within the required time frame and to all participating investigators by the PI, according to the Human Research Protection Office guidelines.

The imaging techniques utilized for this study are all FDA approved. Each scanner has a built-in monitoring system that automatically shuts down the scanner, if parameters exceed safe levels. In addition, imaging technicians constantly monitor the subjects' physiologic status and quality of the raw data.

Subject data will be stored on a secure, limited-access, password protected, WU network shared drive. Access will be granted to members of the study team. If any new investigator is added to the protocol and approved by the IRB, the PI will provide network access to that specific investigator.

Data entry will be done by the research coordinator /research nurse weekly and will be monitored by the PI.

PROJECT TIMELINE

Objective	Months 1-8	Months 9-10	Months 11-12
Perform coregistered FEA with /^{18}F-FDG & ^{11}C-PBR28 PET	✓		
Compare patterns of decreased aortic strength with patterns of increased stress, RPI, and inflammation		✓	
Finalization of data analysis and abstract submission			✓

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