TITLE: PET MYOCARDIAL BLOOD FLOW COMPARISON TO CORONARY CTA and CT-FFR

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I. Rationale: Ischemic heart disease is a major public health problem. Twenty-five percent of men and seventeen percent of women between the ages of 60 to 79 have coronary artery disease (CAD) and these figures increase with age. Ischemic heart disease is also the number one cause of death in men and women (1). A variety of non-invasive testing has been developed to evaluate for CAD in an attempt to guide treatment and revascularization planning. Approaches include both anatomic evaluation of the coronary arteries as well as functional evaluation of the myocardium for ischemia. Modern CT scanners have allowed for coronary CT angiography (cCTA) to provide a reliable anatomic evaluation of coronary vessel patency and a very high negative predictive value for CAD. However, anatomic determination of stenotic degree alone has not proven to be a reliable surrogate for hemodynamic significance. More recently, the development of cCTA fractional flow reserve (cCTA-FFR) has transformed the evaluation from being a solely anatomical study to one that also provides functional hemodynamic data. Still, while the validity of this noninvasive hemodynamic data has been verified in numerous prospective studies at this point, the utility of cCTA-FFR remains limited in most institutions. This has largely been due to the exceptional computations required to create the FFR data and the reliance on a single company (HeartFlow) to provide the computing offsite which can lead to delays in obtaining results. As a different approach to assess CAD, PET myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) have shown great sensitivity in determining both regional and global ischemia. However, the lack of coronary anatomic information hinders the specificity of these methods. Interestingly, Kajander et al have shown the superiority of a hybrid approach (combining PET-cCTA) when compared to either modality alone (2). Modern imaging systems allow this model to be taken one step further, combining PET with cCTA and CT-FFR. Furthermore, at-workstation models of calculating FFR data could help to bring this technique into much wider usage.

We propose to perform a pilot study which will compare N-13 ammonia PET regional MBF and MPR to the presence to coronary artery stenoses on cCTA and their significance by CT-FFR. PET MBF/MPR and CT-FFR will then be compared to the reference standard of invasive coronary catheterization (ICA) with invasive FFR measurements.

II. Objective:

The broad, long-term objective of this pilot study is to develop an optimal, clinically usable, non-invasive evaluation of CAD in the setting of stable angina which provides both anatomic and functional information.

In this study our primary endpoint is significant stenosis for flow limiting lesions (≤ 0.8) by CT-FFR. We will derive sensitivity, specificity, NPV, PPV of CTA-cFFR compared to the reference standard of standard of care ICA with FFR for each epicardial coronary artery.

Our secondary endpoint will be the correlation of segmental PET MBF and MPR to presence or absence of a coronary artery stenosis ≥ 50% diameter, and in patients with stenosis ≥ 50% diameter, correlation with CT-cFFR, and ICA/ICA FFR for which we will perform a Pearson correlation coefficient. We will also compare a hybrid model of PET MPR-CTA-cFFR to standard of care ICA with FFR. We will record patient risk factors. We anticipate that MBF/MPR may not always correlate with anatomic information or FFR, especially in the presence of small vessel disease, and that, in some patients, this information will be complementary.

III. Eligibility Criteria:

Inclusion Criteria:

- 18-90 years of age, of either sex
- Patients presenting with stable angina and a moderate pretest likelihood for CAD and scheduled to undergo ICA for the clinical indication of angina. Subjects will undergo this study within 45 days prior to the cardiac catheterization. This study can also be performed 45 days after the cardiac catheterization if the patient had no interventions.

Exclusion criteria:

- Prior history of stenting, coronary artery bypass graft surgery, or myocardial infarction, unstable angina, atrial fibrillation, second or third degree atrioventricular block, class IV heart failure
- Iodine allergy
- Renal dysfunction (creatinine above normal laboratory limits)
- Symptomatic asthma
- Women who are pregnant or breast-feeding

IV. Methods:

Subjects and Recruitment: This is a single cohort, technology assessment study. Thirty-five patients presenting with stable angina and a moderate pretest likelihood for CAD who are already scheduled to undergo ICA for the clinical indication of angina will be recruited to undergo PET-cCTA-cFFR. Exclusion criteria include: Prior history of stenting, coronary artery bypass graft surgery, or myocardial infarction, unstable angina, atrial fibrillation, second or third degree atrioventricular block, class IV heart failure, iodine allergy, renal dysfunction, symptomatic asthma, and pregnancy.

Patient history will be gathered on the following: gender, age, weight, BMI, risk factors (HTN, DM, DLD, smoking), family history, and medications (statins, Beta blockers, Nitrates, ASA).

Recruited patients will undergo cCTA and concurrent N-13 ammonia stress and rest PET evaluation. Patients will undergo their clinically scheduled ICA with FFR within 2 weeks. ICA with FFR will be compared to each of these modalities alone (cCTA, CTA-cFFR, PET MBF/MPR) as well as a hybrid model of these modalities together (PET-cCTA-cFFR). Patients will be contacted by phone 24-72 hours after scanning to ask about any interval changes in health. The coordinator will also call the patient between 25-30 days following their ICA to assess for major adverse cardiovascular event (MACE) defined as hospital readmission for myocardial infarction, angina, or ventricular arrhythmia, or cardiovascular death. The protocol will be reviewed and approved by the Washington University Human Studies Committee and all patients will receive informed consent.

Patients who have already undergone a cCTA within 45 days of their planned PET/CT will not undergo the cCTA component of the research examination. Rather, their cCTA will be collected retrospectively for research evaluation.

V. Imaging Protocol:

Recruited patients will be evaluated on a Siemens Vision PET/CT scanner (128-slice Siemens Edge).

PET-CTA Examination:

If the subject has not had prior cCTA imaging, a comprehensive cardiac PET-cCTA will be performed with acquisition of PET and cCTA imaging in the same setting.

cCTA: The CT portion of the exam will be obtained first. Intravenous esmolol (500 mcg/kg over 1 min and then 100-250 mcg/kg/min) will be administered before the scan to reach a target heart rate of 65 beats per minute. Blood pressure monitoring will occur at each level to ensure systolic blood pressure stays above 100mmHg. Sublingual nitrate (0.4 mg) will be given immediately before the exam.

Scout imaging and non-contrast AC CT scan will be obtained. Then a noncontrast CT coronary calcium (CAC) examination (EKG-gated, sequential) will be performed. Subsequently, iodinated contrast will be infused (100 mL at 4 mL/sec) intravenously followed by a 50 mL saline bolus at the same injection rate and the cCTA performed.

Stress PET: After a 10 minute delay, to allow the heart rate to return to baseline, regadenoson will be hand injected continuously (prefilled syringe: 0.4 mg / 5 mL) over 10 seconds. After an additional interval of 15-20 seconds, 10-12 mCi N-13 ammonia will be hand injected as a bolus followed by immediate injection of 10 mL saline solution over 30 sec. PET emission scan in list mode will be started scan exactly with or seconds before N-13 ammonia injection.

Rest PET: Approximately 30-40 minutes later, to allow sufficient decay of N-13 ammonia to avoid residual activity in the heart, we will perform the rest imaging. A repeat non-contrast AC CT scan will be obtained andthe rest PET N-13 ammonia perfusion imaging will be performed. After intravenous injection of ≈ 10-12 mCi of N-13 ammonia, PET acquisition over 10 minutes in list mode will be conducted.

If the subject has previously undergone cCTA imaging within 1 month of the scheduled invasive coronary angiogram, the cCTA component of the above examination (to include the CAC) will not be performed.

VI. Image Analysis:

The cCTA will be reviewed by a cardiac CT radiologist (PKW) using a Vital Images workstation for epicardial coronary artery stenoses ≥ 50% diameter. In these lesions ≥ 50% diameter, CT-FFR will be calculated using a computational flow/AI FFR program (Siemens). CAC score will also be obtained using Vital Images software. Segmental MBF at stress and rest, and MPR will be calculated using QPET, Cedar-Sinai software.

VII. Statistical analysis:

Our primary endpoint will be significant stenosis for flow limiting lesions (≤ 0.8) by CT-FFR. We will derive sensitivity, specificity, NPV, PPV of CTA-cFFR compared to the reference standard of ICA with FFR for each epicardial coronary artery.

Our secondary endpoint will be the correlation of segmental PET MBF and MPR to presence or absence of a coronary artery stenosis ≥ 50% diameter, and in patients with stenosis ≥ 50% diameter, correlation with CT-cFFR, and ICA/ICA FFR for which we will perform a Pearson correlation coefficient. We will also compare a hybrid model of PET MPR-CTA-cFFR to ICA with FFR. Spearman's rank correlation coefficient may be used as an alternative if there are issues with the assumption of a linear model. Descriptive statistics will be used to portray demographic and clinical characteristics of study participants and clinical outcomes at 25-30-day follow-up.

CAC in each epicardial artery will be compared to regional MBF.

Sample size justification

The primary aim of this study is to estimate the sensitivity, specificity and other measures of accuracy. As such, the width of the confidence interval around these estimates are important. Based on a study by Driessen et. al, these proportions are expected to be at least 0.75. A sample size of 35 produces a two-sided 95% confidence interval with a width equal to 0.287 or (0.607, 0.893) when the proportion is 0.75. Additionally, a sample size of 35 achieves 80% power to detect a correlation of 0.45 using a two-sided Pearson correlation with a significance level of 0.05.

VIII. Time Line

Patient recruitment/Imaging exams: 4-6 months

Image and data analysis: 1 month

IX. Funding Source: Departmental

X. References

1) Fihn SD et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. Circulation. 2012;126:e354-e471.

2) Kajander S et al. Cardiac positron emission tomography/computed tomography imaging accurately defects anatomically and functionally significant coronary artery disease. Circulation. 2010;122:603-613.

3) Driessen RS et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol. 2019;73:161-73.

Appendix -- Biograph Vision PET/CT System (Siemens Medical Systems) Description:

The Biograph Vision PET scanner is the first detector with 3.2 mm LSO crystals, allowing for better spatial resolution. It also has the fastest time-of-flight imaging on the market (214 picoseconds). This helps to improve contrast and signal-to-noise ratio, significantly reducing scan time and injected radiotracer dose (factor of 3.9). This is paired with a new generation 128 slice Siemens Edge CT unit ideal for cardiac imaging. This unit was purchased under an S10 NIH grant this year.