3/9/22

Quantification of Myocardial Blood Flow by 3D Positron Emission Tomography with High and Low Rate Rb82 Infusion Profiles

PRINCIPAL INVESTIGATORS: ROBERT BOBER, MD, FACC

CO- INVESTIGATORS: NICHOLE POLIN, MD, FACC

MERRILL STEWART, MD

JOSEPH ENGLERT, MD

1.0 BACKGROUND

Positron Emission Tomography (PET) is the gold standard for non-invasive measurement of resting myocardial blood flow (rMBF) and stress myocardial blood flow (sMBF) (1,2). Measurements of MBF by PET using the radionuclides rubidium-82 (Rb-82), nitrogen-13 ammonia (N-13) or oxygen-15 labeled water have been well correlated with direct invasive measurements via doppler velocity and flow wires. The constellation of data has validated the upper limits of rMBF and sMBF in healthy, young volunteers as well as the lower limits in tissue with transmural myocardial infarctions (MI)(3-8). Furthermore, test-retest methodological precision of global PET myocardial perfusion by serial rest or stress PET minutes apart using a standard infusion bolus as measured of a 2D PET scanner is ±10%.(9) Rb-82 and N-13 are the only FDA approved radiopharmaceuticals for myocardial perfusion imaging. Currently, Rb-82 is the preferred radiopharmaceutical at Ochsner. Given Rb-82's ultra-short half-life of 76 seconds, quantification of MBF poses significant challenges on contemporary 3D PET systems.

An estimated 95% of installed PET scanners are used mainly for whole-body ^{18}F-fluorodeoxyglucose (FDG) oncology applications. Therefore, these systems have not been designed historically with the performance specifications required to achieve accurate MBF quantification and to maintain high quality myocardial perfusion imaging. As opposed to most clinical PET applications that perform static imaging at some delayed time after the tracer biodistribution has stabilized, MBF quantification requires the acquisition of dynamic images starting immediately from time of tracer administration and including the biophysical distribution process.

During early time phase of the acquisition, almost all tracer activity is concentrated in a small bolus of the venous system contained within the scanner field of view resulting in very high detector count rates that risk saturating the photon detection and processing subsystems. In contrast, during late

phases of the acquisition, the activity is distributed widely throughout the body tissues, and only a small fraction of the administered activity resides within the heart and adjacent organs in the scanner field of view. Furthermore, for short-lived tracers such as ^{82}Rb, the isotope activity will decay several half-lives over the course of imaging. Consequently, late- phase count rates (perfusion images) can be orders of magnitude lower than those of the early-phase, risking low-quality perfusion images that are noisy and require the use of smoothing filters at the expense of spatial resolution and image contrast(10). Therefore, for each 3D camera, there is an ideal range of administered Rb-82 activity such that detector saturation is avoided, and perfusion images are diagnostic(11).

Furthermore, during 3D acquisition, there is significant scatter and random detections that are corrected for within the sub-processing systems. These events occur much more frequently with higher activities and are non-linear with decay. Hence, with short lived tracers such as Rb-82, the scatter and random corrections must occur at short intervals (5-10 seconds) and images created from the summed scatter and random corrected intervals(12). The necessary processes to achieve accurate and diagnostic images requires a tremendous amount of computational power and time.

Reconstruction times on first generation 3D PET/CT could take ~45 minutes per dataset when using 5 second intervals. Therefore, a 3/9/22 Rb-82 infusion profile (20mls/min) was developed: 1) to mitigate scatter and the lengthy processing time 2) to mitigate detector saturation 3) to maintain diagnostic quality perfusion images 4) to obtain accurate MBF data. However, on modern day 3D PET/CT scanners with faster internal components and improved processing speeds, the necessity of the low flow profile vs. the standard profile (50mls/min bolus) is under debate. We seek to test these profiles on 3 distinct populations of volunteers.

2.0 Rationale and Hypotheses

As perfusion metrics in the healthy volunteers, patients with risk factors and/or coronary artery disease and in tissue with transmural myocardial infarctions has been well defined(13) AND same day test-retest variability minutes apart using a bolus infusion is ±10%(9), we shall test 3 hypotheses. The first hypothesis is repeated same day test-retest coefficient of variation (COV) of whole heart rMBF and sMBF acquired using a bolus on a modern 3D PET scanner falls within ± 10%. The second hypothesis is repeated same day test-retest COV of whole heart rMBF and sMBF acquired using a low flow profile on a modern 3D PET scanner falls within ± 10%. The third hypothesis is COV of whole heart rMBF and sMBF between bolus and low flow profile is ± 10% where the bolus is considered the standard on a modern 3D PET scanner.

The above testing and hypotheses deal with precision of MBF measurements however does not address accuracy. Measuring accuracy of non-invasive MBF measurements poses significant challenges as a "gold standard" for comparison in not realistically achievable in a clinical setting. Invasive measurements would pose unnecessary risk for patients and non-invasive "gold standard" measurements would require a standardized "phantom pump" which is not available within industry. Instead, PET labs have traditionally relied on patient populations to determine accuracy. As such, this study will not test nor is it powered to answer questions regarding accuracy. As the PET camera is currently being installed and testing prior to a "clinical go-live" is preferable to ensure measured flow metrics are consistent with the literature, as part of quality assurance, testing of the above hypotheses will also allow us to make additional observations to:

1) Confirm healthy volunteers measured rMBF and sMBF fall within published ranges (rMBF 0.69-1.06 cc/min/g and sMBF>2.17cc/min/g) .(13)
2) Confirm clinical volunteers with risk factors and/or CAD measured rMBF and sMBF fall within published ranges (rMBF 0.50-1.10 cc/min/g and sMBF >1.09 to 2.17 cc/min/g).(13)

3) Confirm rMBF in regions of infarct in volunteers with prior large myocardial infarctions fall within published ranges (rMBF <0.45 cc/min/g with minimum <0.19 cc/min/g).(14)

3.0 Study Design and Population

This is a prospective, single center study from the Ochsner Medical Center. We seek to enroll a total of 85 paid volunteers that collectively encompass the range of physiology seen in routine practice. For simplicity sake, the range can be broken down into 3 distinct groups: 1) healthy volunteers without cardiac risk factors or chronic medical conditions ("normal") 2) clinical patients with cardiac risk factors and/or history of clinical coronary artery disease (CAD), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) ("clinical") 3) patients with large myocardial infarctions demonstrated on prior PET stress testing ("infarct"). Volunteers will be recruited by "word-of-mouth" and through electronic records chart review. "Normal" volunteers will be consented and screened by history and laboratory tests for unrecognized cardiovascular risk factors, nicotine and caffeine. "Clinical" and "infarct" volunteers will not require laboratory tests other than caffeine levels. Once screened and consented, volunteers will undergo dipyridamole myocardial perfusion 3-D PET/CT stress testing with variable Rb-82 infusion profiles per the attached protocol. Female volunteers will also be questioned on their menstrual history and undergo urine pregnancy testing if appropriate on the day of the scan. The first 5 volunteers will be not be used in the final analysis but will be used to confirm proper scanner function, reconstruction settings and appropriate filter settings.

4.0 Inclusion/Exclusion Criteria

<u>Normal Volunteers</u>
The normal population will include 40 volunteers (20 men and 20 women).

Inclusion Criteria:

- Adults ≥18 and <40 years old able to give informed consent.
- Ability to abstain from caffeine for 48 hours

Exclusion Criteria:

- Any chronic cardiac disease or condition (e.g., hypertension, hyperlipidemia)
- Any chronic systemic disease or condition (e.g., diabetes, systemic lupus, rheumatoid arthritis)
- Tobacco use
- Family history in a first degree relative with clinical CAD (h/o PCI, MI or CABG) in men <55 or women <65
- Severe claustrophobia
- Positive urine pregnancy test
- Inability to give informed consent
- BMI ≥ 30 or BMI>25 and <30 provided waist to hip ratio >0.80 in women or 0.90 in men.

<u>"Clinical" Volunteers</u>

The "clinical" population will include 20 volunteers.

Inclusion Criteria:

- Adults ≥18 years old able to give informed consent.
- Any cardiac risk factor including hypertension, hyperlipidemia, diabetes mellitus or tobacco use OR
- CAD defined by with history of PCI or CABG, Coronary Ca score>400, or dense coronary calcifications noted on chest CT
- Ability to abstain from caffeine for 48 hours

Exclusion Criteria:

- Severe claustrophobia
- Hemodynamic instability or unstable symptoms
- Positive urine pregnancy test
- Inability to give informed consent

"Infarct" Volunteers

The "infarct" population will include 20 volunteers.

Inclusion Criteria:

- Adults ≥18 years old able to give informed consent.
- Prior cardiac PET scan demonstrating a fixed defect ≥ 15% of the LV myocardium with relative uptake ≤60% maximum uptake.
- In addition, to the perfusion defect, each volunteer requires either:
    - FDG PET or MRI viability studies confirming infarct OR
    - akinesis and wall thinning on ECHO within the same territory as the PET defect in addition to Q-waves on ECG
- Ability to abstain from caffeine for 48 hours

Exclusion Criteria:

- Severe claustrophobia
- Hemodynamic instability or unstable symptoms
- Positive urine pregnancy test
- Inability to give informed consent

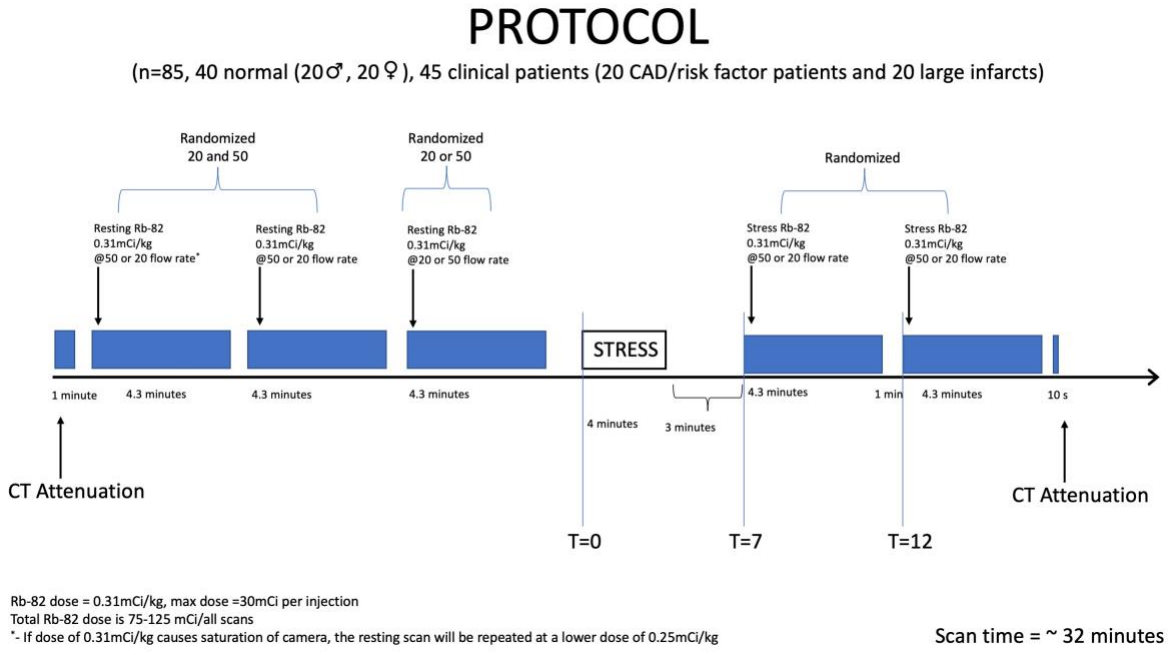
5.0 Study Procedures

All "normal" participants eligible for inclusion will have initial screening by research staff and/or research physicians. Initial screening will consist of an assessment of the volunteer's medical history, a manual blood pressure (BP) measurements, height and weight measurements and when appropriate waist to hip ratio, and venipuncture for fasting lipids, basic metabolic profile and nicotine. If the "normal" volunteer has results for any of the required laboratory testing within the past 90 days, venipuncture will not be required. Informed consent will be obtained if venipuncture is required. Exclusion from the study will result if the "normal" volunteer:

- is noted to have any chronic systemic medical condition on interview
- has a manual SBP≥130 or DBP≥80.
- Has an "abnormal" lipid profile. A "normal" lipid profile is defined as a total cholesterol ≤200 and LDL≤130 and TG≤200 and HDL≥40. Volunteers with values outside of these defined norms will be deemed "abnormal"
- has detectible nicotine levels.
- BMI>30 OR BMI>25 and <30 with waist-to-hip ratio >0.9 in men and >0.80 in women

If the "normal" volunteer is excluded based on results of the initial screen, she/he could meet inclusion criteria for "clinical". If the "normal" volunteer is not excluded based on results of the initial screen, informed consent for participation in the research study in addition to consent for the research PET scan will be obtained. Once informed consent is obtained the patient will be scheduled for the research PET scan. On the day of the PET scan and as part of the PET scan protocol, IV access will be placed. At that time, a blood sample will be obtained and sent for caffeine levels. Female volunteers will also undergo urine pregnancy testing on the day of the scan. If the pregnancy test is positive, the patient will be excluded. The volunteer will than undergo pharmacologic PET stress testing per the attached protocol using a standard weight-based dosing of dipyridamole. Once the PET stress scan is completed, the volunteer's participation is completed.

All “clinical” and “infarct” participants eligible for inclusion will have initial screening by research staff and/or research physicians. Initial screening will consist of an assessment of the volunteer’s medical history and prior PET studies (infarcts). If the “clinical” or “infarct” volunteer is not excluded based on results of the initial screen, informed consent for participation in the research study in addition to consent for the research PET scan will be obtained. Once informed consent is obtained the patient will be scheduled for the research PET scan. On the day of the PET scan and as part of the PET scan protocol, IV access will be placed. At that time, a blood sample will be obtained and sent for caffeine levels. Female volunteers will also undergo urine pregnancy test (if appropriate) on the day of the scan. If the pregnancy test is positive, the patient will be excluded. The volunteer will than undergo pharmacologic PET stress testing per the attached protocol using a standard weight-based dosing of dipyridamole. Once the PET stress scan is completed, the volunteer’s participation is completed.



- Rb-82 dose = 0.31mCi/kg, max dose =30mCi per injection
- Total Rb-82 dose is 75-125 mCi/all scans
- *- If dose of 0.31mCi/kg causes saturation of camera, the resting scan will be repeated at a lower dose of 0.25mCi/kg

Scan time = ~ 32 minutes

6.0 Measurements of Myocardial Blood Flow

Baseline absolute coronary flow, CFR and coronary flow capacity will be obtained for each major coronary artery territory [left anterior descending (LAD), left circumflex (LCx), right coronary (RCA)] using FDA-approved software HeartSee for each scan obtained. For the "infarct" group, region of interests will be drawn around the infarct territory where average and minimum resting myocardial blood flow will be determined for each scan.

7.0 Statistical Analysis

This is a measurement reliability study in a 2x2 factorial design. Study factors are infusion flow rate (20 or 50) at rest and stress. The linear nature of data acquisition takes about 45 minutes and yields five absolute values for each subject: three resting values and 2 stress values. The first 2 resting values and the 2 stress values condition are obtained in a cross-over fashion by infusion flow rate (infusion level assigned randomly for first resting scan and for first stress scan). The third resting value will be obtained at either a 20 or 50 infusion flow rate and will be used to determine precision (test-retest variability) against the same infusion profile obtained in the first two infusions.

Precision and variability will be determined for global, average quadrant, and individual pixel values of rest flow, stress flow and CFR. Standard summary statistical tests will be used. Applicable tests are 2-tailed, and $p < 0.05$ will be considered statistically significant. Linear regression will be reported between rest perfusion and rest pressure rate product (PRP). Paired or unpaired Student *t* test will be used to evaluate continuous variables where appropriate. The Pitman-Morgan *F* test will be used to test for differences in variability of perfusion between groups. To compare the histogram distribution between groups of stress perfusion and CFR for each of 1344 pixels as percentage of LV in color-

coded ranges of coronary flow capacity, we will use the Kolmogorov-Smirnov (KS) test for differences in histogram distribution.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events or unanticipated problems will be reported to Robert Bober, MD or Nichole Polin, MD at 504-842-2420 and the Internal Review Board as directed by Ochsner Medical Center IRB rules and regulations.

9.0 Radiation Risks

Participants who enroll in the study will receive ionizing radiation. The effective dose of a cardiac PET scan is approximately 6.2mSV or less. This is about 12% of the occupational exposure allowed for a radiation worker. This is also about twice the annual amount of natural background radiation exposure.

10.0 Study Withdrawal/Discontinuation

Participants opting to withdraw from the study will not have the PET scan performed.

11.0 Privacy/Confidentiality Issues

All hard copies of participant data will be kept securely in the PET department where only PET and research staff have access. All PET workstations are encrypted, and password protected. All participant data and PET results will be de-identified of individual health information.

12.0 Follow-up and Record Retention

This study is estimated to take approximately 6 weeks to obtain a total of 85 participants. Hard copies of PET scans are kept securely the PET department where only PET and research staff has access.

The electronic PET data is encrypted, and password protected. Only study personnel will have access to the files.

13.0 Budget

Funding for this quality improvement project will be through the Ochsner Cardiology Nuclear research funds that were obtained philanthropically. All volunteers will be paid $100 US dollars after completion of the PET scan.

14.0 References

1. Araujo LI, Lammertsma AA, Rhodes CG et al. Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. Circulation 1991;83:875-85.
2. Bergmann SR, Fox KA, Rand AL et al. Quantification of regional myocardial blood flow in vivo with H215O. Circulation 1984;70:724-33.
3. Sdringola S, Johnson NP, Kirkeeide RL, Cid E, Gould KL. Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. JACC Cardiovasc Imaging 2011;4:402-12.
4. Renaud JM, DaSilva JN, Beanlands RS, DeKemp RA. Characterizing the normal range of myocardial blood flow with ^{82}rubidium and ^{13}N-ammonia PET imaging. J Nucl Cardiol 2013;20:578-91.
5. Merlet P, Mazoyer B, Hittinger L et al. Assessment of coronary reserve in man: comparison between positron emission tomography with oxygen-15-labeled water and intracoronary Doppler technique. J Nucl Med 1993;34:1899-904.
6. Kern MJ, Bach RG, Mechem CJ et al. Variations in normal coronary vasodilatory reserve stratified by artery, gender, heart transplantation and coronary artery disease. J Am Coll Cardiol 1996;28:1154-60.
7. Gewirtz H, Fischman AJ, Abraham S, Gilson M, Strauss HW, Alpert NM. Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction. J Am Coll Cardiol 1994;23:851-9.
8. Rivas F, Cobb FR, Bache RJ, Greenfield JC. Relationship between blood flow to ischemic regions and extent of myocardial infarction. Serial measurement of blood flow to ischemic regions in dogs. Circ Res 1976;38:439-47.
9. Kitkungvan D, Johnson NP, Roby AE, Patel MB, Kirkeeide R, Gould KL. Routine Clinical Quantitative Rest Stress Myocardial Perfusion for Managing Coronary Artery Disease: Clinical Relevance of Test-Retest Variability. JACC Cardiovasc Imaging 2017;10:565-577.
10. Murthy VL, Bateman TM, Beanlands RS et al. Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Cardiol 2018;25:269-297.

11. Renaud JM, Yip K, Guimond J et al. Characterization of 3-Dimensional PET Systems for Accurate Quantification of Myocardial Blood Flow. Journal of Nuclear Medicine 2017;58:103-109.
12. Bui L, Kitkungvan D, Roby AE, Nguyen TT, Gould KL. Pitfalls in quantitative myocardial PET perfusion II: Arterial input function. J Nucl Cardiol 2020;27:397-409.
13. Gould KL, Bui L, Kitkungvan D, Patel MB. Reliability and Reproducibility of Absolute Myocardial Blood Flow: Does It Depend on the PET/CT Technology, the Vasodilator, and/or the Software? Curr Cardiol Rep 2021;23:12.
14. Stewart, Merrill, Bober M, Robert. Quantification of resting myocardial blood flow using rubidium-82 positron Emission Tomography in regions with MRI-confirmed myocardial scar. Annals of Nuclear Cardiology. ACCEPTED. Advanced publish date: October 30, 2021