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Multi-Center Evaluation of Feasibility of SPECT Measurement of Myocardial Blood Flow and Reserve

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Investigator Statement

I agree to the terms and conditions relating to this study as defined in this protocol. I will conduct this study as outlined and will make a reasonable effort to complete the study within the time designated.

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. In particular, I will obtain the approval of a Research Ethics Board or Institutional Review Board (REB/IRB) for this protocol prior to its implementation.

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Principal Investigator (Printed Name)

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Signature

_____

Date

1. Introduction

1.1 Background and Rationale

Absolute myocardial blood flow (MBF) and myocardial flow reserve (MFR) using positron emission tomography (PET) provide additional diagnostic and prognostic power compared to relative perfusion results [1–8]. Myocardial perfusion imaging is much more widely carried out with single photon emission tomography (SPECT) than with PET. However, measurements of MBF or MFR are rarely obtained with SPECT due to technical reasons (need for attenuation and scatter correction and the requirement of the camera to rotate around the patient for 3-dimensional imaging). An estimate of MFR without a direct measurement of MBF can be determined with a combination of dynamic planar followed by static SPECT acquisitions [9] and provides useful prognostic information [10]. If the camera can perform serial rapid rotations, then dynamic tomographic data can be acquired with conventional SPECT cameras and accurate measures of MBF might be possible with SPECT [11–13].

The recent development of dedicated solid state cardiac SPECT cameras has made the possibility of MBF measurement much more feasible and practical. Cameras such as the NM 530c/570c cameras (GE Healthcare, Haifa, Israel) and the DSPECT system (Spectrum Dynamics Medical Inc., Palo Alto, CA) have greatly improved sensitivity and are stationary [14]. These features allow dynamic imaging with high temporal resolution and improved count density, thereby facilitating MBF measurement with SPECT.

For the first time, Dr. Glenn Wells and our group recently demonstrated the accurate quantification of MBF in a pig model of rest and transient occlusion at stress [15] using the NM530c camera. The three standard SPECT tracers, ^{201}Tl, ^{99m}Tc-tetrofosmin and ^{99m}Tc-sestamibi, were separately shown to correlate with simultaneously injected microspheres (between r=0.75 and r=0.83; p<0.01 for all). These experiments demonstrated that non-invasive measurement of absolute MBF with a stationary dedicated cardiac SPECT is feasible using common perfusion tracers. In human studies, Ben-Haim et al [16] showed using ^{99m}Tc-sestamibi that an index of global MFR was lower (p=0.02) in regions supplied by obstructed vessels (>50% occluded by coronary angiograph (CA)) than in non-obstructed vessels. Ben Bouallèque et al [17] showed that the accuracy of regional MFR measured with ^{99m}Tc-tetrofosmin was 81% for the detection of obstructed vessels with CA and 85% for the detection of abnormal fractional flow reserve (FFR). Shiraishi et al [18] found that the accuracy of ^{201}Tl for the prediction of left main or triple-vessel disease, identified by CA, was 80%. Finally, more recent studies have shown that the flow parameter K1 calculated from kinetic analysis of ^{99m}Tc-tetrofosmin studies yields an MFR-index that predicts the presence of abnormal MFR as measured by PET ^{82}Rb and ammonia studies with an accuracy ≥ 75% [19,20]. However, while extremely promising, these studies have all been performed in single centers with relatively small numbers of patients. To successfully translate this technology into a wide-spread, routinely employed

tool for cardiac imaging requires demonstration of the feasibility of implementing an MBF protocol in multiple centers which may or may not have previous experience with MBF imaging.

The primary objective of this study is to perform a multi-center trial to demonstrate the feasibility of measuring MBF and MFR using ^{99m}Tc-tetrofosmin and a CZT-based NM530c cardiac SPECT camera.

A secondary objective is to evaluate the need for delayed imaging for relative MPI assessment (per ASNC 2016 guidelines: 15-45-minute delay for Stress; 30-60 minutes for Rest [21]) ("delayed imaging"). The current MBF protocol requires additional imaging sessions to accommodate a dynamic acquisition during tracer injection for MBF calculation and delayed imaging post-injection for static MPI evaluation. PET protocols with ^{82}Rb and ^{13}N-ammonia use the latter portion of the dynamic imaging series for relative MPI assessment. Studies that have considered this for SPECT tracers have had mixed results [22,23]. Images acquired as part of the feasibility study will provide pilot data for evaluating the potential to use the latter portion of the SPECT MBF dynamic acquisition for relative MPI assessment. Additional secondary objectives are to assess the impact of measuring SPECT MBF on patient throughput and to evaluate a 50% reduction in the activity used to measure SPECT MBF.

1.2 Hypotheses

a) Primary hypotheses

1. Feasibility: It is practical to obtain reliable SPECT measurements of MBF routinely within the workflow of a standard clinical practice.
2. MBF reproducibility: Global MBF measured at remote sites will agree within 10% with the same data processed at an expert core laboratory.

b) Secondary hypotheses

1. Impact on throughput: Routine implementation of a SPECT MBF protocol will have at most minimal impact on patient throughput (defined as <10% reduction in patient volumes).
2. Delayed imaging: static reconstruction of the last 6 min of the dynamic acquisition will provide images that are clinically equivalent (less than 10% change in patient diagnosis from normal (summed stress score < 4) to abnormal or vice versa), compared to standard static images obtained following a 45-min delay post-injection.
3. Half-dose MBF measurement: The difference between MBF measurements with full-data and half-data dynamic acquisitions will be less than or equal to the inter-observer variation in MBF measurements with full-data.

2. Study Objectives

To demonstrate that the proposed approach to measuring SPECT MBF can be applied routinely in a clinical setting and produce consistent data with minimal reduction in patient throughput.

To explore optimization of the acquisition using 1) early imaging post-stress instead of delayed imaging and 2) half-data instead of full-data acquisitions (leading to half dose MBF radiotracer studies).

3. Study Design

Patients will be recruited from those referred to the local site's Diagnostic Imaging Department for SPECT myocardial perfusion imaging (MPI) and who have an intermediate to high pre-test likelihood of disease (Diamond-Forrester criteria ≥ 30%). Research imaging will consist of a SPECT acquisition at the time of rest and stress radiotracer injection in addition to the standard (delayed) clinical stress/rest SPECT scan with ^{99m}Tc-tetrofosmin. This is an observational study; patients will be managed according to the standard clinical care of the local site. Where available, a CT scan will also be acquired for attenuation and/or scatter correction. Studies may be one day (rest/stress or stress/rest) or two day (rest and stress on separate days)

Study end will be defined as completion of all SPECT imaging at rest and stress.

A core lab will be established at the University of Ottawa Heart Institute. Initial studies acquired at the local site according to the protocol will be evaluated for technical image quality (e.g. patient positioning, CT-SPECT coregistration, noise levels, patient motion and motion correction, artifacts). The core lab will work with local sites, as needed, to implement the protocol and ensure adequate data quality. All studies will be analyzed locally but the raw data will also be anonymized and forwarded to the core facility for reprocessing. Central processing will allow comparison between sites and the repeat processing will provide an estimate of inter-operator variability in the measurements. The core lab will also compare the relative perfusion from immediate and delayed imaging for image quality and diagnostic accuracy (visual and quantitative).

Studies will be acquired at 6 initial sites with mixed prior experience at MBF imaging, to demonstrate feasibility of use in a clinical setting. Each site will acquire 5 studies during an initial start-up period to become comfortable with the SPECT MBF protocol for data acquisition and processing. Studies acquired during the start-up period will not be used in the final analysis but will be processed by the core lab and used to evaluate site training. Following the start-up period, each site will acquire 25 studies within 60 working days to show that the protocol can be implemented without major disruption to clinical throughput.

Timeline (12 months):

For each site, we anticipate 2-3 months for protocol approval by local ethics committees, 1-2 month for local site training and initial training studies, 2 months for feasibility study acquisitions. We will stagger the entry of sites into the study to facilitate "one-on-one" consultation between the core (Ottawa) site and local sites during initial training period. Reprocessing of local data sets by the core lab will be ongoing with final review and analysis of results during the last quarter.

4. SPECT MBF Imaging with Tetrofosmin

4.1 Camera

The camera used in this study will be the Discovery NM 530c (GE Healthcare, Haifa, Israel). This camera is a dedicated cardiac camera that uses 19 cadmium-zinc-telluride (CZT) based detectors [24]. Each detector is 8 x 8 cm divided into a 32x32 array with a pixel pitch of 2.46mm. Each detector has a single-pinhole collimator with an effective diameter of 5.1mm. The detectors are arranged in an arc around the field-of-view, providing sufficient angular sampling for 3D reconstruction without the need to rotate the camera. The sensitivity of the system is approximately 4-times higher than a standard dual-head gamma camera.

4.2 Patient Preparation

Patient preparation will be the same as for a standard clinical myocardial perfusion study. Participants will be instructed to fast per local procedures (3 hours per ASNC guidelines[21]), and to abstain from products containing caffeine for no less than 12 hours prior to imaging.

4.3 Radiotracer

The tracer to be used is ^{99m}Tc-tetrofosmin. ^{99m}Tc-tetrofosmin will be mechanically delivered using a syringe pump at a constant rate over a 30 s period, followed immediately by a saline flush at the same injection rate as the tracer. The volume of the saline flush should be greater than the volume of the lines connecting the pump to the patient to ensure that the full tracer activity is delivered. There should be no delay between tracer and saline flush injections. Manual injection of radiotracer will not be used for this study to increase standardization but will be evaluated in future studies.

The measurement of CFR with CZT SPECT has been validated with full doses of radiotracer but is most likely possible with half doses. For this feasibility study, full doses will be used to provide the best CFR results possible. The listmode data from the full-dose studies with be reprocessed by the core laboratory to simulate half doses and

confirm that half doses are adequate. The planned subsequent studies of diagnostic accuracy and prognosis would evaluate half doses.

The activity of the radiotracer injected at stress and rest will be full clinical doses with a minimal activity of 370 MBq for the first study and 1100 MBq for the second study for a one day protocol. Injected doses will be 370 MBq at both rest and stress for 2-day protocols.

4.4 Image Acquisition

Images will be acquired using either a 1-day rest/stress, a 1-day stress/rest, or a 2-day protocol according to local site preferences. Protocols illustrated in Appendix A.

4.4.1 Stress Imaging

Patient will be positioned according to standard clinical practice for myocardial perfusion imaging with the heart centered in the field of view. Image data will be acquired in listmode for 11 min starting just prior to tracer injection. There should be no movement of the patient or camera from the start of the vasodilator injection through to the end of image acquisition. Stress will be induced using a vasodilator, either dipyridamole, adenosine, Adenosine Tri-phosphate or regadenoson according to local site preference.

- Dipyridamole: Dipyridamole (0.14 mg/kg/min over 4 or 5 min depending on local laboratory practice) will be given intravenously. ^{99m}Tc-tetrofosmin is injected at 3-5 minutes following the end of the dipyridamole infusion. Stress imaging will start immediately prior to the ^{99m}Tc-tetrofosmin injection. Aminophylline will be administered intravenously as needed, no earlier than 3 minutes following injection of tracer.
- Adenosine/Adenosine Tri-phosphate: Protocol will follow ASNC guidelines.
- Regadenoson: Protocol will follow ASNC guidelines.

The usual post-stress images (delayed stress) will be acquired as per standard clinical practice.

4.4.2 Resting Images

If a stress-first protocol is being used, then the acquisition of additional resting imaging will be decided based on local-site standard clinical practice.

For rest imaging, the patient will be positioned according to standard clinical practice for myocardial perfusion imaging with the heart centered in the field of view. Image data will be acquired in listmode for 11 min starting just prior to tracer injection. There should be no movement of the patient or camera from the start of the tracer injection through to the end of image acquisition.

Acquisition of a clinical resting relative perfusion image (delayed rest) will be acquired as per standard clinical practice.

4.4.3 Patient positioning dose

A 40 MBq positioning tracer dose may be injected to aide in positioning of the patient, prior to injection of the tracer for dynamic imaging. If a positioning dose is used, an additional 5-min static image of the tracer will be acquired prior to injection of the tracer used for dynamic imaging. There should be no movement of the patient or camera between the static image of the positioning dose and the acquisition of the dynamic imaging for flow measurement. To note, injection of positioning dose should take place ~20 minutes prior to injection of tracer for dynamic imaging. However, the patient should be on the imaging table only during the static scan prior to the injection for dynamic imaging, and throughout the dynamic imaging which follows.

4.4.4 Pre-dynamic imaging

Prior to the second scan of a 1-day protocol (ie the rest imaging in a stress-first protocol), a pre-dynamic static image is required to correct for residual activity from the first injection. A 5 min listmode static acquisition is obtained prior to injection of the radiotracer for dynamic imaging (and prior to injection of the vasodilator in the case of rest/stress protocols). There should be no movement of the patient or camera between the static image and the acquisition of the dynamic imaging for flow measurement.

4.5 Image Processing and Analysis

Following acquisition, the listmode data will be rebinned into 9x10s, 6x15s, 4x120s frames. The projection data for each frame will be independently reconstructed using manufacturer supplied MLEM iterative reconstruction that includes point-spread function modeling and a noise-suppression prior. A total of 60 iterations will be used corresponding to the manufacturer recommendation for resting (low-count) studies. Images will be filtered post-reconstruction using a 3D 5^{th}-order Butterworth filter with a cut-off frequency of 0.37 cycles/cm. Images will be reconstructed without corrections (NC), and with attenuation correction (AC) when a CT attenuation scan is available. When applied, AC will be based on a CT scan acquired separately with the patient on the same configuration as used for the SPECT dynamic acquisitions.

The reconstructed dynamic image series will be processed using the kinetic analysis software tools provided by the manufacturer (GE Healthcare). With this semi-automatic software, a 1-tissue-compartment model will be fit to the myocardium time-activity data to generate a parameterized map of the uptake rate constant K1 (ml/min/g) for the heart. K1 values will be scaled to MBF based on the K1-MBF relationship determined from previous single-site comparisons of clinical SPECT and Rb82 PET studies [20].

5. Sample Size and Analysis

Adverse events will be listed on an individual basis. All safety variables and demographic data will be tabulated with descriptive statistics, if appropriate.

Bland-Altman plots will be used to determine significant bias and the coefficient of repeatability of global and regional MBF and MFR measurements for the core versus local reproducibility studies and for measurements of MBF with full and half data reconstructions. The mean difference in MBF between core and local-site processing will be assessed with a paired t-test. A sample size of 25 studies per center provides 88% power (alpha=0.05) to detect a 10% difference, assuming a standard deviation in repeated MBF measurement of 15%[1] (effect size of 0.67). Each center will recruit 5 practice patients and 25- 35 patients for analysis. There will be 6 centers and each center will recruit 30 - 40 patients for a minimum of 180 patients to a maximum of 240 patients(30 practice patients and 150 - 210 patients for analysis). Global and regional MBF at rest and stress will be separately compared. Differences in MFR will be similarly assessed.

To evaluate impact on patient throughput, the following information will be collected for each site and each MBF study:

Time patient enters the room

Time of radiotracer injection (for dynamic imaging sessions)

Start times of each image series (static and dynamic)

Time patient exits the room

Number of MPI studies done per day.

Each site will also provide number of MPI studies done per day for the 2-month period prior to starting to apply the MBF protocol and similar timing and demographic data for 25 standard (non-MBF) MPI studies.

MBF/MFR analysis will be repeated with attenuation corrected images for those data sets which include a transmission imaging.

Image quality will be assessed at the core lab. The following factors will be considered:

- Tracer bolus quality: start of bolus is imaged, bolus duration is appropriate (total activity in the FOV is within 10% of final frame value 3 minutes after start), single peak
- Positioning: Heart is within the quality FOV – no truncation.

[1] G*Power software, version 3.1.3. Faul F, Erdfelder E, Lang A-G, and Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39:175–191, 2007

- Sufficient injected activity: total counts in the left ventricle in the final 2-min frame is > 1 M
- Artifacts: no evidence of patient motion (or adequate motion correction), no other visible artifacts in the images
- Number of segments with physiologically unreasonable MFR (MFR <0.8 or > 5)

MBF analysis will be repeated for the half-dose MBF data sets. Studies will be read at the Core Laboratory by two experienced readers to provide intra- and inter-observer repeatability of evaluation.

To assess the need for delayed imaging, data sets will be reprocessed at the core lab. The last 6 min of each dynamic acquisition will be used to generate a late-dynamic static MPI image series (immediate imaging). The immediate and delayed images will be reviewed blindly by two experienced readers to provide data on intra- and inter-observer repeatability. The summed rest, summed stress, and summed difference scores will be recorded for a 17-segment heart model, along with a final clinical evaluation and a subjective assessment of image quality (on a scale of 1-5). All evaluations will be done by the core lab to ensure consistency in processing and evaluation.

Subjective image quality scale will be:

1 – non-diagnostic: noise or poor contrast in the myocardium prevent clinical interpretation, or artifact or extra-cardiac uptake prevent interpretation of the myocardium.

2 – poor quality: poor contrast and noise in myocardium make interpretation difficult, artifacts and extra-cardiac interference are moderate and reduce confidence in image interpretation

3 - adequate quality: adequate myocardial contrast, artifacts and extra-cardiac interference are mild and may reduce confidence in image interpretation

4 – good quality: good myocardial contrast, artifact and extra-cardiac activity may be present but do not interfere with interpretation

5 – excellent quality: good myocardial contrast, no artifacts, no interference from extra-cardiac activity

6. Study Population

6.1 Source of Participants

The study population will be adult male and female patients who are referred to the outpatient cardiology clinics and/or the non-invasive Diagnostic Imaging Department at the local site and have known or suspected CAD.

6.2 Inclusion Criteria

- Age ≥ 18 years old
- BMI ≤ 40 kg/m^2
- Able and willing to comply with the study procedures
- Written informed consent
- Intermediate to high probability of CAD
- Suspected or known CAD on a stable medication regime.

6.3 Exclusion Criteria

- History or risk of severe bradycardia (heart rate < 50 beats per minute) not related to chronotropic drugs
- Known second- or third-degree AV block without pacemaker
- Dyspnea (NYHA III/IV), wheezing asthma or COPD
- Coronary artery bypass graft (CABG) surgery within 60 days prior to screening or within 45 days after consent (early revascularization)
- Percutaneous coronary intervention (PCI) within 30 days prior to screening or within 45 days following consent (early revascularization)
- Recent use of dipyridamole, dipyridamole-containing medications (e.g. Aggrenox)
- Known hypersensitivity to dipyridamole or adenosine
- Breastfeeding or pregnancy
- Claustrophobia or inability to lie still in a supine position
- Unwillingness or inability to provide informed consent

6.4 Withdrawal from Study

Participants may withdraw from the study at any time without penalty or prejudice. No data will be collected from the time of withdrawal.

6.5 Early Termination

Participants may be terminated for reasons such as, but not limited to:

- Noncompliance with study procedures.
- Participant experiences a cardiac event within 45 days following consent.
- Secondary illness requiring intervention during the study.
- Pregnancy.
- Participant safety may be compromised in the opinion of the investigator.
- Study may be stopped at the request of a regulatory authority or the REB.

If study discontinuance occurs, the date and reason must be documented in the CRF

7. Data Collection

All participant information and data will be collected respecting participant confidentiality and privacy and following written informed consent.

7.1 Demographic Information

Demographic information will include the participant's date of birth (mm/yyyy), gender, height and weight.

7.2 Medical History

Medical history and results from any standard of care testing related to a participant's cardiovascular disease and inclusion/exclusion criteria will be collected. Clinical data obtained at scan visits will be included as part of the study data.

7.3 Clinical Status

The blood pressure, heart rate and clinical status will be monitored according to current clinical protocols during imaging procedures. Clinical protocol will be followed for dipyridamole stress testing.

7.4 Caffeine Ingestion

The ingestion of caffeine will be restricted for 24 hours prior to all imaging procedures as per standard clinical practice.

7.5 Pregnancy Assessment

A woman of child bearing potential will have a urine pregnancy test performed on the days of imaging. For elderly female patients, verbal confirmation is sufficient.

8. Risk Benefit Assessment

8.1 SPECT Imaging

Patients will not receive any radiation exposure beyond that clinically indicated for their SPECT or SPECT/CT MPI study.

8.2 Dipyridamole Pharmacological Stress

Dipyridamole is a vasodilator commonly used in the clinical practice of nuclear cardiology and will be used as the stress agent for all stress studies. Rare serious adverse reactions associated with the administration of intravenous dipyridamole for MPI have been reported. These have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke and transient cerebral ischemia. The infusion rate is monitored to minimize this risk and the symptoms can generally be reversed with an intravenous injection of 50 - 250 mg of aminophylline over several minutes. As this does not deviate from the standard practice used in the clinical test, there is no increase in the risk associated with the clinical test.

9. Safety and Tolerability

9.1 Safety Variables

Safety variables will include the occurrence of procedure-related adverse events and changes in clinical status.

9.2. Safety Reporting

Adverse events (AE) and Serious Adverse Events (SAE) will be defined and reported according to ICH/GCP and Regulatory Standards. AEs and SAEs will be reported from the signing of the consent and followed until resolution or determined to be not clinically significant.

9.3 Pregnancy

During the conduct of the trial should a pregnancy be actual (positive result with testing) or suspected, the participant will be advised to contact the Investigator immediately. Participation in the trial will be terminated.

10. Study Records

Study files will be divided into two categories: Investigator Study Files and Participant Clinical Trial Files. Study files will be retained for a period of 25 years from the study end. GE Healthcare will have access to deliverables which are generated from this study as specified in the contractual agreement.

10.1 Investigator Study Files

Regulatory files will contain all essential documents relating to trial conduct and management including communications with Ottawa Health Science Network Research Ethics Board (OHSN-REB), the ethics boards of participating local sites, and all regulatory agencies.

10.2 Participant Clinical Trial Files

The participant files will include the consent form, screening and enrollment logs, Master List, source documents and the case report form (CRF). Personal Health Information (PHI) relevant to the conduct of the trial will be collected and will include medical history, inclusion and exclusion criteria details, medical records generated during the conduct of the trial and medical record number (MRN). These documents will be maintained as paper and electronic files under the responsibility of the Principal Investigator.

11. Monitoring/Access to Files for Inspection

The investigator agrees to provide access to all study related files for conduct of inspections or auditing by regulatory authorities.

Ongoing review of safety parameters and events will be recorded and reported according to applicable regulations and local ethics board requirements. No formal Data Safety Monitoring Board will be specified due to the low level of risk associated with this trial.

Periodic study monitoring will be conducted to assure adherence to the protocol, ICH GCP guidelines and that data is accurate, complete and verifiable. An internal monitoring plan, following local SOPs, will be developed. The designated internal monitor will have the training and qualifications necessary to provide an appropriate and thorough verification of the study files. Confidentiality will be consistent with local requirements and national regulations.

12. Publication

Review and Publication will be according to contractual agreements in place at the time of the trial.

13. Budget

13.1 Budget Details (TBD)

14. References

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Appendix A: Protocols for SPECT MBF

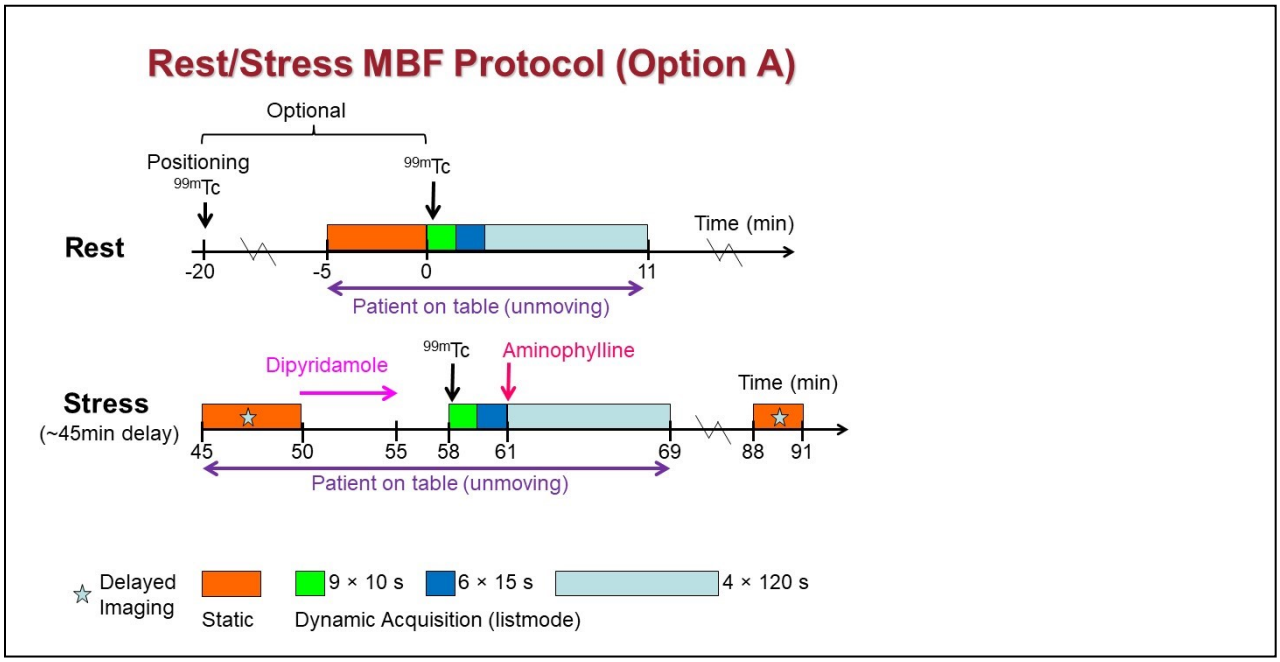

Figure 1a: Rest/Stress protocol (option A). If a positioning dose is used, then a pre-scan is required prior to injection of the resting dose. Patient should be positioned on the table and not be moved throughout imaging. Protocol shows a 5 min rest and 3 min stress delayed acquisition with a 5-min stress infusion protocol followed by a 3min delay before tracer injection. These times may be adjusted as indicated in the protocol text.

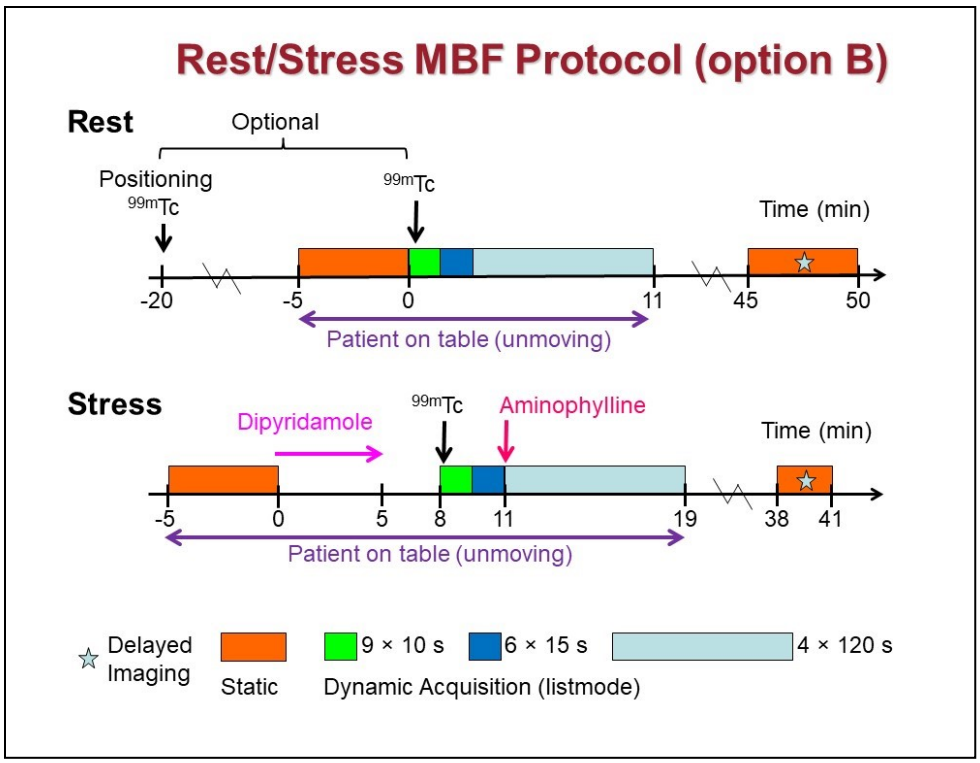

Figure 1b: Rest/Stress protocol (option B). Optionally, a time delay can be introduced between the rest delayed imaging and the stress injection. If this is done, an additional 5 min static image should be acquired of the residual activity just prior to beginning the dipyridamole infusion as indicated in the figure.

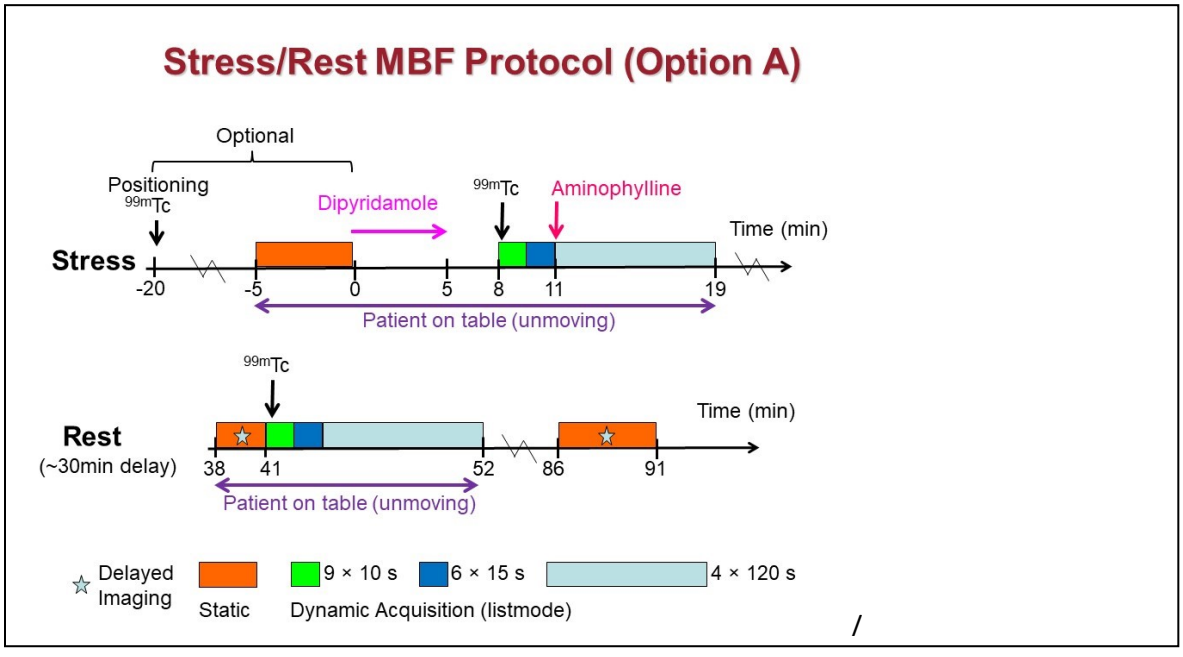

Figure 2a: Stress/Rest protocol (option A). If a positioning dose is used, then a pre-scan is required prior to starting the dipyridamole infusion. Patient should be positioned on the table and not be moved throughout imaging. Protocol shows a 5 min rest and 3 min stress delayed acquisition with a 5-min stress infusion protocol followed by a 3min delay before tracer injection. These times may be adjusted as indicated in the protocol text.

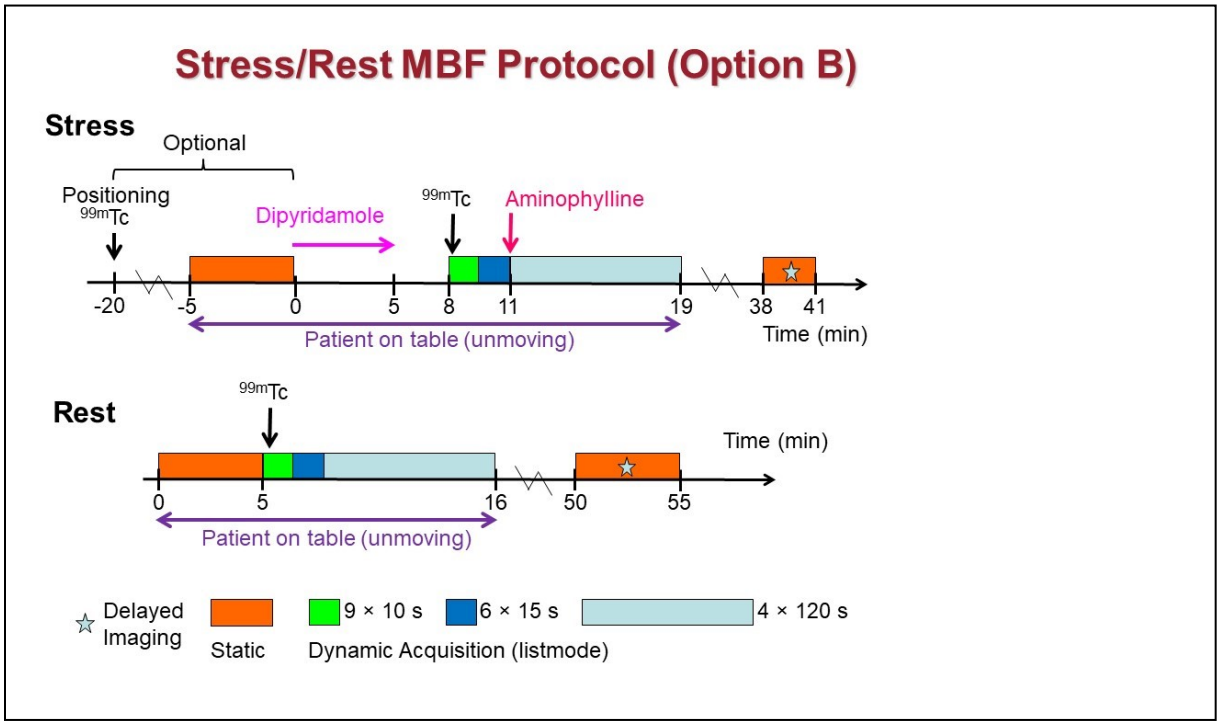

Figure 2b: Stress/Rest protocol (option B). Optionally, a time delay can be introduced between the stress delayed imaging and the rest injection. If this is done, an additional 5 min static image should be acquired of the residual activity just prior to beginning the rest dynamic imaging as indicated in the figure.

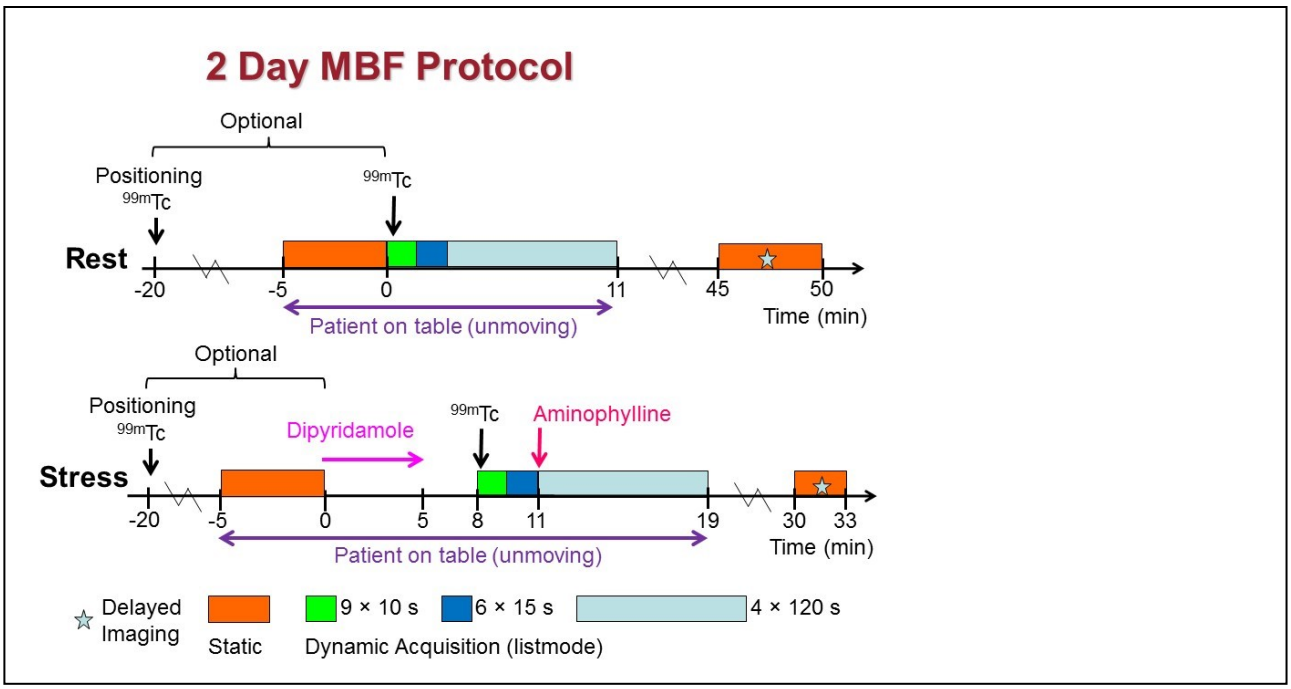

Figure 3: 2-day protocol. If a positioning dose is used, then a pre-scan is required prior to starting the dipyridamole infusion at stress and prior to the resting injection of radiotracer. Patient should be positioned on the table and not be moved throughout imaging. For the 2-day protocol, both stress-first and rest-first can be used. Protocol shows a 5 min rest and 3 min stress delayed acquisition with a 5-min stress infusion protocol followed by a 3min delay before tracer injection. These times may be adjusted as indicated in the protocol text.

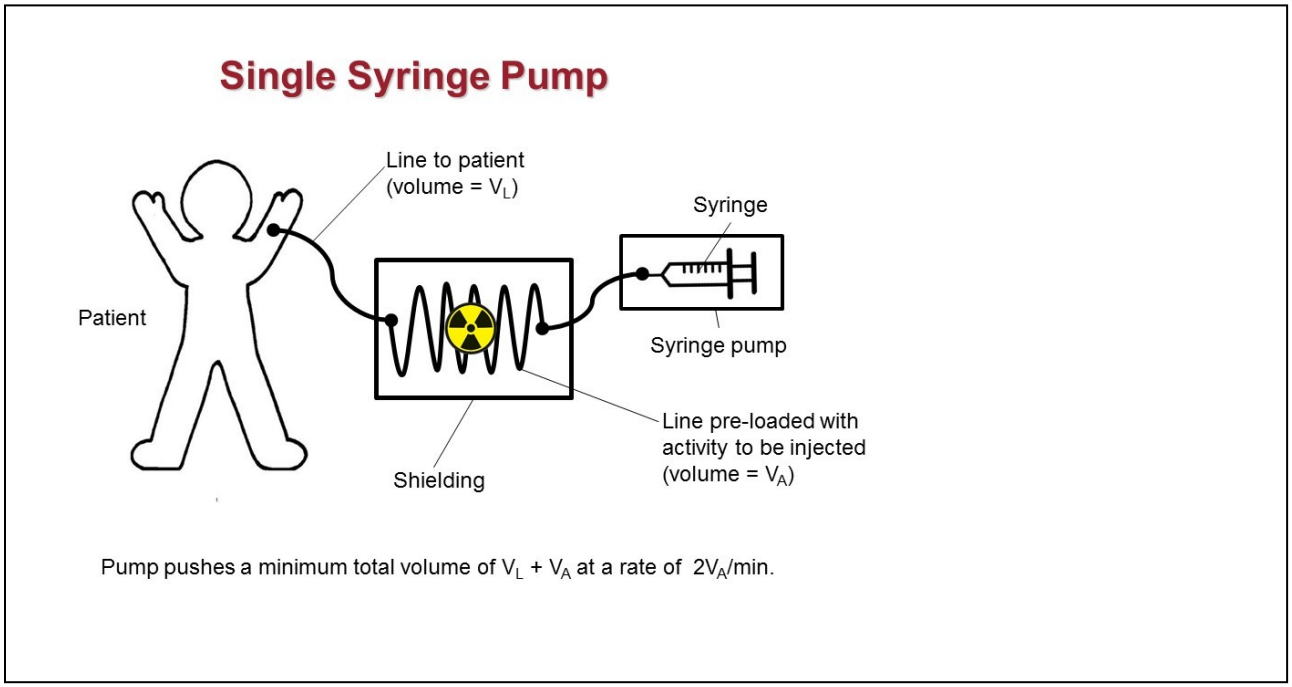

Figure 4: Single-syringe pump configuration. All lines are pre-loaded with saline. Activity to be injected (volume = V_A) is then loaded onto the patient end of the shielded line segment. The pump pushes a minimum volume of $V_L + V_A$ at a rate of $2V_A$/min.

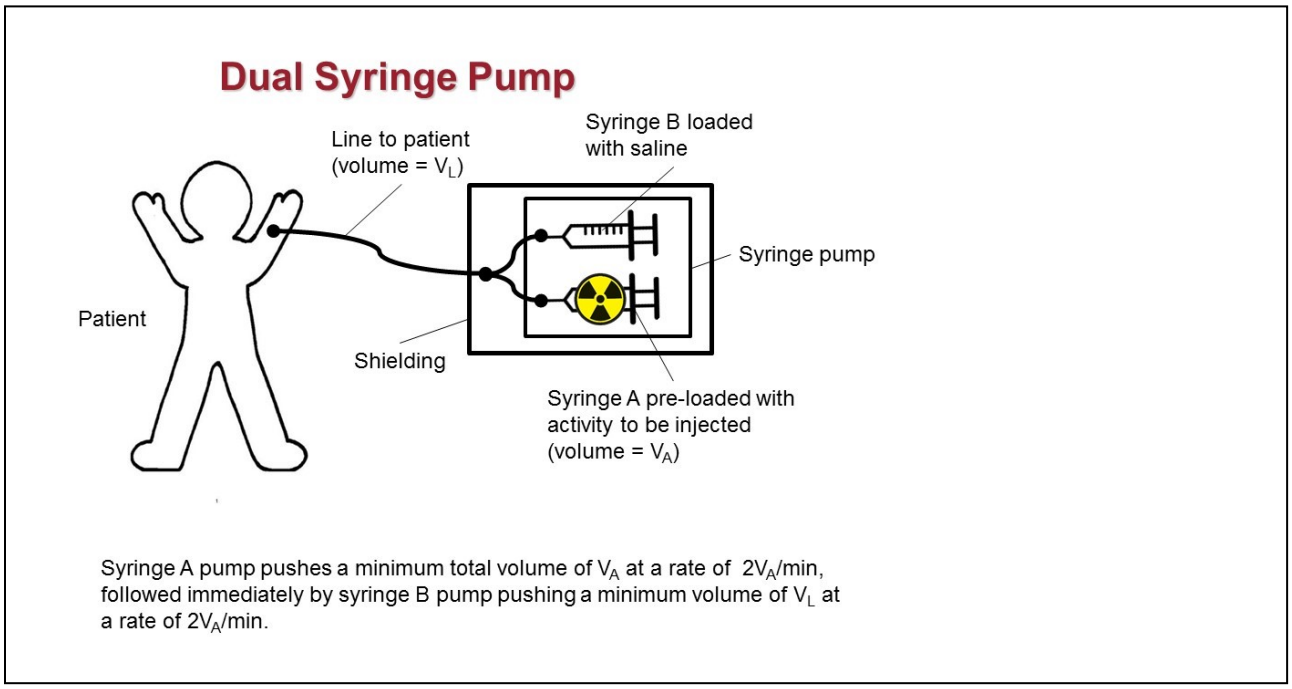

Figure 5: Dual-syringe pump configuration. All lines are pre-loaded with saline. Activity to be injected (volume = V_A) is then loaded onto syringe A. Syringe B is loaded with saline. The pump pushes a volume of V_A at a rate of $2V_A$/min from syringe A, followed immediately by a minimum volume of V_L from syringe B.