ASNC PREFERRED PRACTICE STATEMENT

Patient-centered imaging

E. Gordon DePuey, MD,[a] John J. Mahmarian, MD,[b] Todd D. Miller, MD,[c] Andrew J. Einstein, MD, PhD,[d] Christopher L. Hansen, MD,[e] Thomas A. Holly, MD,[f] Edward J. Miller, MD, PhD,[g] Donna M. Polk, MD, MPH,[h] and L. Samuel Wann, MD, PhD[i]

INTRODUCTION

The continued success of nuclear cardiology demands ongoing re-evaluation of imaging practices to optimize patient care. The first element of this process is to accurately define candidates for imaging. Appropriate use criteria documents provide such guidelines.[1] A second equally important element is choosing the proper imaging procedure for the individual patient. Tailoring imaging to the patient is critical for providing accurate and clinically meaningful information to the physician. There are several integral components to a successful patient-centered imaging approach.

Patient safety is of paramount importance when contemplating any diagnostic and/or therapeutic medical option. For myocardial perfusion imaging (MPI) this approach includes not only the risk of the stress protocol but also the ''risk'' of performing unnecessary additional procedures or administering inappropriate therapy because of a sub-optimally performed test. High-quality imaging limits the latter through improved diagnostic sensitivity and specificity, enhanced risk stratification, and less intra- and inter-observer variability when interpreting clinically significant changes in serial images.

Another safety consideration is the risk from radiation exposure which should be weighed in each individual patient prior to initiating a study. There has been a recent dramatic increase in public awareness and media focus on radiation exposure. Consequently, a major factor influencing the choice of MPI protocol is radiopharmaceutical dose. This issue is particularly relevant to younger patients and in women of childbearing potential. However, even in older individuals and in those in whom the risk/benefit ratio is low, radiation exposure should be limited to that dose required to obtain a diagnostic study. Protocols that minimize radiation exposure have been proposed recently by a different ASNC writing group and should be considered when evaluating a patient.[2] The patient radiopharmaceutical doses cited in this article are based upon effective radiation exposure from tissue dose coefficients, using International Commission on Radiological Protection (ICRP) Publication 103 weighting factors.[2,3]

Once safety concerns are addressed, it is critical to ensure that the proper imaging protocol is used to best answer the clinical question at hand. Meeting this priority requires close communication between the referring physician and those performing the test.

Finally, it is important to consider cost as well as overall patient convenience and satisfaction. Protocols requiring prolonged or return visits are regarded unfavorably by both patients and their referring physicians and significantly decrease laboratory efficiency. Every effort should be made to streamline procedures.

This document will address the advantages and disadvantages of currently available stressor and imaging options as well as provide a framework for imaging specific patients through case-based scenarios.

PART 1: SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) MPI PROTOCOLS

There are several general themes regarding the choice of a SPECT MPI protocol. First, exercise stress is preferred over pharmacologic stress testing in patients who can exercise to a maximal workload. However, in patients unable to exercise, pharmacologic stressors have greatly enhanced nuclear cardiology by providing flexibility and broadening patient accessibility to SPECT procedures. Second, radiopharmaceuticals that

From the St. Luke's-Roosevelt Hospital,[a] New York, NY; Methodist DeBakey Heart and Vascular Center,[b] Houston, TX; Mayo Clinic,[c] Rochester, MN; Columbia University Medical Center,[d] New York, NY; Jefferson Heart Institute,[e] Philadelphia, PA; Northwestern University,[f] Chicago, IL; Boston University School of Medicine,[g] Boston, MA; Hartford Hospital,[h] Hartford, CT; and Wheaton Franciscan Medical Group,[i] Milwaukee, WI.

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limit radiation exposure and improve overall image quality, such as the technetium (Tc)-99m tracers, are generally preferable over thallium (Tl)-201 except in certain specific patients groups, as discussed below. Radiopharmaceutical dosing guidelines recommend administration of an additional 0.31 mCi/kg Tc-99m and 0.04 mCi/kg Tl-201 in patients weighing over 70 kg.[4] Third, 1-day protocols have distinct advantages over 2-day procedures except in large patients (>200 pounds) and in those who are anticipated to have significant attenuation artifacts that might limit study interpretation. Two-day protocols afford administration of initially higher radiopharmaceutical doses which, when coupled with increases in imaging times on conventional SPECT systems, can optimize image quality. Finally, Tc-99m stress/rest protocols are preferable to rest/stress procedures in properly selected patients so as to allow for ''stress-only'' imaging. Provided below is a critical review for each of the most commonly utilized SPECT MPI protocols.

One-Day Tc-99m Rest/Stress Protocol

The 1-day rest/stress Tc-99m-based SPECT protocol is performed as follows:

- 8-12 mCi Tc-99m-based radiopharmaceutical is injected with imaging performed approximately 30-60 minutes post-injection.
- Exercise or pharmacologic stress testing is performed immediately thereafter.
- 24-36 mCi (>3× resting dose) Tc99m-based radiopharmaceutical is injected at peak stress with imaging performed approximately 15-20 minutes post-exercise or 30-60 minutes post-pharmacologic stress.

Advantages

- The rest/stress imaging protocol can be completed within 3 hours. This time can be further reduced to under 2 hours when using new ultrafast camera systems, where image acquisition can be completed in as little as 2 minutes with potentially shorter waiting periods after isotope injection.
- Stress and rest SPECT images are both performed using a Tc-99m radiopharmaceutical. Therefore, spatial resolution, attenuation artifacts, and Compton scatter are relatively similar in the stress and rest images, simplifying interpretation and assessment of fixed versus reversible perfusion defects.
- By acquiring both stress and rest perfusion tomograms, one can evaluate transient ischemic dilatation, an abnormality often associated with severe and/or multivessel stress-induced ischemia.
- If both the rest and the stress SPECT acquisitions are gated, it may be possible (depending on image quality) to compare rest and post-stress left ventricular (LV) function and thereby evaluate stress-induced global and regional dysfunction. This may increase sensitivity for detecting balanced stress-induced ischemia.

Disadvantages

- Performing the rest study first delays the laboratory schedule and may inconvenience the individual supervising the stress test.
- Since stress SPECT will always be performed with residual resting myocardial activity present in the patient, the resting activity ''shine-through'' into the subsequent stress scan could theoretically decrease coronary artery disease (CAD) detection (i.e., sensitivity) or underestimate patient risk by decreasing the stress-induced perfusion defect size and severity. However, it is generally believed that achieving a stress/rest radiopharmaceutical activity ratio of $\geq$3 obviates this concern.
- The relatively low (approximately 8-12 mCi) rest dose may result in suboptimal count density with resultant poor image quality and associated artifacts. This will be particularly evident in larger patients. Moreover, comparison of the low-dose rest to the high-dose stress image may be problematic depending on the degree of differences in count density between the images. Ischemia may also be underestimated, as some defects may appear fixed rather than reversible due to low-count rest images, especially when attenuation is present. Finally, low-count density may preclude accurate quantification of resting LV volumes and ejection fraction (EF) when performing either 8- or 16-frame-gated SPECT. This limitation in part confounds one's ability to assess stress-induced regional and global LV dysfunction.
- Since the resting scan is performed first, a subsequent stress scan must be performed in every patient. This obviates the advantage of employing a stress-only protocol (see below).

Patient Radiation Dose

- Effective radiation dose using a rest-stress protocol with 10.0 and 30.0 mCi is estimated at 11.4 mSv for Tc-99m sestamibi and 9.3 mSv for Tc-99m tetrofosmin.

Planar Imaging as an Alternative to SPECT

- Very occasionally imaging is required for patients too large or too heavy to be accommodated by a SPECT camera, for those unable to lie still for the required

SPECT acquisition time, and for those unable to move their left arm away from the precordial region. In such patients, planar imaging is a reasonable alternative. Planar images should be acquired in an optimized left anterior oblique view, an anterior view 45° less oblique than the optimized left anterior oblique view, and either a cross-table or decubitus left lateral view. Images are acquired for 7 minutes/view when the count rate within the field-of-view is ≥3kcts/second or 10 minutes/view, as tolerated by the patient, when the count rate within the field-of-view is ≤3kcts/second.

One-Day Tc-99m Stress/Rest Protocol

The 1-day stress/rest Tc-99m-based SPECT protocol is performed as follows:

- 8-12 mCi Tc99m-based radiopharmaceutical is injected at peak stress with imaging performed approximately 15-20 minutes post-exercise or approximately 30-60 minutes post-pharmacologic stress.
- 24-36 mCi of Tc99m-based radiopharmaceutical is injected at rest followed by imaging approximately 30-60 minutes later. A 3-hour delay is recommended between injection of the stress and rest Tc-99m doses to allow for adequate decay of the stress activity.
- In order to shorten the 3-hour delay time and minimize stress-to-rest shine-through, the rest dose may be increased to 35-40 mCi. This option should only be considered in patients with either a moderate to high likelihood or known CAD since the radiation exposure will be increased by approximately 20% (see below for details).

Advantages

- Both the stress and the rest SPECT images are performed using a Tc-99m radiopharmaceutical. Therefore, spatial resolution, attenuation artifacts, and Compton scatter are relatively similar in the stress and the rest images.
- There is no delay in stressing the patient, a feature attractive to the individual supervising the stress test. Moreover, if treadmill exercise is performed or if pharmacologic stress is supplemented with low-level exercise, the stress injection-to-imaging interval may be as short as 20 minutes, further improving laboratory efficiency.
- If the stress images are normal, rest imaging is unnecessary. Attenuation correction techniques may decrease or eliminate soft tissue attenuation artifacts, thereby increasing the number of stress SPECT scans judged to be normal and decreasing the need for subsequent resting SPECT. This ''stress-only'' approach significantly shortens the protocol, thereby enhancing patient satisfaction and convenience and decreasing patient radiation exposure by avoiding administration of the higher rest dose. Stress-only imaging also conserves Tc-99m and decreases cost by eliminating the higher rest dose of Tc-99m.

Disadvantages

- From a theoretical perspective, a stress/rest protocol may underestimate ischemia (i.e., defect reversibility) due to ''shine-through'' from the stress activity into the rest image. Although a low dose of Tc-99m is administered to the patient for the initial stress scan there is increased delivery of tracer to the myocardium due to stress-induced hyperemia. There are several solutions to avoid ''shine-through'': (1) the rest dose can be increased; (2) the stress dose can be allowed to decay; or (3) all the above approaches can be implemented to a relative extent depending on the individual patient. Since the physical half-life of Tc-99m is 6 hours, a delay of approximately 3-4 hours from the time of stress to rest injection is recommended if the rest imaging time or injected dose are not appropriately adjusted. Although the theoretical underestimation of ischemia using a stress/rest protocol has not been demonstrated clinically, this protocol is not generally recommended in patients with known CAD or in those with a history of LV dysfunction.
- Because the stress dose is relatively low (8-12 mCi), the images may be prone to artifacts. Artifactual defects on the stress image may be less apparent on the subsequent higher count density rest image resulting in erroneous interpretation of defect reversibility (ischemia). This is the converse argument to the one described above where ischemia is said to be underestimated with a stress/rest protocol. To avoid these potential interpretation dilemmas, patients with a large chest circumference should generally undergo a high dose 2-day stress/rest Tc-99m imaging protocol rather than either a 1-day stress/rest or rest/stress protocol.
- Post-stress stunning may be difficult to assess due to suboptimal count density of the gated images.

Patient Radiation Dose

- Effective radiation dose using a stress-rest protocol with 10.0 and 30.0 mCi is estimated at 12.3 mSv for Tc-99m sestamibi and 9.3 mSv for Tc-99m tetrofosmin. If rest imaging is not performed, effective dose is reduced to 2.7 mSv and 2.3 mSv, respectively.

Optional Radiopharmaceutical Dosing Schema

- In older patients and in those with a moderate- to high-likelihood of CAD, radiation exposure may be less of a concern. Therefore, if the initial stress scan is not entirely normal, the rest study can be performed using one of several dosing options: (1) injection of a high resting dose (24-36 mCi) at a delayed interval, as described above; (2) injection of a higher resting dose (35-40 mCi) with no time delay; or (3) injection of a similar dose as used for the stress study on a subsequent day
- In younger patients and in those with a low- to moderate-likelihood of CAD, conversion to a 2-day stress/rest protocol, as described above, should be considered. An 8-12 mCi resting dose can be administered on the second day, decreasing the radiation exposure from the entire study by approximately 50%.

Two-Day Stress/Rest Tc99m Protocol

This protocol is considered to provide optimal image quality and is performed as follows:

Day #1

- 24-36 mCi Tc99m-based radiopharmaceutical is injected at peak exercise or pharmacologic stress with imaging performed approximately 15-20 minutes post-exercise or approximately 30-60 minutes post-pharmacologic stress.

Day #2

- 24-36 mCi Tc99m-based radiopharmaceutical is injected at rest with imaging performed approximately 30-60 minutes thereafter.

Advantages

- There is no delay in stressing the patient.
- If stress SPECT is normal, rest imaging is unnecessary (i.e., stress-only imaging).
- The stress and the rest SPECT images are performed using a Tc-99m radiopharmaceutical and at a similar dose. Therefore, spatial resolution, attenuation artifacts, and Compton scatter will be relatively similar on the stress and the rest images; and both gated datasets will be of comparable quality facilitating image interpretation and recognition of post-stress stunning.
- The 2-day stress/rest protocol is particularly well-suited for obese patients and patients in whom attenuation artifacts are anticipated (women with large breasts or implants, patients with diaphragmatic elevation, etc.). However, in such patients, higher count density still does not eliminate the problems of soft tissue scatter and loss of spatial resolution with depth.
- By acquiring both stress and rest perfusion tomograms, one can evaluate transient ischemic dilatation, an abnormality often associated with severe and/or multivessel stress-induced ischemia.
- If both the rest and the stress SPECT acquisitions are gated, it is possible to accurately compare them and thereby evaluate stress-induced global and regional LV dysfunction. Since the stress- and the rest-gated SPECT tomograms are of comparable count density and quality, the 2-day protocol may be more reliable than the single day 1 for detecting changes in LV function associated with balanced stress-induced ischemia.

Disadvantages

- Two days of imaging are required if the initial stress study is not unequivocally normal.

Patient Radiation Dose

- The effective radiation dose using the 2-day stress-rest protocol is 14.8 mSv for Tc-99m sestamibi and 11.6 mSv for Tc-99m tetrofosmin based on injection of two 25.0 mCi doses. This exposure is higher than that calculated for a 1-day protocol since both the stress and the rest doses are equivalent and relatively high.[2]

Two-Day Rest/Stress Tc-99m Protocol

In certain circumstances it may be preferable to perform the rest scan on Day #1 and the stress scan on Day #2. This imaging sequence is primarily applicable to patients in whom exercise or pharmacologic stress is inconvenient or contraindicated on the first day such as in the following circumstances:

- Patients with unstable medical conditions where stress testing is not advisable.
- Patients who have eaten within the prior 3-4 hours.
- Patients unable to exercise who have ingested caffeine-containing foods or medications and are scheduled for vasodilator stress.

Details of the protocol are as follows:

Day #1

- 24-36 mCi Tc99m-based radiopharmaceutical is injected at rest with gated SPECT performed approximately 30-60 minutes post-injection.

Day #2

- 24-36 mCi Tc99m-based radiopharmaceutical is injected at stress with gated SPECT performed

approximately 15-20 minutes post-exercise or approximately 30-60 minutes post-pharmacologic stress.

Advantages

- The protocol allows rest imaging to be performed when otherwise the entire study would need to be postponed for another day. This improves laboratory efficiency and partially avoids wasted radiopharmaceutical doses.

Disadvantages

- Patients must undergo both stress and rest imaging on separate days.

Patient Radiation Dose

- The effective radiation dose using the 2-day rest-stress protocol is (14.8 mSv for Tc-99m sestamibi and 11.6 mSv for Tc-99m tetrofosmin based on injection of two 25.0 mCi doses).

Stress-Only Tc-99m Protocol

In a recent ASNC information statement, stress-only imaging was recommended when applied to properly selected patients.[2] In order to perform stress-only imaging, either a 1- or 2-day stress-rest Tc-99m imaging protocol must be used. The choice of imaging protocol will depend on patient body weight and habitus. Two large trials evaluating over 21,000 patients with a normal SPECT study have demonstrated the safety of stress-only imaging as compared to traditional stress/rest imaging.[5,6] Comparably low all-cause[5,6] and cardiac[6] mortality rates were observed with both imaging protocols. This was true irrespective of patient age, gender, cardiac risk factor profile, or stressor employed with SPECT.[5] These results are consistent with earlier studies evaluating patient outcome following normal stress-only imaging.[7,8] The stress Tc-99m imaging procedure is identical to that described above.

Advantages

- Patient convenience/satisfaction and laboratory efficiency are improved.
- There is a marked reduction in patient radiation exposure by eliminating the higher rest Tc-99m dose. In one recent study, the mean Tc-99m dose was significantly lower at 21.3 ± 10.7 mCi with stress-only versus 55.1 ± 11.9 mCi with stress/rest imaging. This was particularly true for patients who received an initial low dose of Tc-99m as part of a same day stress/rest protocol (13.5 ± 2 mCi).[5]
- Conservation of Tc-99m radiopharmaceuticals.
- Reduced cost by eliminating injection of a second Tc-99m dose and the subsequent rest imaging.

Disadvantages

There are no specific disadvantages to a stress-only imaging approach. When properly utilized a normal stress-only study predicts the same excellent prognosis as compared to standard stress/rest imaging.[5,6] However, there are specific issues that need to be considered prior to implementing stress-only imaging in an individual laboratory:

- First, there is a requirement to assess each patient on arrival to the laboratory to choose the most appropriate imaging protocol rather than a ''one test fits all'' approach. This is the foundation of patient-centered imaging and requires staff flexibility so as to optimally manage daily work flow. Second, there is added demand on the physician to confidently interpret the stress image alone without the advantage of a rest image for comparison. Inherent to this approach is that the stress images are of good quality. Differentiation of artifact from a true perfusion abnormality is more difficult without a resting scan and therefore requires the expertise of an experienced reader. In this regard, attenuation correction with either x-ray computed tomography (CT) or line sources may be advantageous if a stress-only protocol is used.[9] Recent data indicate that a stress-only imaging protocol coupled with attenuation correction techniques can be effectively applied to obese patients where a normal study predicts an excellent outcome.[10] Prone imaging can also be used to clarify inferior perfusion defects due to diaphragmatic attenuation observed on supine images.[11] The perfusion images should be unequivocally normal by visual and, preferably, quantitative analysis[12,13] and LV cavity size, LVEF and regional wall motion and thickening should be normal. If these criteria are not met, then a rest image should be performed. Conversely, in patients with a clearly abnormal study who have no prior history of CAD, it may be appropriate and expeditious to forego the resting scan with direct referral for coronary angiography. Third, the physician must be readily available to interpret the stress study prior to administration of the rest dose so as not to delay laboratory throughput. Fourth, patients with prior myocardial infarction or known LV dysfunction usually require rest imaging and are not good candidates for this protocol.

Patient Radiation Dose

- The effective dose using a stress-only protocol with 25.0 mCi is estimated at 6.8 mSv for Tc-99m

sestamibi and 5.8 mSv for Tc-99m tetrofosmin. The effective dose using a stress-only protocol with 10.0 mCi is estimated at 2.7 mSv for Tc-99m sestamibi and 2.3 mSv for Tc-99m tetrofosmin.

One-Day Rest Tl-201/Stress Tc-99m Dual Isotope Protocol

The dual isotope rest Tl-201/stress Tc-99m-based protocol is performed as follows:

- 2.5-4.0 mCi Tl-201 is injected at rest followed by imaging at approximately 10 minutes post-injection. Either a parallel hole high resolution or all-purpose parallel hole collimator may be used.
- There is no delay between completion of the rest image acquisition and performance of the stress test.
- 24-36 mCi Tc-99m-based radiopharmaceutical is injected during peak stress with imaging performed approximately 15-20 minutes post-exercise or approximately 30-60 minutes post-pharmacologic stress.

Advantages

- The dual isotope protocol is shorter than the 1-day rest/stress Tc-99m protocol, making it more convenient for patients. Following resting injection of Tl-201, MPI acquisition may be initiated within 10-15 minutes, thereby partially eliminating the resting injection-to-imaging delay.
- The photon energy of Tc-99m used for the stress scan (140 keV) is higher than the energy of the mercury x-rays emitted by Tl-201 (60-98 keV). Therefore, the potential of rest-to-stress ''shine-through'' described above for the 1-day rest/stress Tc-99m protocol is eliminated.

Disadvantages

- The lower energy of Tl-201 compared to Tc-99m results in relatively greater soft tissue scatter and photon attenuation, loss of resolution with depth, and poorer spatial resolution. Tl-201 SPECT images also have a lower count density than those obtained with Tc-99m due to the smaller administered dose (3-4 mCi). The relatively long half-life of Tl-201 precludes administration of higher doses. Due to the lower count density of Tl-201 as compared to Tc-99m images, filtering during image reconstruction is adjusted by lowering the critical frequency and increasing the order. This results in ''smoother'' tomograms with poorer spatial resolution and potentially poorer resolution of myocardial perfusion defects. If an all-purpose parallel collimator is substituted for a high-resolution collimator to increase count density, spatial resolution is further degraded.
- Comparing the lower resolution rest Tl-201 SPECT to the higher resolution stress Tc-99m SPECT images may compromise study interpretation and diagnostic accuracy. Fixed perfusion defects may appear partially reversible due to the poorer spatial resolution of the resting Tl-201 versus the stress Tc-99m scan. For the same reasons, LV cavity size may appear smaller at rest, giving the false impression of transient ischemic dilatation. Alignment of images may be problematic. In addition, rest-gated Tl-201 SPECT images are often of suboptimal quality, precluding accurate assessment of LVEF and comparison to the stress study. Finally, attenuation correction algorithms have not been validated for Tl-201 and should be applied cautiously.
- Since the resting scan is performed first, a subsequent stress scan must be performed in every patient. This obviates the advantage of employing a stress-only protocol.
- A major concern of the dual-isotope protocol is the associated patient radiation dosimetry.

Patient Radiation Dose

- The effective dose is estimated to be 22.1 mSv based on administration of 3.5 mCi of Tl-201 and 25.0 mCi of Tc-99m sestamibi, and 21.2 mSv based on administration of 3.5 mCi of Tl-201 and 25.0 mCi of Tc-99m tetrofosmin. Furthermore, radiation exposure may be higher in larger patients who receive larger doses of each radiotracer. Because of these concerns, this protocol is currently discouraged.[2]

One-Day Tl-201 Stress/Redistribution Protocol

A stress/redistribution Tl-201 protocol may be substituted for a 1-day rest/stress or stress/rest Tc-99m protocol when Tc-99m is not available.

Details of the protocol are as follows:

- 2.5-4.0 mCi Tl-201 is injected at peak exercise or pharmacologic stress.
- Imaging is performed approximately 10 minutes post-injection due to Tl-201 redistribution. Early redistribution of thallium necessitates image acquisition within 30 minutes. Any delay may reduce the ability to identify stress-induced ischemia due to potential early redistribution.
- Redistribution imaging is performed 3-4 hours after the initial injection.

Advantages

- Stress imaging may be performed first thing in the morning, which is convenient for the individual supervising the stress test.

- Only a single radiopharmaceutical injection is needed.
- Compared to Tc-99m studies, Tl-201 lung uptake, an important prognostic indicator, is more easily assessed.

Disadvantages

Disadvantages of this protocol are related both to the physical characteristics of Tl-201 and the radiopharmaceutical's redistribution properties.

- Due to early redistribution of Tl-201 in selected patients, imaging should begin approximately 10 minutes post-injection so as not to underestimate the stress-induced perfusion defect.
- The low administered dose of Tl-201 (necessary due to its long physical half-life of 73 hours), coupled with its low photon energy (60-80 keV mercury x-rays) may result in suboptimal SPECT images, particularly in larger patients in whom soft tissue attenuation and Compton scatter are more likely. Therefore, Tl-201 is not recommended in large patients in whom soft tissue attenuation and Compton scatter are more likely.
- In patients with stress-induced perfusion defects, Tl-201 may not completely redistribute within 3-4 hours resulting in overestimation of scar and underestimation of ischemia. For these reasons modified Tl-201 protocols have been developed (see below).

Patient Radiation Dose

- Compared to the 1-day rest/stress and stress/rest Tc-99m protocols, radiation exposure is higher with a stress/redistribution Tl-201 protocol (15.3 mSv with a 3.5 mCi dose).[2]

Tl-201 Stress/Redistribution with Optional Additional Imaging Protocols

In order to optimize detection of ischemic myocardium, patients can undergo either: (1) additional delayed imaging or (2) re-injection of Tl-201 after redistribution imaging. Depending upon the laboratory schedule, the patient must again return for repeat imaging approximately 8- to 24-hours post-initial Tl-201 injection. During this prolonged time interval there is generalized washout of Tl-201 from the myocardium, so overall myocardial count density is low, and image quality may be suboptimal—particularly in larger patients. The alternative approach is to administer a 1.0-2.0 mCi ''booster'' dose of Tl-201 in patients showing incomplete redistribution at 3- to 4-hour imaging. This increases the amount of tracer available to ''wash in'' and fill ischemic areas. Detection of ischemia is further enhanced if sublingual nitroglycerin is administered several minutes prior to Tl-201 reinjection.[14]

Patient Radiation Dose

- The disadvantage of this protocol, which entails injection of a ''booster'' dose of Tl-201, is a significant increase in radiation exposure, which rises to 19.7 mSv, assuming a stress dose of 3.0 mCi and a re-injection dose of 1.5 mCi Tl-201. This exposure estimate will increase in larger patients receiving higher doses of Tl-201.[2]

SPECT Protocols for Assessing Patients with Congestive Heart Failure and LV Dysfunction

a. Rest/Delayed Tl-201 Protocol to Assess Myocardial Viability
A limitation of the stress/delayed Tl-201 protocol for assessing myocardial viability is that Tl-201 must redistribute from a stress (ischemic) distribution to that of a resting distribution (which may be affected by resting ischemia) with uptake ultimately into viable myocardial cells. To circumvent the problem, the radiotracer may be injected at rest with delayed imaging to assess further redistribution into viable myocardium. This is important since defects with >50% of normal maximal myocardial count density are more likely to represent viable myocardium as evidenced by recovery of LV function.

Details of the protocol are as follows:

- A rest injection of 3.0-4.0 mCi Tl-201 immediately followed by SPECT within approximately 10-15 minutes.
- Delayed SPECT is performed approximately 3-5 hours thereafter.
- Additional delayed SPECT may be performed at approximately 8-24 hours in patients with minimal redistribution.
- A booster, ''reinjection'' dose of Tl-201 should not be administered prior to the delayed scan since it will obviate the benefit of delayed redistribution of radiotracer in detecting viable myocardium.

Advantages

- Tl-201 is readily available, and the protocol is easy to perform. In contrast to F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) (see below), the protocol is simpler in diabetics and patients with insulin resistance.
- There is no need to perform stress testing. Therefore, it is applicable to patients following

acute myocardial infarction and in those who have severe LV dysfunction.
- The protocol facilitates further clarification of myocardial viability in patients with fixed defects on a rest/stress or stress/rest Tc-99m sestamibi or tetrofosmin study.

Disadvantages

- The rest/delayed Tl-201 protocol may not be as sensitive as F-18 FDG PET for detecting viable myocardium and particularly when perfusion defects are severe.

Patient Radiation Dose

- Effective dose using the rest-delayed Tl-201 viability protocol is 15.3 mSv using a 3.5 mCi dose.

b. Nitrate-Enhanced Tc-99m SPECT to Assess Myocardial Viability.

Nitroglycerin improves resting myocardial perfusion through coronary and collateral vasodilation, reduction in preload and myocardial wall stress and a decrease in afterload. Another means of determining if a resting myocardial perfusion defect is due to scarring or resting ischemia is to administer a Tc-99m radiopharmaceutical following nitrate-enhanced vasodilatation.[15,16]

Details of the protocol are as follows:

- 8-12 mCi Tc99m-based radiopharmaceutical is injected at rest with SPECT performed between approximately 30 and 60 minutes.
- Sublingual or buccal nitroglycerin (0.4-0.8 mg) is administered to decrease systolic blood pressure $\geq$10 mm Hg.
- 32-45 mCi ($\geq$3 times the resting dose) Tc99m-based radiopharmaceutical is then injected. This dose is higher than that used for the stress portion of the 1-day rest/stress protocol because there is no increased delivery of radiotracer to the myocardium as there is with exercise or pharmacologic stress, and greater activity is needed to prevent ''shine-through'' of the baseline scan into the nitrate-enhanced scan.
- SPECT is performed at approximately 30-60 minutes.

Advantages

- The nitrate-enhanced protocol is readily available and easy to perform.
- Due to the higher dose and superior physical properties of Tc-99m, image quality is superior to that of a rest/delayed Tl-201 protocol.

Disadvantages

- Patient radiation exposure using the Tc-99m nitrate-enhanced viability protocol is similar to the 1-day rest/stress protocol.

Patient Radiation Dose

- Dosimetry has not been well modeled for nitrate-enhanced Tc-99m sestamibi and tetrofosmin; however, dosimetry would be expected to be not very different from rest/stress imaging, i.e., 12.7 mSv for Tc-99m sestamibi and 10.4 mSv using Tc-99m tetrofosmin, based on 10.0 mCi and 35.0 mCi doses, respectively.

SPECT Protocols in Acute Chest Pain: Rest Tc-99m Imaging

In patients with a suspected acute coronary syndrome, rest imaging is advantageous to detect acute myocardial infarction or localize resting ischemia.[17,18]

Details of the protocol are as follows:[19]

- 24-36 mCi Tc99m-based radiopharmaceutical is injected at rest.
- Gated SPECT is acquired approximately 30-60 minutes thereafter.

Advantages

- The protocol is simple and rapidly performed.
- A normal rest study virtually excludes the presence of acute myocardial infarction and is cost-effective as compared to a standard clinical assessment for triaging patients with low- to moderate-risk acute chest pain.[20]

Disadvantages

- The protocol is not applicable to patients with a prior myocardial infarction in whom acute myocardial infarction and/or resting ischemia cannot be differentiated from an old myocardial scar.
- Since only one image is available for rest-only MPI, attenuation artifacts pose a serious problem. Gated SPECT imaging cannot be used to adjudicate ischemia from attenuation artifact. However, attenuation correction is useful to differentiate attenuation artifact from true resting ischemic defects.
- The protocol is of limited value in identifying acute ischemia, particularly when the tracer is injected after chest pain resolution. Thus, the nuclear laboratory must be in close communication with the Emergency

Department (ED) to maximize the clinical utility of this protocol.

- Nuclear technologists are generally not on site at night or on weekends. Summoning an on-call technologist results in a delay in performance of the scan and in subsequent patient management.
- Since artifacts due to soft tissue attenuation cannot be easily differentiated from true perfusion defects on a rest study alone, there is limited specificity of rest imaging for diagnosing acute coronary syndrome. Attenuation correction is particularly advantageous in this setting for reducing the number of false positive studies.
- A normal rest study does not exclude the presence of significant CAD.

Patient Radiation Dose

- The effective dose using the rest-only protocol with 25 mCi is 8.0 mSv for Tc-99m sestamibi and 5.8 mSv for Tc-99m tetrofosmin.

Additional Considerations and Advancements for SPECT

a. Body Position

Body position may affect the orientation of the heart within the thorax as well as the position of the breasts and left hemidiaphragm, both of which commonly produce attenuation artifacts. The advantages and disadvantages of various body positions should be taken into account when considering optimal patient-centered imaging protocols.

Supine positioning for MPI SPECT is by far the most commonly employed technique. Lying supine is generally well tolerated by patients. The lumbar spine may be supported and the knees elevated to enhance patient comfort. However, in the supine position the diaphragm is relatively elevated, particularly in patients with protuberant abdomens. Loose clothing or a hospital gown is preferred in women to allow the breasts to assume a pendulous position along the lateral chest wall. However, the breasts may assume different positions in stress and rest SPECT acquisitions if they are constrained by clothing. More commonly, differences in the degree of left arm elevation will result in differences in breast position in stress and rest acquisitions. Elevation of both arms above the head is preferable with supine imaging to decrease attenuation of myocardial counts by the left arm and also to allow the camera detectors to closely approximate the chest wall to avoid loss of spatial resolution with increased distance from the collimator.

Prone imaging is helpful to supplement supine SPECT. In the prone position, the diaphragm is pushed down, and the heart shifts anteriorly and upward, decreasing the degree of diaphragmatic attenuation. Inferior perfusion defects that resolve with prone imaging are attributed to diaphragmatic attenuation. However, anterior perfusion defects that shift in location with prone versus supine imaging are not reliably attributed to breast attenuation artifact. Furthermore, prone imaging is not well tolerated by all patients. Current guidelines recommend prone imaging to supplement but not supplant supine SPECT since normal databases are not presently available for prone SPECT.[4] Ultrafast camera systems facilitate imaging the patient in multiple positions due to the short imaging times.

Upright cardiac SPECT camera systems are commercially available. Upright imaging is generally well tolerated by patients, and may be preferable in very obese individuals. In the upright position the diaphragm is lower resulting in less attenuation of the inferior wall. Due to gravitational effects, shifting breast position may be less likely with the patient upright compared to supine. In women with pendulous breasts, the breasts usually lie lower than with the patient in the supine position. Therefore, inferior breast attenuation artifacts are more commonly encountered than with supine SPECT. To minimize motion in the upright position, a binder holding the patient close to the back of the imaging chair and an armrest/headrest to minimize vertical motion are recommended.

b. Attenuation Correction

Attenuation correction of MPI SPECT is available with either scanning gadolinium (Gd)-153 line sources or single/multi-slice x-ray CT.

Advantages

- Attenuation correction with scanning Gd-153 line sources or CT increases the diagnostic specificity of SPECT by decreasing soft tissue attenuation artifacts, and particularly those due to diaphragmatic attenuation.[21] Attenuation correction is also advantageous in obese patients, but the count density of Gd-153 transmissions maps may be suboptimal. Therefore, CT attenuation correction is preferable.
- By decreasing the frequency and severity of attenuation artifacts, attenuation correction particularly facilitates the stress/rest and stress-only protocols described above.[22] The diagnostic specificity of rest scans is also improved when imaging patients with suspected ACS.

Disadvantages

- A unique artifact associated with x-ray CT attenuation correction is misregistration of the radionuclide emissions scan and the x-ray transmission scan, which are performed sequentially. Although registration software is available on all commercially available systems, x-ray attenuation correction should be used cautiously in patients who are uncooperative or likely to move.
- Attenuation correction may accentuate subdiaphragmatic activity and scatter into the inferior wall of the left ventricle. Therefore, for all the protocols described above an adequate radiopharmaceutical injection-to-imaging interval is essential to assure tracer clearance from the liver. Likewise, stressor modalities (Section 3) that minimize splanchnic uptake are preferable when attenuation correction is employed.

Patient Radiation Dose

- Depending on their age, Gd-153 line sources typically expose the patient to an effective dose of about 0.001-0.01 mSv, (i.e., less than that of a single chest x-ray).[23,24] Alternately, modified CT attenuation correction protocols afford effective doses of 0.05-1 mSv depending on the scanner type and scan parameters employed.[25-27]

c. New Hardware and Software Advances
New camera technology now incorporates solid state cesium iodide (CsI) or cadmium-zinc-telluride (CZT) solid state detectors and focused collimation. These advancements provide significantly greater camera sensitivity (count rate capabilities) as well as improved spatial and energy resolution.[28-31] Several manufacturers have introduced software methods that incorporate iterative reconstruction, resolution recovery, and noise reduction and provide good quality SPECT images despite reduced count statistics.[32-35] These software and hardware methods can be implemented to significantly reduce SPECT acquisition times (as short as 2 minutes per image) and/or injected radiotracer activity, thereby decreasing patient radiation exposure.[36,37]
Although protocol modifications incorporating these new software and hardware techniques have not yet been fully developed, they will undoubtedly provide even more flexibility for patient-centered imaging than the standard protocols described above. With the possibility of either reduced-time or reduced-dose SPECT, there is the opportunity to ''customize'' scan protocols to meet specific patient requirements. For example, in a younger cooperative patient in whom radiation exposure is a concern, a reduced radiopharmaceutical dose and full-time acquisition may be preferable. Radiation exposure can be further reduced if stress-only imaging is performed. In the uncooperative elderly or arthritic patient where motion artifacts may be problematic, rapid half-time imaging with a full radiopharmaceutical dose should improve image quality with the ability to readily repeat imaging if motion occurs. In the obese patient where attenuation artifacts are anticipated, an alternative to weight-based radiopharmaceutical dosing to improve count statistics and image quality would be a full-time SPECT acquisition processed with reduced-time software.[38]

d. Quantitative Analysis of LV Perfusion
Quantitative analysis of PET or SPECT images can be performed using either a semi-quantitative visual [i.e., summed stress score (SSS) approach] or an automated quantitative polar plot assessment. These programs are readily available on most commercial software packages and are complementary to obligatory visual analysis when interpreting a study.
Quantitative analysis can facilitate a ''stress-only'' imaging approach by aiding the interpreting physician in concluding that a stress study is normal. Typically, a 2.0 or 2.5 standard deviation threshold is used to define abnormal pixel counts in a patient's polar plot as compared to a normal data file. In patients with abnormal studies, the quantified perfusion defect size, extent of myocardial ischemia, LVEF and LV volumes can improve risk stratification and guide the referring physician in making therapeutic decisions.[39] Quantitative analysis is also useful for evaluating serial imaging results to determine whether a patient has improved following a therapeutic intervention or developed significant new perfusion abnormalities.[40-42] Recent data suggest that quantitative changes in stress-induced perfusion defect sizes can track subsequent risk for cardiac events..[41-43] Further investigation in this important area is needed.

PART 2: POSITRON EMISSION TOMOGRAPHY IMAGING PROTOCOLS

In addition to commonly used SPECT imaging techniques described above, PET can be used to assess myocardial perfusion and/or viability.

While similar to SPECT imaging in many ways, PET imaging has unique advantages as an imaging modality. PET radiotracers decay by positron emission which leads to the generation of two 511 keV photons when the positron is annihilated in a collision with an electron. The PET camera detects both of these high-

energy photons. The high-energy of these photons and the 'coincidence detection' technique of PET imaging systems result in significant advantages in image quality as compared to SPECT. Both rubidium-82 (Rb-82) and nitrogen-13 ammonia (N-13 ammonia) are approved by the US Food and Drug Administration (FDA) for use in PET MPI. N-13 ammonia generally provides superior image quality. Rb-82 offers the advantage of being generator-produced, as opposed to N-13 ammonia which requires an on-site cyclotron. F-18 FDG is approved for use in cardiac PET viability studies. In the near future, F-18 labeled tracers for use in cardiac PET MPI may be available.[44]

Another advantage of PET imaging is its use of attenuation correction in all PET systems. Older, dedicated PET imaging systems used rotating line-sources (Cesium-137, Germanium-68/Gallium-68) to generate a transmission attenuation map, whereas currently manufactured PET systems use x-ray CT technology for attenuation correction. Both the types of systems are presently used in nuclear cardiology laboratories performing PET imaging. Details of attenuation correction and its effects on acquisition protocols are published in the 2009 ASNC PET Myocardial Perfusion and Glucose Metabolism Imaging guideline.[45]

The acquisition sequence of MPI protocols with cardiac PET follows a 'rest/stress' sequence due to the short half-life of the radiotracers (Rb-82 = 75 seconds, N-13 ammonia = 10 minutes). This allows for completion of an entire cardiac PET acquisition in under 1 hour, and as rapidly as 30 minutes. Furthermore, depending on the camera vendor, studies can be acquired in various modes, either traditional static and gated, or dynamically with or without list mode. List mode acquisition allows for simultaneous acquisition of information required for static and gated images, the ability to correct for motion, and the possibility of compartmental analysis for use by recently FDA-approved myocardial blood flow quantification software.

Most PET studies are performed with pharmacologic stress. Exercise PET is possible but is challenging due to the short half-lives of the radiotracers. However, N-13 ammonia PET can be performed with exercise stress. If F-18-labeled cardiac PET blood flow tracers become available, their longer half-life (110 minutes) will facilitate more widespread exercise stress utilization. Pharmacologic stress protocols using adenosine, dipyridamole, and dobutamine have been developed for Rb-82 and N-13 ammonia. Regadenoson is also being employed as a stress agent for cardiac PET. Initial data suggest that it provides similar results with PET as compared to traditional vasodilators, but confirmatory studies are needed.[46]

Finally, cardiac PET can provide additive information beyond perfusion to allow for patient-specific questions to be answered. With PET/CT systems, customizable CT imaging options include coronary artery calcium scoring (CACS) and/or CT coronary angiography (with 64-slice or greater CT systems). As performed with SPECT, fusion of CT angiography (CTA) with perfusion images can create multi-modality images integrating anatomy and physiology. Unlike SPECT, cardiac PET allows acquisition of gated ''stress'' data during peak hyperemic blood flow with calculation of a peak stress LVEF. This may improve identification of high-risk patients or those with multi-vessel CAD.[47] Furthermore, recent software solutions allow for absolute quantification of regional myocardial blood flow from dynamically acquired Rb-82 and N-13 ammonia cardiac PET studies,[48,49] and this may be particularly important and useful in evaluating multi-vessel and small vessel coronary disease, responses to medical therapy, and transplant vasculopathy. A major advantage of PET over SPECT is less attenuation artifact due to the high-energy photons and built-in attenuation correction, which is not always available with SPECT imaging.

Rest/Stress Rubidium-82 (Standard Gated Protocol using PET/CT)

The Rb-82 imaging protocol is as follows:

- Scout image—a low-dose CT to check the alignment and positioning of the patient in the scanner.
- Non-gated low-resolution CT for attenuation correction—this scan can be used for attenuation correction of both the rest and stress emission scans at the discretion of the imager.
- ''Rest'' Rb-82 injection—bolus injection of 10-60 mCi Rb-82 followed by gated rest acquisition. The dosimetry will depend on scanner type (2D vs 3D), detector crystal (BGO vs LSO vs GSO), and age of the Rb-82 generator.
- Pharmacologic stress with bolus injection of 10-60 mCi Rb-82 at peak hyperemia.
- Gated stress acquisition—approximately 7 minutes in duration.
- Non-gated CT for attenuation correction of ''stress'' acquisition (optional).

Advantages

- Rapidity of the protocol (30-45 minutes).
- Relatively low radiation exposure (1.75-7.5 mSv or lower have been reported).[45,50]
- Accurate attenuation correction.
- Measurement of LVEF at peak stress.

- Quantification of myocardial blood flow reserve using recently FDA-approved commercial software applications.

These advantages make Rb-82 PET a more sensitive and specific imaging technique for the diagnosis of ischemia[51] in patients with a prior equivocal Tc-99m SPECT study.[52] Rb-82 PET is also optimal in patients who require rapid imaging, patients in whom there are radiation exposure concerns (younger patients), and in obese patients in whom attenuation artifacts are anticipated.

Disadvantages

- Limited availability of PET/CT equipment.
- Relatively high procedural cost per study.[53]
- Limited prognostic data as compared to SPECT.
- Requirement for pharmacological stress.

Rest/Stress N-13 Ammonia (Standard Gated Protocol Using PET/CT)

The imaging protocol is as follows:

- Scout image.
- Non-gated low-resolution CT for attenuation correction.
- Bolus injection of 10-20 mCi N-13 ammonia at rest.
- Gated rest acquisition—1-3-minute delay after injection to allow for blood pool clearance with total acquisition time of 10-15 minutes.
- Pharmacologic or exercise stress followed by bolus injection of 10-20 mCi at peak hyperemia.
- Gated stress acquisition—1-3-minute delay with total acquisition time of 10-15 minutes.
- Non-gated CT for attenuation correction of ''stress'' acquisition (optional).

Advantages

- Rapid study acquisition (<1 hour).
- Very low radiation exposure (1.5 mSv effective dose for 10.0 mCi rest and stress dose).
- Accurate CT attenuation correction.
- Allows calculation of a peak stress LVEF.
- Provides superior image quality and more accurately tracks peak hyperemic myocardial blood flow than Rb-82.
- Can be performed with exercise in selected patients due to its longer half-life.

Disadvantages

- Limited availability of PET equipment.
- Relatively high procedural cost per study.[53]
- Limited prognostic data as compared to SPECT.
- Limited availability of N-13 radiopharmaceutical due to its relatively short half-life (10 minutes) and the requirement for delivery from a nearby facility with a cyclotron.

F-18-Fluorodeoxyglucose (FDG) PET

Assessment of myocardial viability with F-18 FDG relies on the plasticity of myocardial metabolism to switch substrate utilization, particularly in response to decreased oxygen delivery. In viable areas of the myocardium with diminished blood flow, cardiomyocytes shift from fatty acid to glucose metabolism as the primary source of energy production. This preferential use of glucose in hibernating, but viable, areas of the heart is the basis for FDG PET viability studies.

In order to maximize glucose uptake in the heart for an FDG PET study, patient preparation is critical. This involves stimulating endogenous insulin release in non-diabetic patients or overcoming myocardial insulin resistance in diabetic patients. The insulin-glucose clamp technique is the optimal method, but technically challenging. Alternatively, oral glucose loading with insulin supplementation can be employed. In non-diabetic patients, a prolonged fast (>6 hours) is recommended, followed by a glucose load of 25-100 g (oral or IV) and additional insulin supplementation if required. The use of FDG PET viability imaging in diabetic patients is more challenging since preparation for the test varies depending on whether the patient requires oral agents only (no breakfast, take oral medications) or insulin (no fast, usual diet and insulin). The ASNC 2009 PET guideline provides detailed descriptions of options for glucose loading and insulin administration.[45]

The imaging protocol is as follows:

- Patient preparation (as above).
- Injection of 5-15 mCi F-18 FDG at rest following glucose/insulin manipulation with image acquisition 45-90 minutes later (up to 3 hours later in diabetics).
- Scout image.
- Non-gated low-resolution CT for attenuation correction.
- 10-30-minute static rest acquisition in list or gated mode.
- Comparison of FDG image to prior perfusion study (Rb-82 or N-13 ammonia). Resting SPECT (Tl-201 or Tc-99m) perfusion image can also be used. Myocardial viability is defined by decreased regional resting perfusion but increased glucose uptake (''flow-metabolism mismatch'').

Advantages

- High sensitivity for detecting viable myocardium.
- Ability to predict improved regional function after revascularization[54] and possibly improved outcomes.[55]
- Relatively low radiation exposure (6.6 mSv effective dose for 10.0 mCi administered)

Disadvantages

- Requirement of a PET scanner.
- Complex patient preparation (particularly in diabetic patients).
- Protocol length (up to 4-5 hours in diabetic patients).

PART 3: STRESS TEST PROTOCOLS

Consideration of Exercise Stress Versus Pharmacologic Stress

Several factors may influence the type of stressor selected for an individual patient. The most practical issue is the patient's ability to exercise. ''Adequate'' exercise during a treadmill test is generally defined as the ability to perform a workload ≥7 metabolic equivalents (METs) (i.e., completion of the first two stages of the Bruce protocol or equivalent) and achieve a heart rate ≥85% of predicted maximal heart rate. Specific criteria depend upon a patient's age and gender and whether the test is being performed primarily for diagnostic or prognostic purposes. A patient's ability to adequately exercise can be assessed informally based on the activity level described in the patient's history or in a more formal manner by applying a physical activity questionnaire.[56]

Advantages of Exercise Stress

Studies have shown similar diagnostic accuracy for stress SPECT when combined with either exercise or pharmacologic stress.[39] An advantage of exercise is the additional prognostic information gained from the stress test. The most important prognostic variables are exercise duration (METs achieved) and the extent of exercise-induced ST-segment depression. Other important variables include exercise-induced angina, hypotension, and ventricular ectopy; chronotropic incompetence; and impaired heart rate recovery after exercise.[57] The well-validated Duke treadmill score combines exercise duration with the presence of ST-segment depression and exercise-induced angina to estimate risk.[58,59] The Duke Treadmill score adds prognostic value to that obtained by nuclear imaging variables alone.[60] The objective measurement of functional capacity can also be important for determining a patient's suitability for employment or disability.[61] Another useful application of the exercise test is to observe whether the patient's chest pain is reproduced during stress to determine whether its etiology is cardiac or non-cardiac. For these reasons, exercise stress is preferred over pharmacologic testing when an adequate exercise effort can be achieved.

Advantages of Pharmacologic Stressors

In the United States approximately one-half of all nuclear stress tests are performed with pharmacologic agents. Other indications for selecting vasodilator stress beyond inability to exercise are the presence of left bundle branch block (LBBB)[62] or a paced ventricular rhythm.[63] In these patients the acceleration in heart rate during exercise leads to a high prevalence of false-positive reversible perfusion defects, primarily in the septum, lowering test specificity.[64] Another unique application of vasodilator stress testing is very early risk stratification of stable patients with AMI.[65] Submaximal exercise testing can be performed 48 hours after admission in such stabilized low-to-intermediate risk patients.[65] In the Adenos*IN*e *S*estamibi SPECT *P*ost-*I*nfa*R*ction *E*valuation (INSPIRE) study, which enrolled patients with both ST- and non-ST-segment elevation AMI, vasodilator stress imaging was safely performed as early as 12 hours after presentation.[66]

Limitations Common to Both Exercise and Pharmacologic Stress

Both exercise and pharmacologic stress tests are generally safe procedures with a very low risk for serious complications. The reported risk of cardiac death or MI during exercise or vasodilator stress testing is between 1 and 4 per 10,000 patients.[67-69] Dobutamine is generally less well tolerated and leads to more frequent side effects than exercise or pharmacologic vasodilator stress.[70] Experience with regadenoson[71] is much more limited but this agent appears to have a low complication rate.

The administration of anti-ischemic medications (i.e., nitrates, beta blockers, and calcium channel antagonists) either alone or in combination can reduce the diagnostic sensitivity of stress SPECT or PET MPI, irrespective of the stressor modality utilized[40] (see Part 4).

Exercise Protocols

The most commonly employed type of exercise in the United States is treadmill testing. All currently used protocols progressively increase workload by increasing treadmill speed and/or incline until the desired endpoint is reached. Most protocols increase workload in distinct stages, although ramp protocols do exist whereby

workload is continuously increased. The Bruce protocol is most commonly used where most patients complete a workload of 7-13 METs over 6-12 minutes. Several other protocols (modified Bruce, Naughton, Balke) increase workload in smaller increments, which is an advantage in elderly or frail patients. Bicycle ergometry is widely applied in Europe. Other forms of exercise testing, such as arm ergometry, exist but are rarely used.

Pharmacologic Agents

The two major classes of pharmacologic agents available for stress testing are coronary artery vasodilators and synthetic catecholamines.

Vasodilators

Pharmacologic vasodilators are the most frequently used agents for performing stress MPI. Three agents are currently FDA approved in the US: dipyridamole, adenosine, and regadenoson. Each one has unique pharmacologic properties and distinct physiologic actions but share in common stimulation of the adenosine A2A receptor with resultant coronary artery vasodilatation. These agents demonstrate similar diagnostic accuracy.[39,71]

Contraindications to the administration of coronary vasodilators vary among the different agents. For example, dipyridamole and adenosine are contraindicated in patients with active wheezing and in those who have either moderate chronic obstructive pulmonary disease (COPD) with a significant reversible component (FEV1 30%-39% of predicted with bronchodilator response >15% or FEV1 40%-100% of predicted with bronchodilator response >30%), or severe COPD (FEV1 <30% predicted). Theoretically, regadenoson, a selective A2A adenosine receptor agonist, should be safer in patients with obstructive airways disease. Recent data indicate no significant effect on pulmonary function in outpatients with clinically stable mild to moderate asthma[72] or moderate to severe COPD.[72,73] Patients with sinus node dysfunction or second- or third-degree atrioventricular (AV) block are at increased risk of sinus arrest or prolonged ventricular pauses and should not be administered any of these agents unless a permanent pacemaker is in place. The average expected decrease in blood pressure with pharmacologic vasodilators is 10-20 mm Hg but more profound decreases (>50 mm Hg) have been reported in individual patients. For this reason, they should be used cautiously in patients with a resting systolic blood pressure <100 mm Hg.

Several medications interact with these agents to either block or enhance their physiologic effects. Drugs which block the adenosine receptor include methylxanthines such as aminophylline (theophylline) and caffeine. Although a small amount of caffeine (e.g., one 8-ounce cup of coffee) does not appear to influence SPECT results,[74] vasodilator stress testing should not be routinely performed in patients who have recently ingested caffeine or a medication containing a methylxanthine. Conversely, other medications such as carbamazepine can enhance the effects of the adenosine A2A receptors and potentially cause profound heart block. In patients taking oral dipyridamole (Persantine, Aggrenox), intravenous adenosine can result in profound heart block although intravenous dipyridamole can usually be safely administered to these patients.

Adenosine is a direct non-selective adenosine receptor agonist. The major advantage of adenosine over dipyridamole and regadenoson is its very short half-life (<10 seconds). Thus, side effects generally resolve within seconds to several minutes of discontinuing the intravenous infusion. Reversal of adenosine's physiologic actions with aminophylline is rarely necessary. For this reason, adenosine is the preferred agent in patients who are at greatest risk for developing side effects (e.g., a patient with borderline low blood pressure).

Dipyridamole is an indirect coronary artery vasodilator, which blocks the intracellular reuptake and deamination of adenosine and thereby boosts adenosine levels in the intravascular space. As an indirect vasodilator, dipyridamole induces less predictable hyperemia as compared to adenosine. Although side effects occur less frequently than with adenosine, they tend to last considerably longer (10-30 minutes) and may require reversal with aminophylline. As noted above, intravenous dipyridamole can be safely administered to a patient taking oral dipyridamole.

Regadenoson is the first selective adenosine A2A receptor agonist to be approved for pharmacologic stress testing. Its affinity for the adenosine A1 receptor is at least 10-fold lower than for the A2 receptor, minimizing the risk for AV block. In the phase 3 ADenoscan Versus regAdenosoN Comparative Evaluation for MPI (ADVANCE MPI) 2 trials, regadenoson had a lower composite side effect profile than adenosine but with comparable imaging results.[71] The half-life of regadenoson is triphasic, and aminophylline can be used to treat side effects. Physiologic effects of this medication can persist for up to 30 minutes after administration. Regadenoson is logistically easier to administer than adenosine or dipyridamole since it is given as an intravenous bolus injection over 10 seconds without the need for an infusion pump.

Synthetic Catecholamines

Dobutamine is the most commonly used synthetic catecholamine for pharmacologic stress testing in the United States. It is administered as a continuous infusion with the dose increased by 10 μg/kg/min at 3-minute intervals. This agent directly stimulates beta 1 and beta 2

receptors, resulting in an increase in heart rate and cardiac contractility that is dose-dependent but nonetheless highly variable in an individual patient. The effect on blood pressure is unpredictable. Systolic blood pressure may progressively increase, progressively decrease, or manifest a biphasic response (initial increase at low dose followed by decrease at high dose). The infusion is terminated if the patient develops intolerable side effects such as chest pain, headache, tremors, palpitations, severe ischemia, or major arrhythmias. In patients who tolerate the medication, the infusion is terminated at a maximal dose of 40-50 μg/kg/min or when the target heart rate (i.e., 85% of predicted maximal heart rate) is achieved. Atropine is commonly administered to patients who do not achieve their target heart rate at a maximally tolerated dose.

The half-life of dobutamine is approximately 2 minutes, but its physiologic effect may persist for 5-20 minutes and may require the administration of a short-acting beta blocker for reversal. The time requirement to perform a dobutamine study is longer than for vasodilator stress. Given the variable physiologic response to dobutamine in individual patients and the more labor-intensive requirements of administering this agent, dobutamine is designated as a secondary pharmacologic stress agent for nuclear cardiology. Its use is reserved for patients who cannot adequately exercise and who have a contraindication to performing vasodilator stress testing. Experience with this agent is much more limited than with exercise or vasodilator MPI but dobutamine appears to have similar diagnostic accuracy.[70]

Contraindications to dobutamine are numerous and include recent MI, unstable angina, hemodynamically significant LV outflow tract obstruction, severe aortic stenosis, poorly controlled atrial tachyarrhythmias, history of ventricular tachycardia, uncontrolled hypertension, history of aortic dissection, and/or aneurysm.[76] Dobutamine is not recommended in patients undergoing SPECT for diagnostic purposes when they are under treatment with beta-blockers. Beta blocker medications may reduce the stress-induced perfusion defect size and, in some patients, prevent detection of a perfusion defect.[77] Atropine is contraindicated in patients with narrow angle glaucoma.

A further description of all stressor modalities can be found in a recent ASNC document on this subject.[76]

PART 4: PATIENT-SPECIFIC EXAMPLES

Imaging of individual patients requires the physician to consider all components of the stress MPI procedure so as to safely obtain a meaningful test result while minimizing cost and inconvenience to the patient. The following cases illustrate how a patient might be approached from an imaging perspective to achieve the above objectives.

The Asymptomatic Patient

ASNC has recently published a comprehensive information statement on the use of radionuclide imaging in the asymptomatic patient which complements appropriateness use criteria guidelines.[1,78] Recommendations are divided into patients with and without a prior history of CAD. In patients without prior CAD, MPI is considered appropriate only in those who: (1) are at high cardiovascular heart disease risk based on standard Adult Treatment Panel (ATP) III criteria; (2) are at high cardiovascular heart disease risk with a moderately abnormal (100-400) CACS by non-contrast CT; or (3) have a severely abnormal CACS (>400) in whom silent myocardial ischemia is known to be prevalent.[79-81] Of note, only 25% of asymptomatic patients will have either a moderate (~15%) or a severe (~10%) CACS.[78,82]

The limited role of MPI in the asymptomatic patient with risk factors for CAD is not due to its inaccuracy in risk stratifying such patients but by the very low prevalence of an abnormal study demonstrating ischemia (~5%).[83-85] Routine testing with MPI would result in unnecessary radiation exposure in the vast majority of patients. However, the likelihood of an abnormal MPI significantly increases to ~25% in asymptomatic patients who have at least a moderate CACS and to ~40% when the CACS is severe.[79-81] The rationale for CACS as an initial test is that it is most sensitive for detecting early atherosclerosis and with relatively low radiation exposure (1-2 mSv). Based on CACS results, MPI can be selectively targeted to the small percentage of asymptomatic patients most likely to have ischemia. If MPI is performed, further radiation exposure should be minimized by tailoring the imaging protocol and the radiopharmaceutical dose to the individual patient, as discussed in Part 1. This would include performing a stress/rest Tc-99m imaging protocol since the rest dose of radiotracer can be avoided if the stress images are normal (i.e., stress-only imaging). Tc-99m radiotracers are recommended over Tl-201 in such patients since they expose the patient to considerably less radiation[86] and provide superior image quality.[87] In addition, asymptomatic patients without known CAD are also more likely to complete a maximal exercise test as compared to their CAD counterparts due to their younger age, better overall fitness and generally less beta blocker usage. Combining exercise with Tc-99m MPI will improve study quality by: (1) reducing splanchnic activity; (2) minimizing attenuation artifacts; and (3) allowing for attenuation correction when

necessary. All the above imaging considerations will increase the likelihood of performing ''stress-only'' imaging since the majority of these patients will not have flow-limiting significant CAD.

The asymptomatic patient with a history of CAD includes those with documented coronary stenosis on angiography or those with an acute coronary syndrome. Appropriateness use criteria provide indications for the timing and frequency of imaging in these patients.[1] The radiotracer and its dosage will be dependent on the size and weight of the patient as discussed in Part 1. ASNC guidelines recommend treadmill exercise as the preferred stressor unless patients have a non-cardiac limitation precluding a maximal effort.[76] This will be true for ~50% of patients referred for MPI. The choice of pharmacologic stressor will be dependent on physician preference and the clinical profile of an individual patient (see Part 3, Stress Test Protocols). The preferred imaging protocol is a 1-day Tc-99m rest/stress or 2-day stress/rest (or rest/stress) procedure. When performed in a single day, the rest/stress protocol is preferable so as to minimize underestimation of ischemia (see Part 1, SPECT Protocols). If a 1-day low dose stress/high dose rest protocol is used, a 3-hour waiting period is recommended between the stress and the rest doses or the rest dose can be appropriately increased.[76] An alternative approach is a dual isotope protocol although this results in considerably higher radiation exposure to the patient and is therefore discouraged (see Part 1). Sublingual nitroglycerin (0.4 mg) prior to rest injection of Tl-201 or Tc-99m tracers will enhance detection of ischemia and may be administered unless the patient is hypotensive or has another contraindication to its use.[14,16,88,89]

The Symptomatic Patient with Suspected CAD

Stress MPI is an accepted, widely used technique for accurately evaluating risk and guiding therapy in patients with suspected CAD.[90] Patients appropriate for stress MPI generally have chest pain and/or other associated symptoms suggestive of ischemia.[1] Strategies for minimizing radiation exposure should be of paramount importance, particularly when evaluating younger individuals and women.[2,3] Based on previous registry data, it is estimated that approximately 50%-60% of symptomatic patients with suspected CAD will have a normal stress MPI and a very low subsequent cardiac event rate.[5,6,91,92] In this regard, a Tc-99m stress/rest imaging protocol would seem optimal with the opportunity for performing stress-only imaging in a large percentage of patients.

Since a stress-only acquisition requires that the initial study be normal, high-quality imaging is pivotal toward its widespread implementation. Even with current technology, stress-only imaging is feasible and safe although more demanding of physician time and expertise (see Part 1). A recent ASNC information statement recommended that by 2014 total radiation exposure should be reduced to <9 mSv for at least 50% of patients referred for PET or SPECT studies.[2] Incorporation of stress-only imaging in routine clinical practice could already achieve this goal in 25% of all patients currently referred for imaging and in ~40% of patients who ultimately have a normal stress MPI exam.[12] New fast camera systems and software applications will further reduce radiation exposure by decreasing administered radiopharmaceutical doses.

CTA is an alternative imaging strategy for evaluating the symptomatic patient with suspected CAD. High-quality CTA is comparable to invasive coronary angiography for identifying patients with non-obstructive versus obstructive lesions.[93,94] The prognostic value of CTA was recently explored in the CONFIRM registry study which followed 24,775 symptomatic patients without prior history of CAD for 2.3 ± 1.1 years.[95] Mortality progressively increased based on the presence of non-obstructive CAD and the extent of obstructive CAD. Importantly, the annualized mortality rate in patients without CAD was exceedingly low at 0.26%. These results are consistent with other published reports.[96] CTA appears most useful for excluding significant CAD in low- to intermediate-risk symptomatic patients. In high-risk patients for CAD, the negative predictive value is reported to be only 83%.[97] As with MPI, limiting radiation exposure is paramount and can be best achieved through dose modulation and particularly prospective ECG gating techniques.

The value of coronary artery calcium scoring as an initial test in symptomatic outpatients with suspected CAD remains controversial. In a recent study of 10,037 low- to intermediate-risk patients, 3.5% of those with a CACS score of zero had >50% stenosis by CTA.[98] However, patients with a CACS of zero had a very low annual all-cause mortality rate of only ~0.5% and irrespective of the CTA results. Major acute cardiac events were significantly higher among those with a CACS of zero and obstructive versus non-obstructive CAD by CTA due to more frequent coronary revascularization in the former group. Similar results have been reported by others.[99,100] Alternately, calcium scoring may have a role in further defining risk in patients referred for stress MPI who have a normal test result.[101-104]

The Symptomatic Patient with Known CAD

Numerous studies over the years have demonstrated the diagnostic and prognostic value of stress MPI in patients with known CAD.[90] This is true for patients with and without a prior history of coronary revascularization. Patients with normal studies are known to have a low annual cardiac event rate. Conversely, in patients with abnormal studies, the size of the stress-induced perfusion defect, the extent myocardial ischemia, and the degree of LV dysfunction further define risk in an individual patient and thereby aid in guiding therapeutic decision-making. These important risk markers can be derived using either a semi-quantitative visual or automated polar plot analysis (see Part 1).

Imaging protocols should be used to optimize detection of perfusion defects and the extent of scintigraphic ischemia. Since these patients have known CAD, they are at higher intrinsic risk for cardiac death and other non-fatal complications. Thus, radiation exposure is of less concern with emphasis on obtaining the highest quality diagnostic (and prognostic) study. A rest/stress single-day or stress/rest separate-day Tc-99m imaging protocol is recommended to ensure adequate detection of ischemia recognizing that many of these patients will have stress-induced perfusion defects. Performing a nitrate-enhanced rest study may further maximize detection of scintigraphic ischemia and improve image quality.[105]

Currently, there is no role for calcium scoring in patients with known CAD and a limited role of CT angiography for assessing patients with prior bypass grafting.

The Patient with Acute Chest Pain in the ED

The evaluation of the patient with acute chest pain is of paramount importance considering that over 7-8 million ED visits occur each year in the US alone at an estimated cost of over 10 billion dollars.[106] Although most acute chest pain (70%-80%) is non-cardiac in origin, clinical evaluation alone is imprecise at diagnosing patients with an acute coronary syndrome. Therefore, there has been greater reliance on non-invasive cardiac imaging.

Patients with a clear-cut acute coronary syndrome by clinical criteria require no further non-invasive evaluation; or do low-risk patients with obvious non-cardiac chest pain. Unfortunately, the majority of patients have chest pain of uncertain cardiac origin characterized by non-diagnostic ECGs and normal initial cardiac biomarkers. Testing strategies for these patients are still evolving but have generally focused on cardiac CT and MPI techniques.

Rest MPI has a very high negative predictive value (>99%) for excluding myocardial infarction in acute chest pain patients.[107] When compared to standard of care, rest MPI can significantly reduce the rate of inappropriate hospital admission and thereby decrease cost.[20] However, it does not necessarily exclude patients with an acute coronary syndrome and is non-diagnostic in patients with prior myocardial infarction where a resting perfusion defect will be present but may not be related to the current chest pain episode (see Part 1). If rest imaging is to be performed, the radiotracer needs to be administered during or within 30 minutes of chest pain resolution for optimal diagnostic results. Rest imaging is problematic in patients receiving sublingual nitroglycerin where the coronary vasodilatory effects of the drug may last 30-60 minutes and thereby mask ischemia. Tc-99m radiotracers are preferable to Tl-201 since the former undergo negligible redistribution whereas the latter requires immediate imaging following injection. These logistical issues have limited the practical application of rest imaging in the ED.

Multiple studies over the past 20 years have defined the prognostic value of stress MPI in patients with unstable angina using either exercise or pharmacologic stress testing.[107] Recent contemporary studies have confirmed these earlier findings in patients presenting for evaluation of acute chest pain in the ED setting.[108,109] The stressor used in conjunction with MPI is at physician discretion. If treadmill exercise is performed, two sets of negative cardiac enzymes over a 4-6-hour time period are recommended. Alternately, pharmacologic vasodilator stress with adenosine or dipyridamole can be safely performed and even in stable patients early after acute myocardial infarction.[66,93] Dobutamine is contraindicated in these patients.[76] The recently developed adenosine A2A agonists have not been studied in patients with acute infarction.

There is considerable interest in the role of CTA in the ED setting. Studies have reported high sensitivity for identifying CAD and with a negative predictive accuracy of over 99%. Cardiac CTA, as reported in several randomized clinical trials, appears to have similar diagnostic accuracy as stress MPI but with faster time to diagnosis and at lower cost.[108,110,111] However, approximately one-third of patients will have a contraindication to performing CTA which commonly include renal insufficiency, cardiac dysrhythmias, poor intravenous access and contrast allergies. Bradycardia with a stable heart rate <65 bpm is critical for obtaining high quality studies on standard 64-slice scanners and, therefore, most patients will require administration of beta blockers. Patients with known CAD are not candidates for CTA and should undergo MPI for assessment of ischemia. Finally, approximately 25% of patients will have equivocal stenosis by CTA and require additional functional testing.[108] The strength of

CTA over MPI is that CT scanners are readily available for imaging 24 hours a day in most hospitals leading to a true ED-based approach.

An alternative strategy is that of CACS. There are no contraindications to performing a CACS from a non-contrast CT scan and it requires no patient preparation, exposes patients to minimal radiation (1-2 mSv), is readily and rapidly interpretable, and has the added advantage of identifying non-cardiac causes of chest pain. Recent studies demonstrate that 50%-60% of ED patients with non-diagnostic clinical findings for an acute coronary syndrome and no prior history of CAD will have a CACS of 0.[112-116] In a recent publication, only 1 of 625 patients with a CACS of zero had an abnormal stress SPECT with an event rate of only 0.4% at 7 month follow-up.[104] This exceedingly low event rate of <0.5% in patients with a CACS of 0 has been confirmed in currently published studies.[110,112-115] The authors suggest that patients with an initial CACS of 0 generally require no further testing, with SPECT reserved for those with a CACS >0.

The most cost-effective imaging algorithm in the ED setting remains to be determined.

The Patient with Recent Myocardial Infarction

Patients with acute ST elevation myocardial infarction (STEMI) are best evaluated by acute coronary angiography with the intent to revascularize. However, appropriateness use criteria guidelines recommend MPI in stabilized patients with STEMI who have not undergone angiography and in medically stabilized patients with an acute coronary syndrome and/or non-STEMI.[1] This recommendation is based on a number of studies where patients randomized to a conservative medial approach with selective testing for ischemia led to an outcome similar to those who had immediate angiography.[107]

If an imaging strategy is chosen, a sub-maximal exercise study is traditionally recommended prior to hospital discharge with a subsequent maximal study at 4-6 weeks.[65] However, evaluating seemingly stable patients for ischemia very early after admission may better identify those who are at high risk prior to a subsequent event. This was apparent in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) study where over half of the events occurred in the conservative strategy prior to the protocol-directed stress test.[117] Likewise, pooled data from the TIMI registry indicate that in patients who receive thrombolytic therapy, there is a 4.2% subsequent rate of reinfarction which occurs approximately 2-3 days following hospital admission and results in a significant increase in overall mortality.[118] With pharmacologic stress testing, imaging can be safely performed once a patient with acute myocardial infarction is stabilized.[107] This concept was explored in the INSPIRE trial where 728 stabilized patients with ST- and non-STEMI underwent adenosine SPECT a mean of 3 days after admission with over 50% imaged by day 2.[66] No patient developed clinical instability or had a serious side effect with adenosine infusion. Adenosine SPECT was shown to accurately risk stratify patients based on the quantified total stress-induced perfusion defect size and the extent myocardial ischemia. Importantly, a very low-risk group (annual event rate 1.8%) was identified who had small generally non-ischemic perfusion defects and represented one-third of all enrolled patients.

Based on the above considerations, patients selected for a non-invasive evaluation should be imaged as soon as they are stable so as to identify (1) low-risk patients who can be targeted for medical therapy and early hospital discharge and (2) high-risk individuals with ischemia who warrant intensive interventional and/or medical therapies. Pharmacologic stress testing with dipyridamole or adenosine when combined with a stress/rest or rest/stress Tc-99m imaging protocol is safe and provides an accurate early assessment for ischemia. Of note, the A2A agonists have not been evaluated as to their safety in patients with recent myocardial infarction.

The Patient Unable to Exercise

Exercise stress is the preferred modality in all patients referred for MPI. However, patients unable to achieve an adequate workload should undergo pharmacologic stress testing. This is also true for patients who have ventricular pacemakers[63] or LBBB.[62]

Pharmacologic stressors can be divided into the pharmacologic vasodilators that induce coronary hyperemia through activation of the adenosine A2A receptor (i.e., adenosine, dipyridamole, and regadenoson) and the beta agonist dobutamine. The choice of pharmacologic agent is based on physician preference and the presence of any contraindications for its administration to a given patient. In general, dobutamine is reserved for patients who have contraindications to both exercise and pharmacologic vasodilator stressors. Contraindications for administering adenosine, dipyridamole, and dobutamine are discussed elsewhere (see Part 3).

Dipyridamole is administered at a dose of 0.56 mg/kg over 4 minutes followed by radiotracer injection 3 minutes later. Aminophylline at a dose of 100-250 mg may be administered to counteract side effects but only after several minutes following radiotracer injection so as to allow clearance from the blood pool prior to reversing the hyperemic effect.

Adenosine is administered via an infusion pump at a standard dose of 140 μg/kg/min for 6 minutes with injection of the radiotracer at minute 3. Various abbreviated adenosine protocols have been published with the most popular one being a 4-minute infusion with radiotracer administration at minute 2.[76]

Dobutamine is administered via an infusion pump at 10, 20, 30, and up to 40 μg/kg/min at 3-minute intervals with injection of the radiotracer 1 minute into the maximally tolerated dose. Atropine at a dose of 1-2 mg may be given to patients who do not achieve 85% of their age-predicted maximal target heart rate. Studies suggest that a normal sub-maximal dobutamine SPECT does not infer the same low risk as in those who achieve a maximal stress effort.[119]

Regadenoson is administered as an intravenous bolus of 400 μg over 10 seconds followed by a 5-ml saline flush and then administration of the radiotracer. Clinical trials have demonstrated non-inferiority of regadenoson as compared to adenosine for the detection of ischemia.[71,120] Likewise, regadenoson induces similar total and ischemic LV perfusion defects as observed with adenosine as assessed by quantitative SPECT analysis.[121] Regadenoson has advantages over adenosine and dobutamine in that the 400 μg dose is the same for all patients regardless of body weight and there is no need for an infusion pump since it is administered as an intravenous bolus. The side effect profile of regadenoson is superior to that of the other coronary artery vasodilators and dobutamine. In the ADVANCE studies, patients better tolerated and preferred regadenoson over adenosine.[71,120] Data also indicate that the regadenoson is safe to administer in patients with clinically stable mild to moderate asthma[72] and/or moderate to severe clinically stable COPD[73,74] with no deterioration in serial pulmonary function test results or oxygen saturation as compared to placebo.

An informed decision can be made as to which stressor a physician may choose in an individual patient based on the above considerations.

The Patient with Heart Failure

The role of MPI in patients with new onset heart failure is to: (1) evaluate whether symptoms are due to underlying CAD; and (2) determine the extent of viable myocardium present so as to guide the appropriateness of coronary revascularization. Both SPECT and PET MPI can accurately diagnose and risk stratify patients with CAD based on the total stress-induced perfusion defect size, the extent of residual ischemia, and the global LVEF.

SPECT and PET techniques can also be used to determine myocardial viability. Identifying an optimal candidate for coronary revascularization is based not only on the presence but also on the extent of viable myocardium present. Myocardial viability by SPECT is traditionally defined by the presence of Tl-201 redistribution within abnormally perfused segments at rest. However, with SPECT it is also important to emphasize that the likelihood of viability increases proportional to relative myocardial count activity of the radiotracer whether evaluated by Tl-201- or Tc-99m-based radiopharmaceuticals. In this regard, the sensitivity and specificity for detecting myocardial viability will depend on what count threshold is used (>50% normal count activity is commonly utilized as a threshold). Thus, any imaging protocol should attempt to maximize count activity as close to reality as possible.

A commonly employed SPECT protocol is rest/redistribution imaging with Tl-201 (see Part 1). An alternative strategy is to perform pharmacologic stress testing with Tl-201 followed by redistribution imaging at ~4 hours so as to determine the extent of both viable and ischemic myocardium. This may better predict improvement in LV function post-revascularization than a rest/redistribution Tl-201 protocol alone since not all viable myocardium is ischemic.[122] If there is no evidence of redistribution at 4 hours, reinjection of 1 mCi Tl-201 can be performed after the administration of 1-2 sublingual 0.4 mg nitroglycerin tablets with imaging performed several minutes later. However, a 3-4-hour late redistribution image is necessary following reinjection if a redistribution image has not been previously acquired. Nitrates may further enhance detection of viable myocardium by increasing collateral blood flow to underperfused regions and thereby maximizing myocardial count activity (see Part 1). Although the radiation exposure for this procedure is approximately 25 mSv, these patients already have a very high clinical risk for death where identification of viable myocardium is paramount to their potential survival. Another alternative approach with SPECT is to perform a rest/stress or stress/rest Tc-99m imaging protocol. As with the Tl-201 protocol,[14] detection of viable myocardium can be improved with the administration of nitroglycerin prior to injection of the rest dose.[15,16,88,89]

Imaging with F-18 FDG PET is the most sensitive non-invasive nuclear technique for predicting improvement in LV function after coronary revascularization. Myocardial viability is defined by F-18 FDG PET as segments demonstrating a perfusion-metabolism mismatch, i.e., myocardial segments that retain metabolic activity despite diminished resting perfusion. A recent meta-analysis was performed from 24 studies in 3,088 patients where dobutamine echocardiography, SPECT, or PET were used to assess myocardial viability.[123] Patients

who had evidence of viable myocardium by any of these non-invasive techniques had a survival benefit when treated with coronary revascularization versus medical therapy. No survival benefit was shown following coronary revascularization in patients with non-viable myocardium. A meta-analysis of 10 studies with FDG PET showed almost identical findings.[124] In contrast, the Surgical Treatment for Ischemic Heart Failure (STICH) trial did not identify patients likely to benefit from coronary artery bypass surgery as compared to intensive medical therapy based on their viability status determined by either SPECT or dobutamine echocardiography.[125,126] However, the patients enrolled in STICH may not be representative of patients generally referred for viability assessment in that most had angina symptoms consistent with ischemia and the majority had only mild (New York Heart Association functional class I/II) heart failure symptoms. In addition, only 50% of enrolled patients underwent a viability assessment and randomization was based on a treatment strategy (medical therapy vs coronary revascularization) rather than one of the viability testings. Finally, most patients imaged (81%) had viable myocardium, thereby limiting detection of a testing advantage for guiding therapy.

Controversy also exists as to which imaging techniques are best at predicting outcome and thereby improving clinical decision-making. One study proposed that an LV perfusion-metabolism mismatch of >20% by PET best identified a high risk cohort for sudden death.[127] This was further confirmed in a meta-analysis showing a 4.9% survival advantage of revascularization over medical therapy for every 1% increase in viable myocardium by FDG-PET.[128] The optimal threshold for a survival benefit with revascularization was the presence of 25.8% viable myocardium. For SPECT, a similar 3.9% survival advantage for every 1% increase in viable myocardium was demonstrated with an optimal threshold of 38.7% viable myocardium. A substudy from The PET and Recovery Following Revascularization (PARR2) study further suggested that FDG PET-guided coronary revascularization may improve survival over standard of care which could include other imaging techniques for assessment of viability.[55] The sensitivity/specificity of PET for predicting improvement in regional LV function (92% and 63%) may be somewhat better than that observed with either Tl-201 (87% and 54%) or Tc-99m (83% and 65%) SPECT. However, there are no randomized clinical trials demonstrating superiority of PET over SPECT for guiding therapy and improving patient outcome. Indeed, all non-invasive techniques including dobutamine echocardiography and MRI have inherent limitations depending on the outcome variables being measured. Since SPECT has far greater availability than PET approaches, most patients undergoing a nuclear assessment for viability will currently undergo SPECT imaging (see Part 2).

The Patient With Pulmonary Disease

Current guidelines recommend that patients with a history of COPD or asthma who have wheezing on physical examination undergo dobutamine stress.[76] In patients without active wheezing, adenosine can be administered with close patient monitoring for bronchospasm and/or a decrease in oxygen saturation. Inhaled Albuterol is commonly administered prior to administration of adenosine.

The new selective adenosine A2A agonists may be administered to patients with reactive airway disease and wheezing. Initial clinical trials in mild to moderate asthmatics have demonstrated no deterioration in pulmonary function test parameters or oxygen saturation with binodenoson[129] or regadenoson[72] as compared to when patients received placebo. Many of these patients had wheezing or other abnormalities on pulmonary examination at the time of drug administration. Regadenoson has also been studied in patients with moderate to severe COPD with no deterioration in pulmonary function or evidence of oxygen desaturation as compared to placebo.[73] A recent randomized double blind placebo-controlled study in 999 patients with either asthma (n = 532) or COPD (n = 467) confirmed that regadenoson causes no deterioration in pulmonary function.[74] Regadenoson is the only adenosine A2A agonist currently FDA approved for use in the United States. Regadenoson, therefore, is an alternative stressor to dobutamine in such patients.

Patients with pulmonary hypertension can undergo pharmacologic vasodilator stress unless they have systemic hypotension (SBP <90 mm Hg).

The Patient with ECG Conduction Abnormalities

Pharmacologic stressor agents are recommended when performing MPI in patients with LBBB or ventricular paced rhythms (see Part 3). This is to minimize the potential for false-positive septal artifacts which can occur in 30%-90% of patients with treadmill exercise.[130,131] With LBBB there is asynchronous relaxation of the septum at rest and therefore delayed diastolic filling. However, this delay is enhanced with tachycardia resulting in septal blood flow differences during systole and diastole and reversible septal perfusion defects. The likelihood for septal perfusion defects increases with the heart rate. Similar findings occur in patients who have a

ventricular paced rhythm.[63] Therefore, vasodilator pharmacological stress testing is the preferred testing modality in such patients.[132] Dobutamine stress should be avoided since the diagnostic and prognostic accuracy of the test is predicated on the patient developing tachycardia and achieving their predicted target heart rate.[119]

Pharmacologic non-selective vasodilator agents are contraindicated in patients with second or third degree AV block or sick sinus syndrome without a pacemaker.[76] Transient atrio-ventricular conduction abnormalities occur in approximately 7.6% of patients receiving vasodilator agents but do not usually require termination of the infusion.[76] Patients with atrio-ventricular conduction abnormalities beyond first degree AV block should undergo exercise stress testing. In patients who cannot adequately exercise, dobutamine stress can be performed.

The Patient with Likely Attenuation

Potential attenuation artifacts should be anticipated in all patients at the time of arrival to the laboratory. Patient positioning, the choice of imaging protocol, the radiotracer dose and the need for attenuation correction should all be preemptive considerations to optimize imaging. Large patients (>200 pounds or BMI > 30) benefit from 2-day protocols to avoid potential poor image quality from the low dose portion of a 1-day protocol. In patients without a history of CAD, stress-only imaging may be considered. Higher energy Tc-99m-based radiopharmaceuticals should be used in these patients and particularly among women so as to improve image quality.[87] Weight-based additional dosing of Tc-99m at 0.31 mCi/kg in patients weighing >70 kg and/or increasing acquisition time should be performed to optimize count statistics. As an alternative to weight-based dosing, which increases patient radiation exposure, increased SPECT acquisition times may be used, as tolerated by the patient. PET imaging is particularly useful in large patients due to accurate attenuation correction and the use of high energy (511 keV) radiotracers.

Great care should be taken to position patients similarly, including arm position, for rest and stress scans particularly if they are on separate days. Note should be made in female patients if they have breast implants and whether images are acquired with the bra on or off. It is imperative that breast positioning be similar on the stress and the rest images. Partial myocardial coverage on the stress images and complete coverage on the rest images can result in what falsely appears to be myocardial ischemia.

As with all potential artifacts, diaphragmatic attenuation should be evaluated by reviewing the rotating raw image data immediately after the study is acquired. If significant diaphragmatic attenuation is present, prone imaging can be performed to optimize image quality. In patients with fixed perfusion defects on the stress and the rest images, gating can help differentiate scarred myocardium, with its associated regional wall motion abnormalities, from attenuation artifact where the wall motion is normal. Attenuation correction can be performed with either sealed radioactive line sources (gadolinium-153) or CT, as outlined in Part 1.

The Uncooperative Patient

Patients often are uncomfortable during image acquisition and efforts must be made to ensure patient comfort. Rotating raw images should be reviewed by the interpreting physician and/or technologist for motion in the horizontal and vertical planes. A static sinogram or linogram can also help evaluate for motion. Applying motion correction software can help correct for vertical motion of <2 pixels, but is less reliable when horizontal or rotational motion is present. Therefore, images should be immediately reviewed after the acquisition is complete and repeated when significant motion is observed.

New software programs and gamma cameras are now available which can markedly shorten image acquisition times and thereby improve image quality and patient comfort. Software algorithms using iterative reconstruction and resolution recovery can be incorporated within standard SPECT operating systems so as to shorten acquisition times without compromising image quality. Likewise, gamma cameras with enhanced crystal sensitivity can reduce study acquisition times to several minutes. These developments are particularly relevant to the uncooperative patient in whom imaging needs to be performed rapidly with immediate reimaging if the study quality is suboptimal (see Part 1).

The "Caffeinated" Patient Unable to Exercise

Vasodilator agents such as dipyridamole, adenosine and regadenoson induce hyperemia through activation of the adenosine A2A receptor. Xanthine-containing substances such as caffeine and theophylline compete for adenosine receptors and can potentially blunt the vasodilator response and thus cause false-negative tests. Therefore, it is recommended that patients not consume methylxanthines, such as aminophylline, caffeine, or theobromine, for at least 12 hours prior to the test.[76] Although recommended, there are no specific data to support this long a time delay (except for long-acting theophylline preparations) to successfully stress a patient with a pharmacologic vasodilator.

Xanthines compete for the adenosine receptor based on concentration. Thus, a high concentration of a pharmacologic vasodilator could displace a xanthine readily from the adenosine receptor. A recent study showed that the small amount of caffeine found in a single cup of coffee does not mask the presence or severity of adenosine-induced reversible defects.[75] Conversely, another study demonstrated a significant reduction in adenosine-induced perfusion defects 1 hour after drinking 200 mg of caffeine (2 cups of coffee) when using a standard infusion of 140 μg/kg/min but not if the infusion rate was increased to 210 μg/kg/min.[133] Of interest, a higher percentage of patients had a serum caffeine level >4.0 mg/L in this study (83%) than in the study by Zoghbi et al[134] (37%). All these data illustrate the relative impact of caffeine and adenosine concentrations on perfusion results. A recent small crossover study using O-15 water PET also demonstrated no effect of 200 mg caffeine versus placebo on regadenoson-induced coronary hyperemia.

Although adenosine and regadenoson may be considered in patients who consume a small cup of coffee, it must be emphasized that caffeine content can vary significantly across brands.[135,136] If the physician is unsure as to the amount of caffeine ingested by a patient and the stress testing cannot be delayed, then the patient should undergo pharmacologic stress with dobutamine, unless contraindicated.

The Patient Taking Anti-Anginal Agents

There is growing recognition that anti-anginal medications, when given alone or in combination, can alter the presence and the extent of stress-induced perfusion defects. This is true whether imaging is performed with SPECT or PET.[40]

Beta blockers decrease blood pressure, heart rate, and myocardial contractility and increase diastolic filling time. All these effects reduce myocardial oxygen demands and improve cardiac efficiency.[137] Following beta-blocker therapy, resting myocardial blood flow significantly decreases due to a decrease in oxygen demands with a significant increase in coronary flow reserve.[138] Beta blocker therapy is known to decrease exercise[139]- and dobutamine[77]-induced myocardial ischemia. The effect of beta blockade when using pharmacologic vasodilators is less clear. A reduction in the diagnostic sensitivity of dipyridamole SPECT and reduction in perfusion defect size has been reported following acute intravenous administration of metoprolol.[140] Conversely, no difference or a larger defect size was reported with dipyridamole SPECT following chronic treatment with atenolol.[141] One study demonstrated less of an effect of beta blockers on reducing defect size when patients with CAD underwent serial adenosine as compared to exercise stress.[142] Based on these results, it is recommended that patients taking beta blockers generally undergo pharmacologic stress rather than exercise if these agents cannot be withheld 24 hours prior to testing and if the patient's exercise effort is judged to be limited.

Calcium channel blockers decrease myocardial oxygen consumption by increasing myocardial blood flow and decreasing demand. The former is achieved by direct coronary artery vasodilation and the latter through peripheral arterial vasodilation, reduction in heart rate by specific agents, and enhanced myocardial diastolic relaxation. Chronic administration of nifedipine decreases exercise-induced SPECT ischemic perfusion defect size as assessed by serial imaging pre- and post-treatment.[143] Calcium channel blockers have not been specifically studied with pharmacologic stressor agents.

Nitrates decrease myocardial oxygen demand by significantly reducing preload and afterload. They also improve myocardial blood flow through direct coronary artery and coronary collateral vasodilatation. Randomized studies using serial exercise SPECT imaging have demonstrated significant reductions in total and ischemic perfusion defect size with transdermal nitroglycerin patches[144] and isosorbide mononitrate preparations.[145] Finally, combination of anti-ischemic medical therapy has been demonstrated to reduce both dipyridamole[146]- and adenosine-induced total and ischemic perfusion defect sizes.[41]

Quantitative SPECT analysis is a reproducible method for evaluating serial changes in stress-induced perfusion abnormalities following intensive medical therapy.[147] In the INSPIRE trial, stabilized patients post-infarction who had large total (>20%) and ischemic (>10%) adenosine-induced perfusion defects were randomized to either coronary revascularization or intensive medical therapy.[41] Medical therapy reduced ischemic LV perfusion defects to the same extent as revascularization (−15.0% vs −16.2%, $P = .44$) and in a similar percentage of patients (80% vs 81%, $P = .76$). Similar results were reported in the substudy to the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial.[42] In this latter study, 314 patients with chronic stable CAD underwent serial exercise or pharmacologic stress MPI pre and post either intensive medical therapy or coronary revascularization with intensive medical therapy. Both strategies significantly reduced stress-induced ischemic perfusion defect size but the effect was more pronounced in the revascularization limb (−2.7% vs −0.5%, $P < .001$) and in a greater percentage of

patients (78% vs 52%, $P = .007$). However, irrespective of the anti-ischemic therapy administered, the extent of residual ischemia post-therapy predicted outcome (100% event-free survival, no ischemia vs 60.7% event-free survival, >10% ischemia, $P = .09$). COURAGE confirms earlier reports that serial SPECT imaging may not only assess initial patient risk but also track subsequent risk based on the therapeutic benefits from either intensive medical or interventional therapies.[43,148]

Deciding on which stress protocol should be used in a given patient needs to be individualized. In patients without a prior history of CAD, where testing is being performed for diagnostic purposes, anti-ischemic medications should be withheld for a minimum of 24 hours. This is particularly true when contemplating exercise stress in patients that are taking beta blocker and/or nitrate preparations. If a patient cannot achieve their 85% predicted target heart rate during exercise, then the stress test should be terminated with subsequent administration of a pharmacologic vasodilator, such as dipyridamole, adenosine, or regadenoson. In patients with a prior history of CAD, medications should be continued so as to evaluate their therapeutic effects on perfusion and subsequent patient outcome. A symptom-limited exercise test is preferred except in patients who have non-cardiac physical limitations. In these patients pharmacologic stress testing is recommended. Although serial imaging appears to be a promising method for assessing the benefits of recently administered medical and/or interventional therapies, it cannot be routinely justified at this time until further information becomes available.

The Patient Pre-/Post-Transplant

Stress MPI can be used to identify CAD and risk stratify patients prior to liver and renal transplantation and following cardiac transplantation. The stressor used in conjunction with SPECT will generally depend on the patient's ability to exercise and any contraindications to pharmacologic stress testing. In patients post-cardiac transplantation, there has been concern with using adenosine due to enhanced hypersensitivity of the AV node and the risk of high degree block. A recent study in 102 patients post-cardiac transplantation demonstrated a higher incidence of second- and third-degree AV block with adenosine (15%) than in historical controls (5%, $P = .01$) but these effects were self-limiting and resulted in no untoward side effects or need for additional therapy.[149] Regadenoson has also been studied in patients with renal insufficiency,[150] those on dialysis[151] or with liver failure awaiting transplantation[152] and in patients post-cardiac transplantation.[153] Initial results from these small initial studies demonstrate no significant untoward side effects.

Patients referred for liver transplantation have a relatively low prevalence of CAD but significantly increased peri-operative mortality when it is present.[154] As in the general population of patients referred for SPECT, a normal test result predicts very low risk for cardiovascular events in the peri-operative period.[155] In a recent study by Aydinalp et al,[156] exercise SPECT showed high sensitivity (100%) but lower specificity (61%) for detecting severe CAD in patients being evaluated for liver transplantation. The lower specificity may have been in part due to inferior defects from ascites and concomitant diaphragmatic attenuation. This emphasizes the need to routinely review raw image SPECT data as part of the interpretation process so as to identify potential artifacts.

Patients undergoing renal transplantation often have multiple cardiovascular risk factors and therefore a high prevalence of CAD. Cardiac event rates are known to significantly increase as the eGFR falls below 60 mL/minute/m^2.[157] Patients who have an abnormal MPI prior to renal transplantation have a high cardiovascular mortality rate post-transplantation.[158] Several studies have demonstrated the interaction between eGFR and the presence of diabetes mellitus with SPECT results in predicting subsequent outcome.[159] Hakeem et al reported that patients with an eGFR <60 and perfusion defects by SPECT had a 10-fold higher event rate than those with normal SPECT and preserved renal function (9.5% vs 0.8%, respectively). Furthermore, the presence and the size of a perfusion defect by MPI better discriminates risk than the anatomic extent of CAD.[160-162]

Patients who undergo cardiac transplantation are at risk for allograft vasculopathy as defined by coronary angiography. SPECT MPI may identify transplant vasculopathy and also predict subsequent patient outcome. Several investigators have found that SPECT MPI provides incremental prognostic information for predicting cardiac death in heart transplant patients over clinical and angiographic findings.[163-165] Manrique et al[164] recently reported that a normal gated SPECT study is associated with a very low risk of cardiac death or retransplantation hard events.

At this juncture, recommendations for pre-organ transplantation evaluation follow those for MPI prior to other non-cardiac surgical procedures.[166] Routine evaluation of patients prior to liver transplantation is not recommended since the vast majority of patients will have normal studies. Most patients prior to renal transplantation will already fit into a higher risk category based on their clinical profile and warrant preoperative evaluation. Patients post-heart transplantation can undergo

assessment with treadmill exercise, dobutamine, or reg-adenoson stress from both a diagnostic and safety perspective.

The Patient with High Liver/Gut Activity

The quality and interpretability of SPECT studies may be affected by tracer uptake in the liver and/or gut which is common with Tc-99m radiopharmaceuticals. High sub-diaphragmatic count activity can affect image interpretation in three ways by: (1) creating a ramp filter artifact and thereby reducing apparent myocardial count activity in adjacent walls; (2) scattering photons into adjacent walls, or (3) obscuring walls with overlying liver and/or gut. In addition, by artificially increasing counts in one segment, other segments may appear relatively hypoperfused leading to erroneous perfusion defects. This is dramatically illustrated by the scan of a woman where a hot loop of bowel overlays the inferior wall and the breast overlays the anterior wall leading to the false impression of a moderate to severe stress-induced anterior perfusion defect. This scenario is further worsened if the relative counts differ on the stress and rest portions of the study due to varying degrees of bowel and breast overlap. Therefore, it is imperative that the rotating raw images always be reviewed to alert the reader to potential artifacts.

In order to avoid liver and gut interference, the technologist must be cognizant of imaging times and attempt imaging during the ''optimal window'' when both liver and gut activity are minimal. In addition, tracer activity in the liver and gut can be reduced by exercise which shunts blood from the liver to the periphery. In patients undergoing vasodilator stress, the addition of low level exercise can reduce tracer activity in the liver and improve image quality.[167,168] If hepatic activity continues, a light fatty meal (i.e., milk, candy bar) can enhance clearance of activity from the liver or the patient can simply be reimaged 30-60 minutes later prior to enhancement of gut activity. Additionally, if the tracer is localized to the stomach cavity or small bowel the patient can be given water to drink to promote gastric emptying and bowel motility and thus reducing photon scatter from overlying bowel. In the case of adjacent (but not overlying) gut activity that will not clear, image processing can be performed using iterative reconstruction rather than the ramp filter as part of filtered back projection. Alternatively, if the patient is relatively thin, imaging can be repeated with Tl-201 which is not excreted by the liver.

SUMMARY

A patient-centered imaging approach will improve the diagnostic and prognostic performance of MPI. The one-test-fits-all approach to imaging is no longer acceptable in an era where safety concerns and quality assurance are of paramount importance to the future of nuclear cardiology. This document provides a necessary framework for imaging physicians to better tailor nuclear cardiac procedures to the individual patient.

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Disclosures

The table represents the relationships of writing group members with industry and other entities that were reported by authors to be relevant to this document. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

Participant	Consultant/ Advisory Board	Speaker/ Honoraria	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
E. Gordon DePuey, MD Co-Chair)	Forest Laboratories UltraSpect Ltd.	Cardinal Health Digirad	None	Astellas Digirad Inc. Lantheus Michael J. Fox Foundation UltraSpect Ltd.	None	None
John J. Mahmarian, MD (Co-Chair)	Astellas GE Healthcare Gilead	Astellas	None	Astellas Gilead	None	None
Todd D. Miller, MD (Co-Chair)	Astellas Lantheus Medical Imaging	None	None	Forest Laboratories	None	None
Andrew J. Einstein, MD, PhD	None	Spectrum Dynamics	None	GE Healthcare Spectrum Dynamics	None	None
Christopher L. Hansen, MD	Digirad	None	None	Digirad	GE Healthcare	None
Thomas A. Holly, MD	None	None	None	None	None	None
Edward J. Miller, MD, PhD	None	None	None	None	None	None
Donna M. Polk, MD, MPH	None	None	None	None	None	None
L. Samuel Wann, MD, PhD	None	None	None	None	None	None

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