ASNC IMAGING GUIDELINES FOR NUCLEAR CARDIOLOGY PROCEDURES

Stress protocols and tracers

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EXERCISE STRESS TEST

Exercise is the preferred stress modality in patients who are able to exercise to an adequate workload (at least 85% of age-adjusted maximal predicted heart rate and five metabolic equivalents).

Exercise Modalities

1. Treadmill exercise is the most widely used stress modality. Several treadmill exercise protocols are described which differ in the speed and grade of treadmill inclination and may be more appropriate for specific patient populations. The Bruce and modified Bruce protocosls are the most widely used exercise protocols.
2. Upright bicycle exercise is commonly used in Europe. This is preferable if dynamic first-pass imaging is planned during exercise. Supine or semi-supine exercise is relatively suboptimal and should only be used while performing exercise radionuclide angiocardiography.

Indications

Indications for an exercise stress test are:

1. Detection of obstructive coronary artery disease (CAD) in the following:
   (a) Patients with an intermediate pretest probability of CAD based on age, gender, and symptoms.
   (b) Patients with high-risk factors for CAD (e.g., diabetes mellitus, peripheral, or cerebral vascular disease).
2. Risk stratification of post-myocardial infarction patients before discharge (submaximal test at 4-6 days), and early (symptom-limited at 14-21 days) or late (symptom-limited at 3-6 weeks) after discharge.
3. Risk stratification of patients with chronic stable CAD into a low-risk category that can be managed medically or into a high-risk category that should be considered for coronary revascularization.
4. Risk stratification of low-risk acute coronary syndrome patients (without active ischemia and/or heart failure 6-12 hours after presentation) and of intermediate-risk acute coronary syndrome patients 1-3 days after presentation (without active ischemia and/or heart failure symptoms).
5. Risk stratification before noncardiac surgery in patients with known CAD or those with high-risk factors for CAD.
6. To evaluate the efficacy of therapeutic interventions (anti-ischemic drug therapy or coronary revascularization) and in tracking subsequent risk based on serial changes in myocardial perfusion in patients with known CAD.

Absolute Contraindications

Absolute contraindications for exercise stress testing include:

1. High-risk unstable angina. However, patients with chest pain syndromes at presentation, who are otherwise stable and pain-free, can undergo exercise stress testing.
2. Decompensated or inadequately controlled congestive heart failure.
3. Uncontrolled hypertension (blood pressure >200/110 mm Hg).
4. Uncontrolled cardiac arrhythmias (causing symptoms or hemodynamic compromise).

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Approved by the American Society of Nuclear Cardiology Board of Directors on June 24, 2008. Last updated on January 16, 2009.

Unless reaffirmed, retired or amended by express action of the Board of Directors of the American Society of Nuclear Cardiology, this guideline shall expire as of March 2014.

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J Nucl Cardiol
1071-3581/$34.00

doi:10.1007/s12350-009-9062-4

5. Severe symptomatic aortic stenosis.
6. Acute pulmonary embolism.
7. Acute myocarditis or pericarditis.
8. Acute aortic dissection.
9. Severe pulmonary hypertension.
10. Acute myocardial infarction (<4 days).
11. Acutely ill for any reason.

Relative Contraindications

Relative contraindications for exercise stress testing include:

1. Known left main coronary artery stenosis.
2. Moderate aortic stenosis.
3. Hypertrophic obstructive cardiomyopathy or other forms of outflow tract obstruction.
4. Significant tachyarrhythmias or bradyarrhythmias.
5. High-degree atrioventricular (AV) block.
6. Electrolyte abnormalities.
7. Mental or physical impairment leading to inability to exercise adequately.
8. If combined with imaging, patients with complete left bundle branch block (LBBB), permanent pacemakers, and ventricular pre-excitation (Wolff-Parkinson-White syndrome) should preferentially undergo pharmacologic vasodilator stress test (not dobutamine stress test).

Limitations

Exercise stress testing has a lower diagnostic value in patients who cannot achieve an adequate heart rate and blood pressure response due to a noncardiac physical limitation such as pulmonary, peripheral vascular, or musculoskeletal abnormalities or due to lack of motivation. These patients should be considered for pharmacologic stress with myocardial perfusion imaging.

Procedure

1. Patient preparation: Nothing to eat 2 hours before the test. Patients scheduled for later in the morning may have a very light (cereal, fruit) breakfast.
2. A large-bore (18- to 20-gauge) intravenous (IV) cannula should be inserted for radiopharmaceutical injection during exercise.
3. The electrocardiogram should be monitored continuously during the exercise test and for at least 5 minutes into the recovery phase or until the resting heart rate is <100 beats/minute and/or dynamic exercise-induced ST-segment changes have resolved. A 12-lead electrocardiogram should be obtained at every stage of exercise, at peak exercise, and at the termination or recovery phase.
4. The heart rate and blood pressure should be recorded at least every 3 minutes during exercise, at peak exercise, and for at least 5 minutes into the recovery phase.
5. **All exercise tests should be symptom-limited. Achievement of 85% of maximum, age-adjusted, predicted heart rate is not an indication for termination of the test.**
6. The radiopharmaceutical should be injected as close to peak exercise as possible. Patients should be encouraged to exercise for at least 1 minute after the radiotracer injection.
7. In patients who cannot exercise adequately and are being referred for a diagnostic stress test the patients may be considered for conversion to a pharmacologic stress test.
8. Blood pressure medication(s) with antianginal properties (β-blocker, calcium channel blocker, and nitrates) will lower the diagnostic accuracy of a stress test. Generally, discontinuation of these medicines may be left to the discretion of the referring physician.

Indications for Early Termination of Exercise

Indications for early termination of exercise include:

1. Moderate-to-severe angina pectoris.
2. Marked dyspnea or fatigue.
3. Ataxia, dizziness, or near-syncope.
4. Signs of poor perfusion (cyanosis and pallor).
5. Patient's request to terminate the test.
6. Excessive ST-segment depression (>2 mm).
7. ST elevation (>1 mm) in leads without diagnostic Q waves (except for leads V_1 or aVR).
8. Sustained supraventricular or ventricular tachycardia.
9. Development of LBBB or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia.
10. Drop in systolic blood pressure of >10 mm Hg from baseline, despite an increase in workload, when accompanied by other evidence of ischemia.
11. Hypertensive response (systolic blood pressure >250 mm Hg and/or diastolic pressure >115 mm Hg).
12. Technical difficulties in monitoring the electrocardiogram or systolic blood pressure.

PHARMACOLOGIC VASODILATOR STRESS

There are currently three vasodilator agents available: dipyridamole, adenosine and, most recently approved, regadenoson. They all work by producing stimulation of A2A receptors. Methylxanthines (caffeine, theophylline, and theobromine) are competitive inhibitors of this effect which requires withholding methylxanthines prior to testing and permits the reversal of the effect with theophylline when clinically indicated.

Note: Some of the pharmacologic stress protocols described in this section fall outside of manufacturer package insert guidelines but have been documented in the literature and are now used commonly in the clinical practice of nuclear cardiology. The practitioner should be familiar with the package insert for each medication.

Adenosine

Mechanism of Action. Adenosine induces direct coronary arteriolar vasodilation through specific activation of the A2A receptor. This results in a 3.5- to 4-fold increase in myocardial blood flow. Myocardial regions supplied by stenotic coronary arteries have an attenuated hyperemic response. Depending upon the severity of coronary stenosis and coronary flow reserve limitation, a relative flow heterogeneity is induced. Adenosine generally does not cause myocardial ischemia since myocardial blood flow increases to a variable degree in all coronary artery vascular beds with minimal or no increase in rate-pressure product (i.e., myocardial oxygen demand). However, in a small percentage of patients with severe CAD, true ischemia may also be induced because of a coronary steal phenomenon. Since the myocardial tracer uptake is proportional to the regional myocardial blood flow, a heterogeneous distribution of radiotracer occurs in the myocardium. Activation of A1, A2b, and A3 receptors may cause undesirable side effects of adenosine infusion: AV block (A1 receptor), peripheral vasodilation (A2b receptor), and bronchospasm (A2b and A3 receptors).

Adenosine Dose. Adenosine should be given as a continuous infusion at a rate of 140 mcg/kg/min over a 6-minute period. A shorter-duration adenosine infusion, lasting 4 minutes, has been found to be equally effective for the detection of CAD compared to the standard 6-minute infusion. For shorter duration protocols, the minimum time to tracer injection should be 2 minutes and the infusion should continue for at least 2 minutes after tracer injection.

Side Effects of Adenosine.

1. Minor side effects are common and occur in approximately 80% of patients. The common side effects are flushing (35-40%), chest pain (25-30%), dyspnea (20%), dizziness (7%), nausea (5%), and symptomatic hypotension (5%). Chest pain is nonspecific and is not necessarily indicative of the presence of CAD.
2. AV block occurs in approximately 7.6% of cases. However, the incidence of second-degree AV block is only 4%, and that of complete heart block is less than 1%. Most cases (>95%) of AV block do not require termination of the infusion.
3. ST-segment depression of 1 mm or greater occurs in 5-7% of cases. However, unlike chest pain, this is usually indicative of significant CAD.
4. Fatal or nonfatal myocardial infarction is extremely rare.
5. Due to an exceedingly short half-life of adenosine (<10 seconds), most side effects resolve in a few seconds after discontinuation of the adenosine infusion, and aminophylline infusion is only very rarely required.

Hemodynamic Effects. Adenosine results in a modest increase in heart rate and a modest decrease in both systolic and diastolic blood pressures.

Indications. The indications for adenosine stress perfusion imaging are the same as for exercise myocardial perfusion imaging and in the presence of the following conditions:

1. Inability to perform adequate exercise due to noncardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Of note, as with exercise testing, anti-ischemic cardiac medications (including β-blockers, nitrates, and calcium antagonists) have been reported to decrease the diagnostic accuracy of vasodilator stress testing.
2. Baseline electrocardiographic (ECG) abnormalities: LBBB, ventricular pre-excitation (Wolff-Parkinson-White syndrome), and permanent ventricular pacing. Falsely positive imaging results are much less frequent with adenosine (approximately 10%) as compared to stress imaging with exercise (approximately 50%).
3. Risk stratification of clinically stable patients into low- and high-risk groups very early after acute myocardial infarction (≥1 day) or following presentation to the emergency department with a presumptive acute coronary syndrome.

Contraindications. Contraindications for adenosine stress testing include:

1. Asthmatic patients with ongoing wheezing should not undergo adenosine stress testing. However, it has

been reported that patients with adequately controlled asthma can undergo an adenosine stress test and can have pre-treatment with two puffs of albuterol or a comparable inhaler. Bronchospasm is listed as an absolute contraindication in the package insert.
2. Second- or third-degree AV block without a pacemaker or sick sinus syndrome.
3. Systolic blood pressure **<90** mm Hg.
4. Recent use of dipyridamole, dipyridamole-containing medications (e.g., Aggrenox).
5. Methyl xanthines such as aminophylline caffeine or theobromine block the effect of adenosine and should be held for at least 12 hours prior to the test. Pentoxifylline (Trental) does not appear to block the effects of adenosine.
6. Known hypersensitivity to adenosine.
7. Unstable acute myocardial infarction or acute coronary syndrome.

Relative Contraindications. Relative contraindications for adenosine stress testing include:

1. Profound sinus bradycardia (heart rates <40/min).

Procedure.

1. Patient preparation: Nothing to eat for at least 2 hours; no caffeine-containing beverages or medications for at least 12 hours prior to testing.
2. An infusion pump is required for adenosine to be administered at a constant infusion rate.
3. An IV line with a dual-port Y-connector is required for the injection of the radiotracer during adenosine infusion.
4. ECG monitoring should be carried out as with exercise stress testing. A 12-lead electrocardiogram will be recorded every minute during the infusion.
5. Blood pressure should be monitored every minute during infusion and 3-5 minutes into recovery or until stable. Adenosine infusion should be given at a rate of 140 mcg/kg/min for 3 minutes followed by the injection of the radiotracer. The infusion should be continued for another 3 minutes. For patients deemed to be at a higher risk for complications (borderline hypotension, controlled asthma), adenosine infusion may be started at a lower dose (70-100 mcg/kg/min). If this dose is tolerated well for 1 minute, the infusion rate should be increased to 140 mcg/kg/min and should be continued for 4 minutes. The radiotracer should be injected 1 minute after starting the 140 mcg/kg/min dose.

Combination of Low-Level Exercise with Adenosine Infusion. The combination of low-level upright treadmill exercise (1.7 mph, 0% grade) during the adenosine infusion has been found to be safe. This results in a significant reduction in the side effects of adenosine (flushing, dizziness, nausea, and headache) and attenuates the adenosine-induced drop in blood pressure. Image quality is improved by decreasing high hepatic and gut radiotracer uptake, which is common with pharmacologic stress perfusion imaging. Therefore low-level exercise may be performed in combination with pharmacologic stress. However, since it is desirable not to increase the heart rate of patients with LBBB undergoing pharmacologic stress, low-level exercise supplementation is not recommended in patients with LBBB.

Indications for Early Termination of Adenosine Infusion. The adenosine infusion should be stopped early under any of the following circumstances:

1. Severe hypotension (systolic blood pressure <80 mm Hg).
2. Development of symptomatic, persistent second-degree or complete heart block.
3. Wheezing.
4. Severe chest pain associated with ST depression of 2 mm or greater.
5. Signs of poor perfusion (pallor, cyanosis, and cold skin).
6. Technical problems with the monitoring equipment.
7. Patient's request to stop.

Regadenoson

Mechanism of Action. Regadenoson is an A2A adenosine receptor agonist that is a coronary vasodilator. Regadenoson is a low affinity agonist (Ki $\approx$ 1.3 μM) for the A2A adenosine receptor, with at least 10-fold lower affinity for the A1 adenosine receptor (Ki $>$ 16.5 μM), and weak, if any, affinity for the A2B and A3 adenosine receptors. Activation of the A2A adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow (CBF), the same way adenosine and dypyridamole produce coronary vasodilation. The maximal plasma concentration of regadenoson is achieved within 1-4 minutes after injection and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2-4 minutes. An intermediate phase follows, with a half-life on average of 30 minutes coinciding with loss of the pharmacodynamic effect. The last phase consists of a decline in plasma concentration with a half-life of approximately 2 hours.

Regadenoson Dose. The recommended intravenous dose of regadenoson is 5 mL (0.4 mg regadenoson) and should be given as a rapid (approximately 10 seconds) injection into a peripheral vein using

a 22 gauge or larger catheter or needle. Administer a 5-mL saline flush immediately after the injection of regadenoson. Administer the radionuclide myocardial perfusion imaging agent 10-20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as regadenoson.

Side Effects of Regadenoson.

1. The most common reactions to administration of regadenoson during MPI are shortness of breath, headache, and flushing.
2. Less common reactions are chest discomfort, angina pectoris or ST, dizziness, chest pain, nausea, abdominal discomfort, dysgeusia, and feeling hot.
3. In patients with a prior adenosine stress study, rhythm or conduction abnormalities were seen in 26% with regadenoson (30% for Adenosine). First degree AV block was detected in 3% with regadenoson (7% with adenosine), second degree AV block in 0.1% (1% with adenosine).
4. Most adverse reactions begin soon after dosing and generally resolve within approximately 15 minutes, except for headache which resolves in most patients within 30 minutes.
5. Aminophylline may be administered in doses ranging from 50 to 250 mg by slow intravenous injection (50-100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to regadenoson.

Hemodynamic Effects. In clinical studies, the majority of patients had an increase in heart rate and a decrease in blood pressure within 45 minutes after administration of regadenoson. Maximum hemodynamic changes after regadenoson or adesosine were as follows: increase in heart rate of more than 40 bpm in 5% (3% for adenosine), decrease in systolic blood pressure of more than 35 mm Hg in 7% (8% for adenosine), and decrease in diastolic blood pressure of more than 25 mm Hg in 4% (5% with adenosine).

Indications. Regadenoson injection is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress, more specifically in the presence of the following conditions:

1. Inability to perform adequate exercise due to noncardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Of note, as with exercise testing, anti-ischemic cardiac medications (including β-blockers, nitrates, and calcium antagonists) should be discontinued for at least 48 hours prior to performing a diagnostic imaging test.

Contraindications. Contraindications for regadenoson stress testing include:

1. Patients with second or third degree AV block or sinus node dysfunction unless these patients have a functioning artificial pacemaker.
2. Patients with bronchospasm. The safety profile of Regadenoson has not yet been definitively established in patients with bronchospasm. Two pilot studies reported on the use of regadenoson in patients with bronchoconstrictive disease. The incidence of bronchoconstriction (FEV1 reduction >15% from baseline) was assessed in a randomized, controlled study of 49 outpatients with stable, moderate to severe COPD. A bronchoconstriction rate of 12% and 6%, for Regadenoson and placebo groups, respectively, was observed. In a randomized, controlled study of 48 patients with stable mild-to-moderate asthma who had previously been shown to have bronchoconstrictive reactions to adenosine monophosphate, the rate of bronchoconstriction was the same (4%) for both the Regadenoson and placebo groups. In both studies, dyspnea was reported as an adverse reaction in the Regadenoson group (61% for patients with COPD; 34% for patients with asthma) while no subjects in the placebo group experienced dyspnea. As these small sample size studies were pilot in nature, inadequate data exists to confidently use regadenoson in patients with these conditions.
3. Systolic blood pressure <90 mm Hg. Adenosine receptor agonists including regadenoson induce arterial vasodilation and hypotension. Decreased systolic blood pressure (>35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (>25 mm Hg) was observed in 4% of patients within 45 minutes of regadenoson administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.
4. Use of dipyridamole, dipyridamole-containing medications in last 48 hours, aminophylline in last 24 hours or ingestion of caffeinated foods (e.g., chocolate) or beverages (e.g., coffee, tea, and sodas) within the last 12 hours should be avoided.
5. Known hypersensitivity to regadenoson.

Relative Contraindications. Relative Contraindications for regadenoson stress testing include:

1. Profound sinus bradycardia (heart rate <40/minute).

Procedure.

1. Patient preparation: avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products, and theophylline for at least 12 hours prior to the testing. Dipyridamole should be withheld for at least 2 days prior to regadenoson administration.
2. ECG monitoring should be carried out as with exercise stress testing. A 12-lead electrocardiogram will be recorded every minute during the infusion.
3. Blood pressure should be monitored every minute during infusion and 3-5 minutes into recovery.
4. Regadenoson (5 mL, containing 0.4 mg of regadenoson) should be given as a rapid (approximately 10 seconds) injection into a peripheral vein using a 22 gauge or larger catheter or needle. Administer a 5-mL saline flush immediately after the injection of regadenoson. Administer the radionuclide myocardial perfusion imaging agent 10-20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as regadenoson.

Indications for Reversal of Regadenoson Infusion. Indications for reversal of regadenoson include:

1. Severe hypotension (systolic blood pressure <80 mm Hg).
2. Development of symptomatic, persistent second-degree or complete heart block.
3. Wheezing.
4. Severe chest pain associated with ST depression of 2 mm or greater.
5. Signs of poor perfusion (pallor, cyanosis, and cold skin).
6. Technical problems with the monitoring equipment.
7. Patient's request to stop.

Dipyridamole

Mechanism of Action. Dipyridamole is an indirect coronary artery vasodilator that increases the tissue levels of adenosine by preventing the intracellular reuptake and deamination of adenosine. Dipyridamole-induced hyperemia lasts for more than 15 minutes.

Dipyridamole Dose. Dipyridamole is administered at 0.56 mg/kg intravenously over a 4-minute period (142 mcg/kg/min).

Side Effects. Over 50% of patients develop side effects (flushing, chest pain, headache, dizziness, or hypotension). The frequency of these side effects is less than that seen with adenosine, but they may last for a longer period of time (15-25 minutes) and may vary significantly in individual patients. Aminophylline (125-250 mg intravenously) is often required to reverse these side effects. The incidence of AV block with dipyridamole is less than that observed with adenosine (2%). Aminophylline should also be used in the presence of ischemic ECG changes after dipyridamole.

Hemodynamic Effects. Dipyridamole results in similar hemodynamic changes as seen with adenosine with a modest increase in heart rate and a modest decrease in both systolic and diastolic blood pressures.

Indications. The indications for dipyridamole stress perfusion imaging are the same as for adenosine myocardial perfusion imaging.

Contraindications. The contraindications for dipyridamole stress testing are the same as with adenosine. In patients taking oral dipyridamole, IV dipyridamole may be administered safely and efficaciously.

Procedure.

1. Patient preparation: Nothing to eat for at least 2 hours and no caffeine-containing beverages or medication at least 12 hours prior to testing.
2. The drug is infused intravenously over 4 minutes. Although an infusion pump is preferable, dipyridamole can also be administered by hand injection or drip. The radiotracer is injected 3-5 minutes after the completion of dipyridamole infusion. The half-life of dipyridamole is approximately 30-45 minutes.

Combination of Low-Level Exercise with Dipyridamole Infusion. Patients who are ambulatory may undergo low-level treadmill exercise (1.7 mph, 0% grade) for 4-6 minutes soon after the completion of dipyridamole infusion. Radiotracer is injected during this low-level exercise, and the exercise continues for two additional minutes to allow for tracer uptake in the myocardium. This significantly reduces the side effects and improves image quality. Low-level exercise supplementation is not recommended for patients with LBBB.

Dobutamine

Mechanism of Action. Dobutamine infusion results in direct β_1 and β_2 stimulation with a dose-related increase in heart rate, blood pressure, and myocardial contractility. Dobutamine increases regional myocardial blood flow based on physiologic principles of coronary flow reserve. A similar dose-related increase in subepicardial and subendocardial blood flow occurs within vascular beds supplied by normal coronary arteries. However, blood flow increases minimally within

vascular beds supplied by significantly stenosed arteries, with most of the increase occurring within the subepicardium rather than the subendocardium. However, at a dose of 20 mcg/kg/min, dobutamine-induced coronary flow heterogeneity is similar to exercise but less than that induced by adenosine or dipyridamole.

Dobutamine Dose. Dobutamine is infused incrementally starting at a dose of 5-10 mcg/kg/min, which is increased at 3-minute intervals to 20, 30, and 40 mcg/kg/min. The half-life of dobutamine is approximately 2 minutes. As with exercise stress, achieving >85% of the predicted heart rate is desirable.

Side Effects. Side effects occur in about 75% of patients. The common side effects are palpitation (29%), chest pain (31%), headache (14%), flushing (14%), dyspnea (14%), and significant supraventricular or ventricular arrhythmias (8-10%). Ischemic ST-segment depression occurs in approximately one-third of patients undergoing dobutamine infusion. Severe side effects may require IV administration of a short-acting β-blocker (esmolol, 0.5 mg/kg over 1 minute).

Indications. Indications for dobutamine stress testing include:

1. Dobutamine is a secondary pharmacologic stressor that is recommended only in patients who cannot undergo exercise stress and who also have contraindications to pharmacologic vasodilator stressors (mainly bronchospastic airway disease).
2. Dobutamine perfusion imaging has not been studied as extensively as adenosine or dipyridamole perfusion imaging in the evaluation and prognostication of patients with CAD.

Contraindications. Contraindications for dobutamine stress testing include:

1. Recent (<1 week) myocardial infarction.
2. Unstable angina.
3. Hemodynamically significant left ventricular outflow tract obstruction.
4. Severe aortic stenosis.
5. Atrial tachyarrhythmias with uncontrolled ventricular response.
6. Prior history of ventricular tachycardia.
7. Uncontrolled hypertension (blood pressure >200/110 mm Hg).
8. Patients with aortic dissection or large aortic aneurysm.
9. Patients who are on β-blockers where the heart rate and inotropic responses to dobutamine will be attenuated.

Procedure.

1. Patient preparation: Nothing to eat for at least 2 hours.
2. An infusion pump is necessary for dobutamine administration.
3. An IV line with a dual-port Y-connector is required for injecting radioisotope during dobutamine infusion.
4. ECG monitoring and blood pressure monitoring should be performed as with other pharmacologic stressors.
5. Dobutamine infusion should start at a dose of 5-10 mcg/kg/min. The dobutamine dose should then be increased at 3-minute intervals up to a maximum of 40 mcg/kg/min. The radiotracer should be injected at 1 minute into the highest dobutamine dose, and dobutamine infusion should be continued for 2 minutes after the radiotracer injection.
6. Some investigators recommend the addition of atropine (divided doses of 0.25-0.5 mg up to 1-2 mg) in patients who do not achieve target heart rate with dobutamine alone.

Indications for Early Termination of Dobutamine. The indications for early termination of dobutamine are similar to those for exercise stress. Termination for ventricular tachycardia or ST-segment depression is more likely with dobutamine than with other stressors.

RADIOTRACERS AND PROTOCOLS

Currently utilized myocardial perfusion tracers for myocardial perfusion imaging include thallium 201 and two technetium 99m agents (Tc-99m sestamibi and Tc-99m tetrofosmin). Information related to PET perfusion radiotracers are described in the PET Imaging Guidelines. Characteristics for each tracer, injected doses (Table 1), typical protocol, and dosimetry are presented.

Note: The suggested radiopharmaceutical doses in this section are for current camera and processing protocols as defined in the SPECT Imaging Guidelines. Some of the radiopharmaceutical doses described in this section fall outside of the manufacturer package insert guidelines but are now commonly used in the clinical practice of nuclear cardiology.

Note: The radiation dosimetry values are point estimates of doses to a typical patient. Doses were determined using average administered activities, most recent International Commission on Radiological Protection (ICRP) dose coefficients, and ICRP Publication 103 tissue weighing factors. TC-99m doses represent an average for sestamibi and tetrofosmin.

Gated imaging is recommended where feasible. Results of gating are most reliable with higher doses of technetium-based perfusion tracers but satisfactory results have been reported with lower dose technetium as well as thallium-201.

Table 1. Suggested radiopharmaceutical doses for myocardial perfusion imaging protocols

Tl-201 Protocol	Stress (mCi)	Rest (mCi)	Reinjection (mCi)
Stress/Rest	2.5-4.0	-	-
Stress/Rest/Reinjection	2.5-4.0	-	1.0-2.0
Viability Only	-	3.0-4.0	-
Tc-99m Protocol	**Stress (mCi)**		**Rest (mCi)**
Two day	24-36		24-36
One day, Stress/Rest	8-12		24-36
One day, Rest/Stress	24-36		8-12
Dual isotope	24-36		2.5-4.0

Tl-201

Mechanism of Action. Tl-201 is an analog of potassium (monovalent cation), with a physical half-life of 73.1 hours, decay by electron capture to Hg-201 with principal emission of 68-80 keV x-rays, high first-pass extraction (85%), active membrane transport into the myocyte, rapid clearance from the intravascular space, and monoexponential washout (redistribution) which starts 10-15 minutes after injection. Washout depends on initial tracer concentration in the myocyte and on myocardial blood flow. Clearance occurs via the kidneys. The whole body effective dose for Tl-201 is approximately 6.3 mSv per mCi of Tl-201 injected.

Imaging Protocols. A single dose of 2.5-4.0 mCi of Tl-201 is injected prior to peak exercise stress or at peak pharmacologic vasodilatation, and SPECT imaging starts 10-15 minutes later. Redistribution (rest) imaging is done 2.5-4.0 hours later. In cases where standard stress-redistribution imaging shows a fixed or minimally reversible perfusion abnormality, myocardial viability can be assessed with a rest image at 18-24 hours or following reinjection of an additional 1-2 mCi dose of Tl-201. An alternative method for viability assessment is injection of 3-4 mCi of Tl-201 at rest followed by 3- to 4-hour redistribution imaging. Protocol options and timing for assessment of perfusion and viability are shown in Figure 1.

Tc-99m-Labeled Tracers

Mechanism of Action. Tc-99m sestamibi and Tc-99m tetrofosmin have very similar characteristics: lipid-soluble, cationic, physical half-life of 6 hours, produces 140-keV photons, first-pass extraction less than Tl-201, uptake and mitochondrial retention dependent on blood flow and transmembrane energy potentials. Their myocardial washout (redistribution) is clinically negligible. These agents are excreted via the hepatobiliary system and excreted into the gastrointestinal tract. Lacking significant redistribution, Tc-99m-labeled tracers require two separate injections at stress and rest. The two agents have sufficiently similar characteristics that the recommended protocols use similar camera setup and acquisition times and vary only in the optimal time for image acquisition following rest, exercise, and pharmacologic stress. Optimal validation

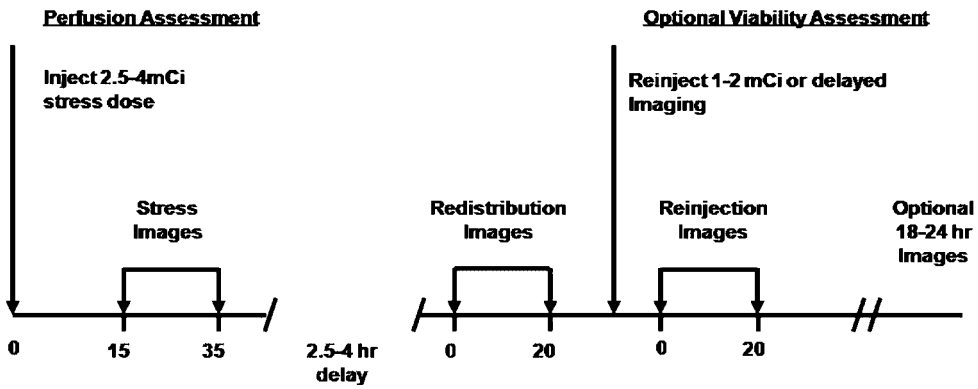

Figure 1. Stress/redistribution/reinjection/18- to 24-hour Tl-201 imaging protocol.

of imaging times has not been extensively studied, and factors such as camera availability and the presence of liver and gastrointestinal activity influence the optimal imaging times. In the figures, a range of imaging times is suggested. The whole body effective dose for Tc-99m is approximately 0.3 mSv per mCi of Tc-99m injected.

Imaging Protocols. *Tracer-Specific Imaging Times* For Tc-99m sestamibi, minimum delays of 15-20 minutes for exercise, 45-60 minutes for rest, and 60 minutes for pharmacologic stress are recommended. For Tc-99m tetrofosmin, minimum delays of 10-15 minutes for exercise, 30-45 minutes for rest, and 45 minutes for pharmacologic stress are optimal. Since there is minimal redistribution with these agents, longer delays, up to 2 hours, between the radiotracer injection and imaging can be used when needed.

Two-Day Protocol Ideally, stress and rest imaging with Tc-99m agents should be performed on two separate days, as shown in Figure 2, to avoid having residual activity from the first study contaminate the second study. In overweight patients (i.e., >250 lb or body mass index >30) or in female patients where significant breast attenuation is anticipated, a low dose of Tc-99m radiotracer may result in suboptimal images and a 2-day imaging protocol is preferable.

One-Day Protocols For most patients, 2-day imaging is impractical; stress and rest studies are usually performed using a 1-day protocol as shown in Figures 3-7 for exercise and pharmacologic stress. This requires administration of a low dose (one-fourth of the total dose, or 8-12 mCi) for the first study and a larger dose (three-fourths of the total dose, or 24-36 mCi) for the second study. One-day rest/stress Tc-99m protocols are now performed almost universally with no delay between the rest and subsequent stress images. The initially proposed 1990 protocol specified a 2-hour delay between rest and stress to allow the rest dose to decay in order to maximize the stress/rest count density ratio and minimize rest-to-stress ''shine-through'' or ''crosstalk.'' However, simply increasing the stress dose provides the same stress/rest count density ratio achieved by letting the rest dose decay (20% in 2 hours). Thus a 3:1 stress/rest dose ratio with a 2-hour delay and a 3.5-4:1 ratio with no delay provide the same result. Note that the 2-hour delay is the total time between rest injection and starting the post-stress imaging. Thus the waiting time to stress is not fixed but depends on the sum of intervals from rest injection to the post-stress imaging. In contrast, for the 1-day stress/rest protocol, wherein the stress scan is performed first and relative tracer uptake in the myocardium is increased consequent to the stress-induced coronary hyperemia, a delay between the stress injection and the subsequent resting injection is essential and should be as close to 4 hours as possible between the stress injection and starting the post-rest imaging. Stated administered activities are commonly used in the United States, but these vary in other countries. Issues regarding the imaging sequence (stress vs. rest first) and the minimum time interval between the two radiotracer injections are not fully settled.

In patients without a prior history of CAD with an intermediate pre-test likelihood based on risk factors, a low-dose stress/high-dose rest Tc-99m protocol may have theoretical advantages since a significant percentage of these patients will have normal stress studies, thereby avoiding additional radiation exposure from a rest study. Due to higher tracer uptake during low-dose stress, the waiting time to high-dose rest imaging needs to be longer (3-4 hours) or the rest dose needs to be higher to achieve a rest/stress ratio of at least 1:4.

Dual-Isotope Imaging Use of Tl-201 for initial rest imaging and a Tc-99 labeled tracer for stress perfusion imaging, as shown in Figure 8 allows a shorter duration of the entire imaging protocol, but there is a significantly higher radiation dose to the patient. Use of rest/3- to 4-hour redistribution Tl-201 imaging prior to the stress, Tc-99m study provides valuable information on myocardial viability and should be considered in patients with prior infarction or heart failure.

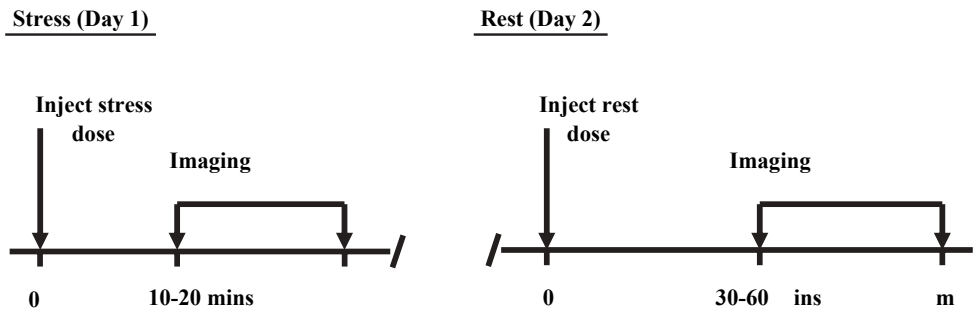

Figure 2. Tc-99m imaging protocols: Two-day exercise stress/rest.

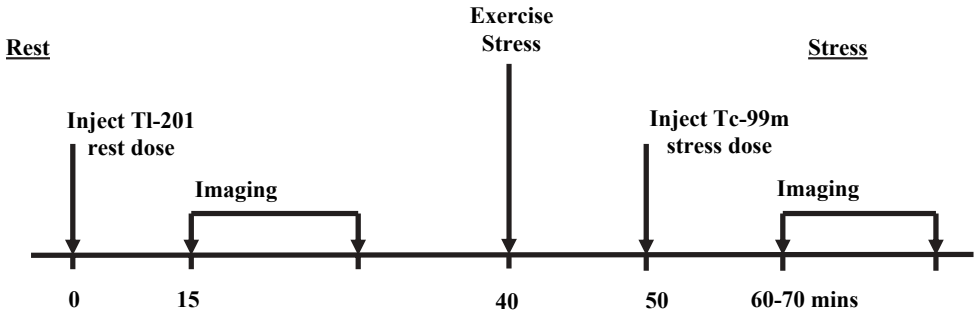

Figure 3. Rest Tl-201/stress Tc-99m separate-acquisition dual-isotope protocol.

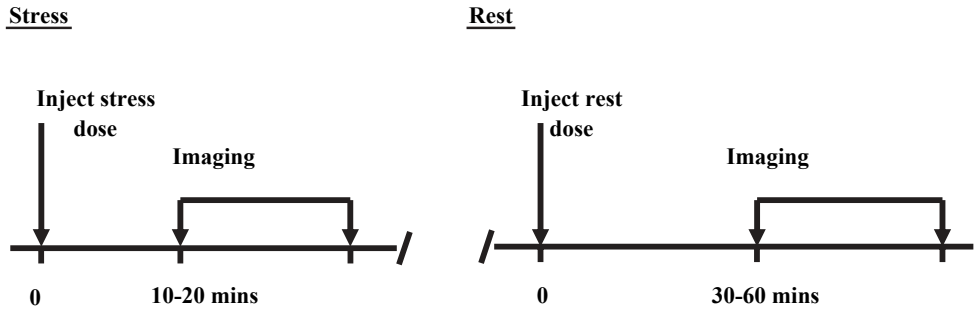

Figure 4. Tc-99m imaging protocols: One-day exercise stress/rest.

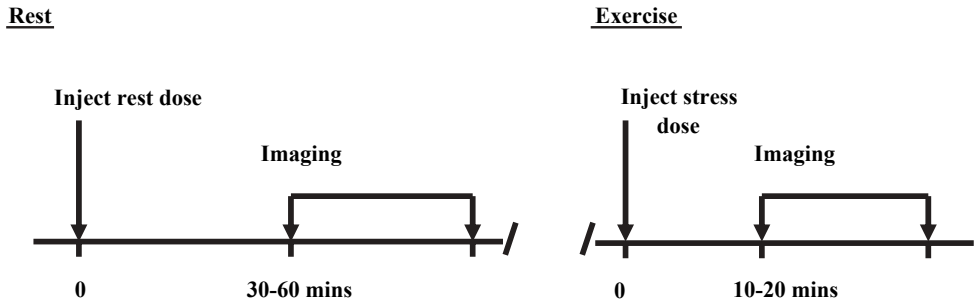

Figure 5. Tc-99m imaging protocols: One-day rest/exercise stress.

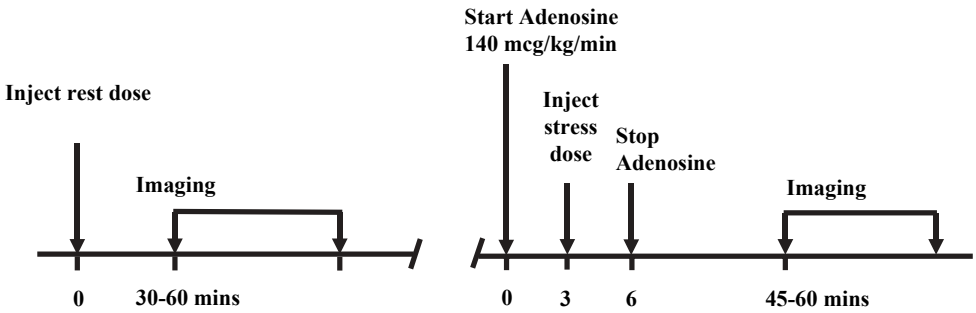

Figure 6. Tc-99m imaging protocols: One-day rest/adenosine pharmacologic stress.

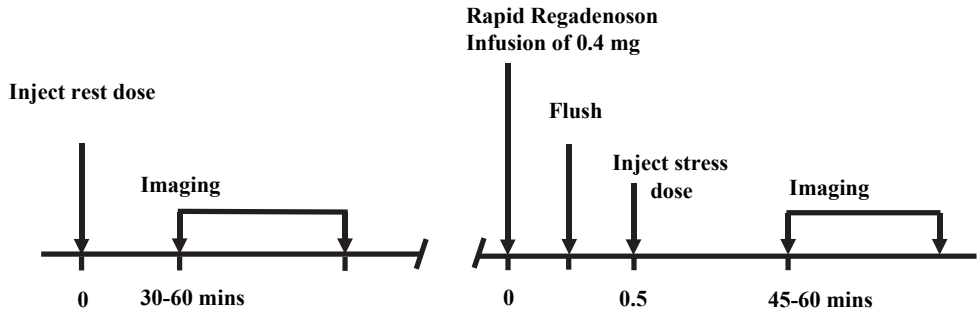

Figure 7. Tc-99m imaging protocols: One-day rest/regadenoson pharmacologic stress.

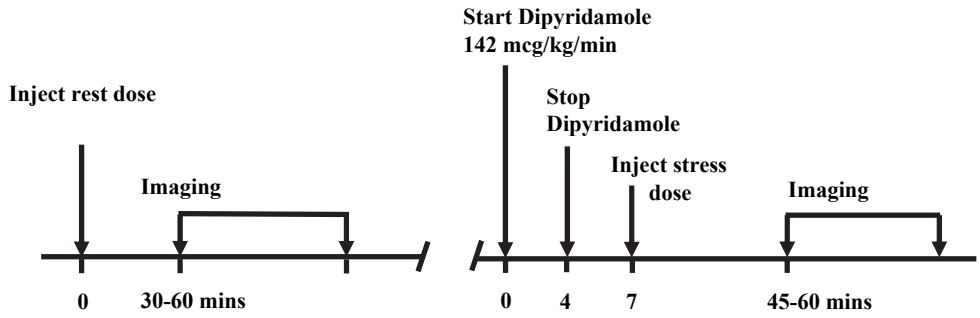

Figure 8. Tc-99m imaging protocols: One-day rest/dipyridamole pharmacologic stress.

Acknowledgment

The authors have indicated that they have no financial conflicts of interest.

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