

# Pharmacologic Stress Testing with Myocardial Perfusion Imaging

Robert A. Paganelli, BSRT (R)(N), CNMT, NCT, FSNMMI-TS, and Heidi L. Camposano, BSBA, CNMT

*Department of Radiology, Duke Regional Hospital, Durham, North Carolina*

**CE Credit:** For CE credit, you can access the test for this article, as well as additional *JNMT* CE tests, online at <https://www.snmlearningcenter.org>. Complete the test online no later than December 2020. Your online test will be scored immediately. You may make 3 attempts to pass the test and must answer 80% of the questions correctly to receive 1.0 CEH (continuing education hour) credit. SNMMI members will have their CEH credit added to their VOICE transcript automatically; nonmembers will be able to print out a CE certificate upon successfully completing the test. The online test is free to SNMMI members; nonmembers must pay \$15.00 by credit card when logging onto the website to take the test.

The preferred method for performing stress testing with myocardial perfusion imaging is physical exercise. However, many patients are unable to reach an adequate endpoint. As an alternative, various pharmacologic options are available, which are explored in this article.

**Key Words:** cardiology; myocardial perfusion imaging; pharmacologic stress; vasodilator

**J Nucl Med Technol 2017; 45:249–252**

DOI: 10.2967/jnmt.117.199208

A radionuclide myocardial perfusion procedure is used to assess blood flow to the myocardium and evaluate cardiac function. There are several methods of stressing the heart, with the two primary being physical exercise and pharmacologic stress. Physical exercise stress testing has many advantages over pharmacologic stress testing. Therefore, stress testing should be performed with exercise if an adequate endpoint can be reached. Additional information such as the patient's exercise capacity, symptoms, and hemodynamic response to exercise is gained. Image quality is improved because there is less hepatic uptake of  $^{99m}\text{Tc}$ -labeled tracers when injected during physical exercise. As stated in guidelines, patients should not be injected during a physical exercise stress test unless they experience symptoms such as shortness of breath or chest pain or become fatigued once achieving target heart rate. Achieving target heart rate alone is not an adequate reason for termination. If an adequate stress endpoint is not reached, the study should be converted to pharmacologic stress (*1*).

Over the past several years, the adoption of appropriate-use criteria and the requirement for preauthorization have caused the number of myocardial perfusion studies performed in the United States to decline. This guidance has significantly reduced the number of “healthier” patients undergoing the procedure, who would likely be good candidates for physical exercise. As a result, the percentage of patients having the procedure performed with pharmacologic stress is higher.

Again, when undergoing a physical exercise stress test, the patient should exhibit a symptomatic endpoint such as overall fatigue, moderate to severe chest pain, or extreme shortness of breath. Patients also should exercise at least to the level of 5 metabolic equivalents. The achievement of target heart rate alone, which is 85% of a predicted maximum heart rate, is not an acceptable reason to terminate an exercise stress test. Even if a patient is under the target heart rate and reaches a level of 5 metabolic equivalents, the appearance of the patient's symptoms is an adequate stress endpoint.

With radionuclide myocardial perfusion imaging, pharmacologic stress may be performed with an inotropic agent or vasodilator. Guidelines suggest vasodilators as the first option (*1*). There are currently 3 vasodilators approved for myocardial perfusion stress testing—dipyridamole, adenosine, and regadenoson. Additionally, there is dobutamine, an inotropic agent, which is not approved by the Food and Drug Administration for stress testing. Their characteristics are presented in Table 1. They are indicated for patients who cannot reach an adequate endpoint with physical exercise stress testing. Vasodilators are adenosine receptor agonists. There are 4 known types of adenosine receptors:  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$ . Activation of the  $A_{2A}$  receptors results in the desired effect, coronary artery vasodilation. Activation of the others results in less desirable effects. Activation of the  $A_1$  receptor results in decreased atrioventricular conduction. Activation of the  $A_{2B}$  and  $A_3$  receptors can result in bronchospasm.

## DIPYRIDAMOLE

Dipyridamole was the first vasodilator used for myocardial perfusion stress testing. Dipyridamole is an indirect

Received Jul. 12, 2017; revision accepted Sep. 22, 2017.  
For correspondence or reprints contact: Robert A. Paganelli, Duke Regional Hospital, 3643 N. Roxboro St., Durham, NC 27704.  
E-mail: [pagna0001@mc.duke.edu](mailto:pagna0001@mc.duke.edu)  
Published online Oct. 17, 2017.  
COPYRIGHT © 2017 by the Society of Nuclear Medicine and Molecular Imaging.

**TABLE 1**  
Vasodilator Characteristics

Pharmacologic agent	Class	Mechanism of action	Dose	Duration	Infusion pump required	Half-life	Increase in coronary flow	Incidence of atrioventricular block (vasodilators)
Adenosine	Direct coronary artery vasodilator	Nonselective adenosine receptor agonist	140 µg/kg/min (up to 125 kg)	6-min infusion with radiopharmaceutical injection at 3 min	Yes	<10 s	3.5–4 times baseline	8% of studies
Dipyridamole	Indirect coronary artery vasodilator	Nonselective adenosine receptor agonist	142 µg/kg/min (up to 125 kg)	4-min infusion with radiopharmaceutical injection at 3–5 min afterward	No	30–45 min	3.8–7 times baseline	2% of studies
Regadenoson	Direct coronary artery vasodilator	Selective A <sub>2A</sub> receptor agonist	400 µg	10-s infusion with radiopharmaceutical injection at 20–30 s afterward	No	Initial phase, 2–4 min; intermediate, 30 min; terminal, 2 h	2.5 times baseline	3% of studies
Dobutamine	Inotropic agent	Direct β <sub>1</sub> and β <sub>2</sub> stimulation	3-min incremental stages: 10, 20, 30, 40 µg/kg/min	Until target heart rate or 12-min maximum is reached	Yes	<3 min	2–3 times baseline	Not applicable

coronary artery vasodilator. Its mechanism of action is the building up of adenosine in tissues by blocking the cellular reuptake of endogenous adenosine. This indirect process results in a slow onset. Dipyridamole is infused over 4 min, with the radiotracer being injected 3–5 min after the completion of the dipyridamole infusion, which coincides with peak hyperemia. The dosage is 0.142 µg/kg/min, or 0.57 µg/kg (2). Patients generally have a modest increase in heart rate and a modest decrease in blood pressure. The infusion results in a 3.8- to 7-fold increase in coronary blood flow over baseline. Given that dipyridamole has a half-life of approximately 30–45 min, patients may experience side effects longer than with other pharmacologic stress agents.

Dipyridamole is contraindicated in patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease, a systolic blood pressure of less than 90 mm Hg, uncontrolled hypertension (systolic pressure of over 200 mm Hg or diastolic pressure of over 110 mm Hg), caffeine intake in the previous 12 h, or a known hypersensitivity to dipyridamole. Relative contraindications include bradycardia (heart rate < 40 beats/min), second- or third-degree atrioventricular block without a functioning pacemaker, severe aortic stenosis, or a seizure disorder (1).

## ADENOSINE

Adenosine is a direct coronary artery vasodilator. Adenosine acts on the 4 known types of receptors. The indicated dose for adenosine is 0.14 µg/kg/min. By package insert recommendations, the drug is infused for 6 min, with the radiotracer injection given at 3 min, or midpoint (3). There is literature supporting the effectiveness of 4-min infusions with the radiotracer injection given at 2 min, with the benefit of reducing the pharmaceutical dose and the duration of side effects (4). Like dipyridamole, adenosine generally produces a modest increase in heart rate and a modest decrease in blood pressure. The infusion results in a 3.5- to 4-fold increase in coronary blood flow over baseline. Adenosine has a half-life of less than 10 s. Both the short half-life and its activation of the A<sub>1</sub> receptor and potential to cause heart block dictate that an infusion pump must be used to ensure a sustained infusion. It is strongly recommended that 2 intravenous lines be used. Should a single intravenous line be used, there is the potential to administer most of the adenosine in the intravenous line as a bolus when the radiopharmaceutical is pushed through the line, which will increase the chance of heart block. There is also the urge for the person administering the radiopharmaceutical to kink the line to block the adenosine infusion during the radiotracer injection, therefore decreasing the adenosine dose and vasodilator effect during the time of radiotracer uptake. Because the adenosine half-life is short, the sensitivity of the procedure would likely be decreased.

Adenosine is contraindicated in patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease, second- or third-degree

atrioventricular block without a functioning pacemaker, sinus node disease without a functioning pacemaker, a systolic blood pressure of less than 90 mm Hg, uncontrolled hypertension (a systolic pressure of over 200 mm Hg or a diastolic pressure of over 110 mm Hg), caffeine intake in the previous 12 h, a known hypersensitivity to adenosine, or the use of dipyridamole in the last 2 d. Adenosine is also contraindicated in patients with acute coronary syndrome or unstable angina or who experienced a myocardial infarction less than 2 d previously. Relative contraindications include bradycardia (heart rate < 40 beats/min), Mobitz type I (Wenckebach), caffeine intake within the previous 12 h, severe aortic stenosis, or a seizure disorder (1).

## REGADENOSON

Regadenoson is another direct coronary artery vasodilator. It is a selective  $A_{2A}$  receptor agonist. Regadenoson has a 10 times greater affinity for the  $A_{2A}$  receptor than for the  $A_1$  receptor and little to no affinity for the  $A_{2B}$  and  $A_3$  receptors. Regadenoson is infused over 10 s. The dosing is not weight-based like the other available vasodilators. All adult patients receive 0.4 mg, which is available only in a prefilled 5-mL syringe. The regadenoson dose is immediately followed by a saline flush. The radiotracer is administered 10–20 s later, immediately followed by another saline flush (5). At the time of radiotracer infusion, there is generally a 2.5-fold increase in coronary blood flow over baseline, which is maintained for about 2.3 min. The half-life of regadenoson is triphasic. The first phase is 2–4 min, the intermediate phase is approximately 30 min and coincides with loss of effect, and the terminal elimination phase is approximately 2 h and coincides with a decline in plasma concentration.

Regadenoson is contraindicated in patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease, second- or third-degree atrioventricular block without a functioning pacemaker, sinus node disease without a functioning pacemaker, a systolic blood pressure of less than 90 mm Hg, uncontrolled hypertension (systolic pressure > 200 mm Hg or diastolic pressure > 110 mm Hg), a known hypersensitivity to adenosine or regadenoson, or use of dipyridamole in the last 2 d. Regadenoson is also contraindicated in patients who have acute coronary syndrome or unstable angina or who experienced a myocardial infarction less than 2 d previously. Relative contraindications include bradycardia (heart rate < 40 beats/min), Mobitz type I (Wenckebach), caffeine intake within the previous 12 h, severe aortic stenosis, or a seizure disorder (1).

Methylxanthines, including caffeine, are competitive adenosine receptor antagonists and will therefore compete for adenosine receptors, blocking the effect of vasodilators. Guidelines and package inserts suggest abstaining from these substances for at least 12 h before testing because they may lead to false-negative results.

Caffeine is commonly offered to patients after the stress testing procedure, as it will likely reverse undesirable side effects. It is particularly helpful with regadenoson and, especially, dipyridamole, as they have a longer half-life than adenosine. Because habitual caffeine drinkers abstain from caffeine for the stress testing procedure, they will often have headaches and will benefit from and appreciate the caffeine. More severe side effects may be treated with aminophylline, another methylxanthine, and adenosine receptor antagonist. If possible, aminophylline should not be administered for at least 1 min after radiotracer administration to preserve the sensitivity of the procedure. Typical dosing is 50–250 mg by slow intravenous injection over 30–60 s. Recent safety data suggest that methylxanthines not be used in patients who have a seizure related to vasodilator administration (3,5).

## DOBUTAMINE

Dobutamine is an inotropic option for myocardial perfusion stress testing. Dobutamine is not Food and Drug Administration–approved for pharmacologic stress testing but has been routinely used for both radionuclide myocardial perfusion and stress echocardiography testing for years. For myocardial perfusion procedures, dobutamine is indicated for patients who cannot reach an adequate endpoint with exercise stress testing and have a contraindication to vasodilators. Dobutamine is a  $\beta$ -adrenergic agent that results in direct  $\beta_1$  and  $\beta_2$  stimulation. It is administered as an incremental infusion beginning at 5 or 10  $\mu\text{g}/\text{kg}/\text{min}$  for 3 min. It is increased to 20, 30, then 40  $\mu\text{g}/\text{kg}/\text{min}$ , also for 3-min intervals, for a maximum of 12 min or until the target heart rate is reached. Atropine may additionally be given in increments of 0.25–0.5 mg (up to 1–2 mg total) if target heart rate is not reached with dobutamine alone (1). The half-life of dobutamine is less than 3 min (6). If necessary, a short-acting  $\beta$ -blocker, such as esmolol, can be administered as a reversal agent.

A pump must be used for the infusion. Two separate intravenous lines or a single line with a Y-connector should be used to allow infusion of an uninterrupted flow of dobutamine during the radiotracer injection and to prevent a bolus of dobutamine.

Dobutamine is contraindicated in patients who have unstable angina or acute coronary syndrome; patients who experienced an acute myocardial infarction less than 2 to 4 d previously; and patients who have hemodynamically significant left ventricular outflow tract obstruction, atrial tachyarrhythmias with uncontrolled ventricular response, a prior history of ventricular tachycardia, uncontrolled hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg), aortic dissection, or a known hypersensitivity to dobutamine. Relative contraindications include patients who are on  $\beta$ -blockers and in whom the heart rate and inotropic responses will be attenuated, as well as patients who have severe aortic stenosis, a symptomatic or large aortic aneurysm, a left bundle branch block, or paced ventricular rhythm (1).

Incorporating low-level exercise into vasodilator stress tests has been shown to have several advantages, including reduced side effects, better image quality, and the availability of prognostic information gained from exercise (7–9). There may be two components to the reduced side effects. The physical exercise may lessen the drop in blood pressure from the vasodilator. Patients will also be focused on walking on the treadmill, likely a difficult task for this population of patients, resulting in distraction. When undergoing physical exercise stress, there is increased oxygen demand and therefore increased blood flow to the legs. As a result, blood is shunted away from abdominal organs, resulting in less  $^{99m}\text{Tc}$ -labeled myocardial perfusion tracer uptake in the liver. As a result, it is less likely that a patient will require a rescan because of extracardiac activity. In fact, images can be acquired earlier, as they are with exercise stress protocols.

Although protocols slightly vary, with adenosine and regadenoson the patient often undergoes low-level exercise (1.6–2.7 km/h [1.0–1.7 mi/h]) during the pharmacologic infusion and continuing until 1–2 min after the radiotracer administration. With dipyridamole, shortly after the 4-min infusion the patient undergoes low-level exercise until 1–2 min after the radiotracer administration.

Despite proper screening and conversations with patients, some will attempt physical exercise but not reach an adequate endpoint. Exercise should be aborted in these patients and the type of stress converted to pharmacologic. Recent data suggest that regadenoson stress can safely be performed 3 min after inadequate exercise. The most common events were similar in type and incidence for subjects stressed 3 min after inadequate exercise versus those stressed 1 h after inadequate exercise (10). It has been documented that the likelihood of a left bundle branch

artifact, reducing septal tracer uptake, increases with increased heart rate. Therefore, incorporating low-level exercise into the pharmacologic stress protocol is not suggested in this patient population (1).

## CONCLUSION

Physical exercise stress is the preferred method of stress testing, as it is a more physiologic procedure. Pharmacologic agents offer an alternative to the population who cannot reach an adequate endpoint with physical exercise.

## REFERENCES

1. Henzlova MJ, Duvall WL, Einstein AJ, et al. Erratum to: ASNC imaging guidelines for SPECT nuclear cardiology procedures: stress, protocols, and tracers. *J Nucl Cardiol*. 2016;23:640–642.
2. Dipyridamole injection [package insert]. Eatontown, NJ: West-Ward Pharmaceutical; 2011.
3. ADENOSCAN® (adenosine) injection for intravenous use [package insert]. Northbrook, IL: Astellas Pharma US Inc.; 2014.
4. Ficaro BS, McCallister BD. Adenosine stress protocols for myocardial perfusion imaging. *J Nucl Cardiol*. 2007;14:415–416.
5. LEXISCAN® (regadenoson) injection for intravenous use [package insert]. Northbrook, IL: Astellas Pharma US Inc.; 2017.
6. Dobutamine in 5% dextrose injection. [package insert]. Lake Forest, IL: Hospira; 2016.
7. Ahlberg AW, Baghdasarian SB, Athar H, et al. Symptom-limited exercise combined with dipyridamole stress: prognostic value in assessment of known or suspected coronary artery disease by use of gated SPECT imaging. *J Nucl Cardiol*. 2008;15:42–56.
8. Thomas GS, Prill NV, Majmundar H, et al. Treadmill exercise during adenosine infusion is safe, results in fewer adverse reactions, and improves myocardial perfusion image quality. *J Nucl Cardiol*. 2000;7:439–446.
9. Thomas GS, Thompson RC, Miyamoto MI, et al. Safety of regadenoson during submaximal exercise testing: a randomized, double-blind, placebo- and active-controlled trial (the RegEx trial). *J Nucl Cardiol*. 2009;16:63–72.
10. Thomas GS, Cullom SJ, Kitt TM, et al. The EXERRT trial: “EXercise to Regadenoson in Recovery Trial”: a phase 3b, open-label, parallel group, randomized, multicenter study to assess regadenoson administration following an inadequate exercise stress test as compared with regadenoson without exercise for myocardial perfusion imaging using a SPECT protocol. *J Nucl Cardiol*. 2017;24:788–802.