

Pharmacologic and Exercise Stress Tests

Pharmacologic Stress Test: Adenosine

OVERVIEW

The purpose of this document is to specifically identify the critical components involved in performing a pharmacologic stress test with adenosine. This information serves as a standard for all nuclear cardiology laboratories. This document will cover **dosage and side effects, indications, contraindications, testing procedure, and indications for reversal of infusion.**

ADENOSINE

Adenosine induces direct coronary arteriolar vasodilation through specific activation of the A_{2A} 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. However, in a small percentage of patients with severe coronary artery disease (CAD), true ischemia may 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.

DOSAGE AND SIDE EFFECTS

Adenosine should be given as a continuous infusion of 140 mcg / kg / min. The package insert recommends a 6-

minute protocol with the perfusion agent given at 3 minutes of infusion. Investigators have reported good results with infusion periods as short as 4 minutes (with the perfusion agent injected at 2 minutes).

Due to the short half-life of adenosine (<10 seconds), most side effects resolve in a few seconds after discontinuation of the adenosine infusion. However, the occasional patient may require administration of aminophylline for reversal of persistent symptoms.

Products should be inspected visually for particulate matter and discoloration prior to administration.

Side effects from nonselective activation of A₁, A_{2B}, and A₃ receptors:

A ₁ Receptor	AV Block
A _{2B} Receptor	Peripheral Vasodilation, Bronchospasm
A ₃ Receptor	Bronchospasm

Minor side effects occur in approximately 80% of patients:

Flushing	35% - 40%
Chest Pain*	25% - 30%
Dyspnea	20%
Dizziness	7%
Nausea	5%
Symptomatic Hypotension	5%

*Chest pain is nonspecific and is not necessarily indicative of the presence of CAD



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Other side effects include:

AV Block	7.6%
Second Degree AV Block	4%
Complete Heart Block	<1%
ST-Segment Depression of 1 mm or Greater	5% - 7%
Myocardial Infarction	Extremely rare

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

INDICATIONS

Indications for an adenosine stress test are the same as for an exercise stress test (see Practice Points: Exercise Stress Test, p. 6) and are in the presence of the following conditions:

- 1) Inability to perform adequate exercise due to noncardiac physical limitations or lack of motivation.
- 2) Baseline electrocardiographic abnormalities such as left bundle branch block (LBBB), ventricular pre-excitation (Wolff-Parkinson-White syndrome), or permanent ventricular pacing.
- 3) Risk stratification of clinically stable patients after acute myocardial infarction (≥ 1 day) or following presentation to the emergency department with a presumptive acute coronary syndrome.

CONTRAINDICATIONS

Absolute contraindications for adenosine stress testing include:

- 1) Asthmatic patients with ongoing wheezing
 - a. It has been reported that patients with adequately controlled asthma can undergo an adenosine stress test and can have pretreatment with 2 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 less than 90mm Hg
- 4) Recent use of dipyridamole or dipyridamole-containing medications
- 5) Methyl xanthenes such as aminophylline caffeine or

theobromine block the effect of adenosine and should be held for at least 12 hours prior to the test.

- a. 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 for adenosine stress testing include:

- 1) Profound sinus bradycardia (heart rates < 40 beats/minute)

TESTING PROCEDURE

Patients should not eat 2 hours before the test. Patients may not consume caffeine-containing beverages or medications for at least 12 hours prior to testing.



This test requires an infusion pump and intravenous line with a dual-port Y-connector.

- 1) Adenosine infusion should be given at a rate of 140 mcg / kg / min.
 - a. 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 to 100 mcg / kg / min). The dose may then be increased to 140 mcg / kg / min as tolerated and the injection of the radiotracer given at the halfway point of the protocol.

- 2) Blood pressure should be monitored every minute during infusion and until stable in recovery (minimum of 3 minutes).
- 3) Obtain a 12-lead EKG every minute during the adenosine infusion and until stable in recovery (minimum of 3 minutes).
- 4) The patient should be monitored in recovery until symptoms have resolved and there is no evidence of ischemia.

Note: *Anti-ischemic cardiac medications can decrease the diagnostic accuracy of vasodilator stress testing.*

COMBINATION OF EXERCISE AND ADENOSINE

The combination of low-level upright treadmill exercise (1.7 mph, 0% grade) during the adenosine infusion has been found safe. The combination reduces the side effects of adenosine, attenuates the adenosine-induced drop in blood pressure, and improves image quality by decreasing high hepatic and gut radiotracer uptake.

Low-level exercise may be performed in combination with pharmacologic stress but is not recommended in patients with LBBB or for patients with pacemakers.

INDICATIONS FOR REVERSAL OF ADENOSINE INFUSION

The adenosine infusion should be stopped early under any of the following circumstances:

- 1) Severe hypotension (systolic blood pressure < 80mm Hg)
- 2) Development of symptomatic or 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, cold skin)
- 6) Technical problems with the monitoring equipment
- 7) Patient's request to stop

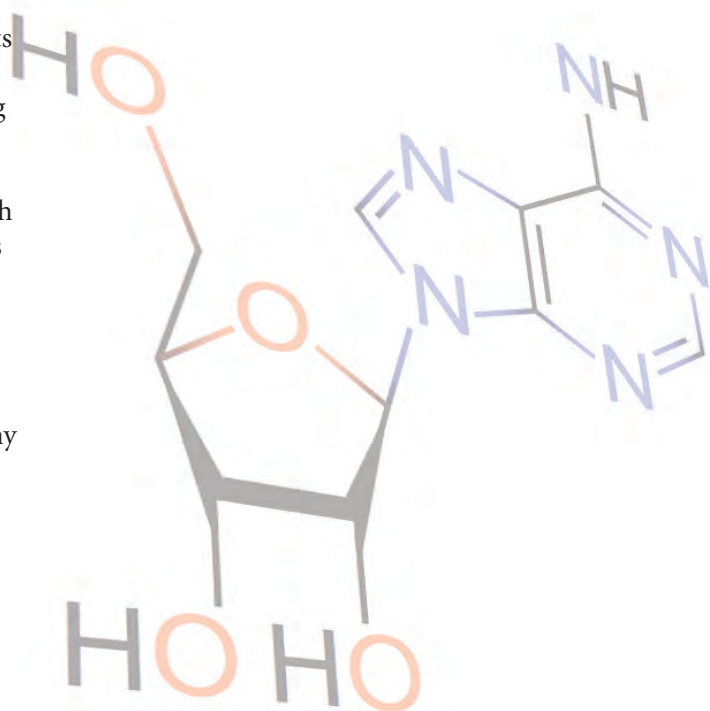
SUGGESTED READING

Bokhari S, Ficaro EP, McCallister BD. Adenosine stress protocols for myocardial perfusion imaging. *J Nucl Cardiol* 2007;14:415-6.

Henzlova MJ et al. ASNC Imaging Guidelines for Nuclear Cardiology Procedures: Stress protocols and tracers. *J Nucl Cardiol* 2009; doi: 10.1007/s12350-009-9061-5.

ASNC thanks the following members for their contributions to this document:

Karthikeyan Ananthasubramaniam, MD; Gabriel Grossman, MD, PhD; Christopher L. Hansen, MD; Habib Samady, MD; and Massimiliano Szulc, PhD.



Adenosine

Pharmacologic Stress Test: Regadenoson

OVERVIEW

The purpose of this document is to specifically identify the critical components involved in performing a pharmacologic stress test with regadenoson. This information serves as a standard for all nuclear cardiology laboratories. This document will **cover dosage and side effects, indications, contraindications, testing procedure, and indications for reversal of infusion.**

REGADENOSON

Regadenoson is a selective A_{2A} receptor agonist. Activation of the A_{2A} adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes after injection and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2 to 4 minutes. An intermediate phase follows with an average half-life 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.

DOSAGE AND SIDE EFFECTS

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.

As with any other parenteral drug, products should be inspected visually for particulate matter and discoloration prior to administration.

The most common reactions to administration of regadenoson are shortness of breath, headache, and flushing. Less common reactions are chest discomfort, angina pectoris or ST, dizziness, chest pain, nausea, abdominal discomfort, dysgeusia, and feeling hot.

Maximum hemodynamic effects of regadenoson:

Increase in Heart Rate (> 40 Beats/Minute)	5%
Decrease in Systolic Blood Pressure (> 35 mm Hg)	7%
Decrease in Diastolic Blood Pressure (> 25 mm Hg)	4%

In patients with a prior adenosine stress study, the following side effects have been noted:

Rhythm or Conduction Abnormalities	26%
First Degree AV Block	3%
Second Degree AV Block	0.1%
Ventricular Conduction Abnormalities	6%

Many adverse reactions begin soon after dosing and generally resolve within 15 minutes, except for headache which resolves in most patients within 30 minutes.

Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30 to 60 seconds) to attenuate severe or persistent adverse reactions to regadenoson.

INDICATIONS

A regadenoson stress test is indicated in patients unable to undergo adequate exercise stress and in the presence of the following condition:

- 1) Inability to perform adequate exercise due to noncardiac physical limitations or lack of motivation

CONTRAINDICATIONS

Absolute contraindications for regadenoson stress testing include:

- 1) Patients with second- or third-degree AV block or sinus node dysfunction without a functioning pacemaker
- 2) Known hypersensitivity to adenosine or regadenoson
- 3) Systolic blood pressure less than 90mm Hg

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Note: *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.*

Relative contraindications for regadenoson stress testing include:

- 1) Profound sinus bradycardia (heart rate < 40 beats/minute)
- 2) Reactive airways disease. The safety of selective adenosine agonists is not definitively established in patients with bronchoconstrictive lung disease such as asthma or COPD. Regadenoson should be used with caution in these patients. Aminophylline, bronchodilators and resuscitative measures should be immediately available.

TESTING PROCEDURE

Studies are currently underway to assess the effect caffeine consumption has on the accuracy of regadenoson imaging. It is currently recommended that patients should avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea, or other beverages, chocolate, caffeine-containing drug products and theophylline for at least 12 hours prior to testing. Dipyridamole should be withheld for at least 2 days prior to regadenoson administration.

- 1) 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.
- 2) Monitor the ECG continuously during the procedure. 12 lead ECGs should be recorded every minute until the patient is stable.
- 3) Blood pressure should be monitored every minute during the procedure, and for at least 3 to 5 minutes into recovery.
- 4) Administer a 5 mL saline flush immediately after the injection of regadenoson.
- 5) Administer the radionuclide myocardial perfusion imaging agent 10 to 20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as regadenoson.

Note: *Anti-ischemic cardiac medications can decrease the diagnostic accuracy of vasodilator stress testing.*

INDICATIONS FOR REVERSAL OF REGADENOSON INFUSION

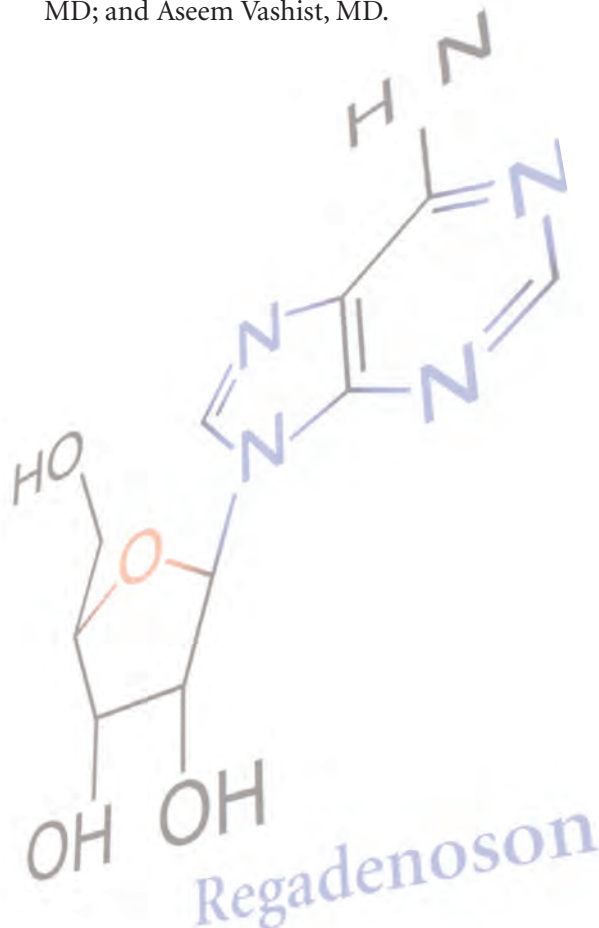
Aminophylline should be considered under any of the following circumstances:

- 1) Severe hypotension (systolic blood pressure <80mm Hg)
- 2) Development of symptomatic, persistent second-degree or complete heart block
- 3) Wheezing
- 4) Persistent chest pain or ST depression
- 5) Signs of poor perfusion (pallor, cyanosis, cold skin)

SUGGESTED READING

Henzlova MJ et al. ASNC Imaging Guidelines for Nuclear Cardiology Procedures: Stress protocols and tracers. J Nucl Cardiol 2009; doi: 10.1007/s12350-009-9061-5.

ASNC thanks the following members for their contributions to this document: Fabio Esteves, MD; Christopher L. Hansen, MD; Sujith Kalathiveetil, MD; Maria Sciammarella, MD; and Aseem Vashist, MD.



Exercise Stress Test

OVERVIEW

The purpose of this document is to specifically identify the critical components involved in performing an exercise stress test. This information serves as a standard for all nuclear cardiology laboratories. This document will cover **indications, contraindications, limitations, testing procedure, and indications for early termination of exercise.**

EXERCISE STRESS TEST

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

Exercise stress testing is a powerful risk stratification tool, and is useful in assessing the efficacy of anti-ischemic drug therapy and/or coronary revascularization.

The treadmill is the most widely used stress modality. The most commonly employed treadmill stress protocols are the Bruce and modified Bruce. Upright bicycle exercise is preferable if dynamic first-pass imaging is planned during exercise.

INDICATIONS

Indications for an exercise stress test are:

- 1) Detection of coronary artery disease (CAD) in patients with an intermediate pretest probability of CAD based on age, gender, and symptoms, or in patients with high-risk factors for CAD (i.e., diabetes mellitus, peripheral or cerebrovascular disease).
- 2) Risk stratification of post-myocardial infarction patients:
 - a. Before discharge: submaximal test (often defined as 70% of the age-adjusted MPHR) at 4-6 days. If test results are negative, then later after discharge: symptom-limited at 3-6 weeks.
 - b. Soon after discharge: symptom-limited at 14-21 days.

- 3) Risk stratification of patients with chronic stable CAD into a low-risk category that can be managed medically or 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 or intermediate-risk acute coronary syndrome patients 1-3 days after presentation.
- 5) Risk stratification before noncardiac surgery in patients with known CAD, diabetes mellitus, peripheral or cerebrovascular disease.
- 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.

CONTRAINDICATIONS

Absolute contraindications 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)
- 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 (less than 4 days)
- 11) Acutely ill for any reason

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 block
- 6) Electrolyte abnormalities
- 7) Mental or physical impairment leading to inability to exercise adequately

LIMITATIONS

Exercise stress testing has a lower diagnostic value in patients who cannot achieve an adequate heart rate and blood pressure response.

Note: *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 a pharmacologic vasodilator stress (not a dobutamine stress test).*

TESTING PROCEDURE

Patients should not eat for 2 hours before the test. Patients scheduled for later in the morning may have a light breakfast.

Exercise Stress Tests require:

- 1) Properly trained nurses, nurse practitioners, and physician assistants to administer tests and an appropriately trained supervising physician immediately available
- 2) Records of the heart rate, a 12 lead ECG, and blood pressure at each stage of exercise, and with any clinical symptoms. All are repeated during recovery, typically

every minute for at least 5 minutes after cessation of exercise.

- 3) Continuous electrocardiographic monitoring during the test and in the recovery period. Monitoring is continued for at least 5 minutes into the recovery period or until the resting heart rate is less than 100 beats per minute, or dynamic ST segment changes have resolved.
- 4) A large bore (18-20 gauge) intravenous cannula for radiopharmaceutical injection
- 5) Radiopharmaceutical injection as close to peak exercise as possible
- 6) Exercise for at least 1 minute after radiopharmaceutical injection

INDICATIONS FOR EARLY TERMINATION OF EXERCISE

All exercise tests should be symptom-limited.

Achievement of 85% of age-adjusted MPPHR is not an indication for termination of the test.

In patients who cannot exercise adequately (e.g., achieve 85% of age-adjusted MPPHR prior to radiopharmaceutical administration and for at least 1 minute following radiotracer administration; achieve 5 METS or 5 minutes total exercise time on a Bruce protocol), the radiotracer should not be injected at peak exercise and a pharmacologic stress test should be considered. Blood pressure medications with antianginal properties will lower the diagnostic accuracy of a stress test. However, testing patients with CAD on their anti-ischemic regimens may be useful in monitoring their response to therapy. 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 (> 2mm)
- 7) ST elevation (> 1mm) in leads without diagnostic Q waves (except for leads V₁ or aVR)
- 8) Sustained supraventricular or ventricular tachycardia

Exercise Stress Test

- 9) Development of LBBB or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
- 10) Drop in systolic blood pressure of greater than 10mm Hg from baseline, despite an increase in workload, when accompanied by other evidence of ischemia
- 11) Hypertensive response (systolic blood pressure > 250mm Hg and/or diastolic pressure > 115 mm Hg)
- 12) Technical difficulties in monitoring the ECG or systolic blood pressure

SUGGESTED READING

Henzlova MJ et al. ASNC Imaging Guidelines for Nuclear Cardiology Procedures: Stress protocols and tracers. J Nucl Cardiol 2009; doi: 10.1007/s12350-009-9061-5.

Gibbons RJ, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Exercise Testing) 2002. Available at: www.acc.org/clinical/guidelines/exercise/dirIndex.htm.

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