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ASNC STRESS TESTING
PRACTICE POINTS

Pharmacological Stress Testing - Regadenoson

OVERVIEW

The purpose of this document is to provide a guide to the performance of pharmacologic stress testing with regadenoson. The critical components of regadenoson stress testing will be specifically outlined in this document and serve as a standard for all nuclear cardiology laboratories. It will cover mechanism of action, indications and patient selection, dosage, side effects, testing procedure, indications for reversal of infusion, contraindications and relative contraindications.

MECHANISM OF ACTION

Regadenoson is an A_{2A} receptor agonist (Figure 1). Regadenoson activation of this A_{2A} adenosine receptor results in coronary vasodilation and increased coronary blood flow. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes of IV administration and this is parallel to the onset of its pharmacodynamic response. The half-life of this initial phase is 2 to 4 minutes. An intermediate phase, with an average half-life of 30 minutes, coincides with the loss of the pharmacodynamic effect. The last phase consists of a decline in plasma concentration with a half-life of approximately 2 hours.

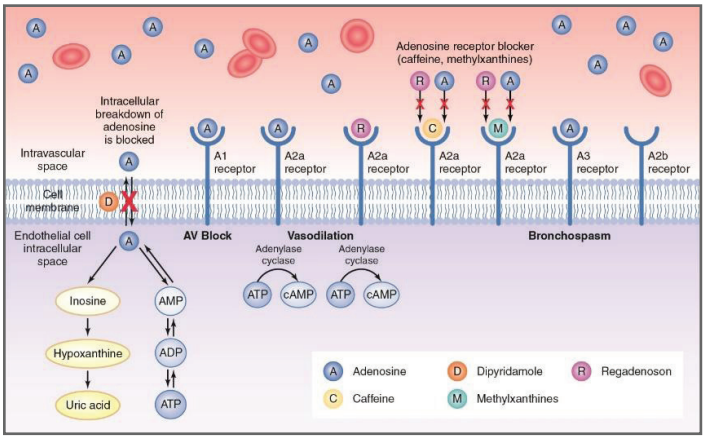


Figure 1: Mechanism of action of coronary vasodilators; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; AV, atrioventricular; and cAMP, cyclic adenosine monophosphate

INDICATIONS AND PATIENT SELECTION

The indications for the use of regadenoson is similar to that for exercise stress testing and with one or more of the following conditions:

- Inability to adequately exercise due to noncardiac physical limitations or lack of motivation
- Baseline electrocardiographic (ECG) abnormalities such as left bundle branch block (LBBB), ventricular pre-excitation (Wolff-Parkinson-White (WPW) syndrome) or permanent ventricular pacing
- Risk stratification of clinically stable patients into low- and high-risk groups after an acute myocardial infarction
- Diagnosis or risk stratification following presentation to the emergency room with a presumptive acute coronary syndrome that has been ruled out by serial cardiac serum markers, ECGs and clinical evaluation

As with exercise testing, anti-ischemic medications such as nitrates, beta blockers, calcium channel blockers have been reported to decrease the diagnostic accuracy of vasodilator stress testing.

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DOSE

The recommended intravenous (IV) dose of regadenoson is 0.4 mg (5-mL solution) and should be given as an approximately 10-second injection into a peripheral vein using a 22-gauge or larger catheter or needle. A 5-mL saline flush is administered immediately after the injection of regadenoson. The radionuclide tracer is injected 10 to 20 seconds after the saline flush using the same IV line used for the regadenoson. See Figure 2.

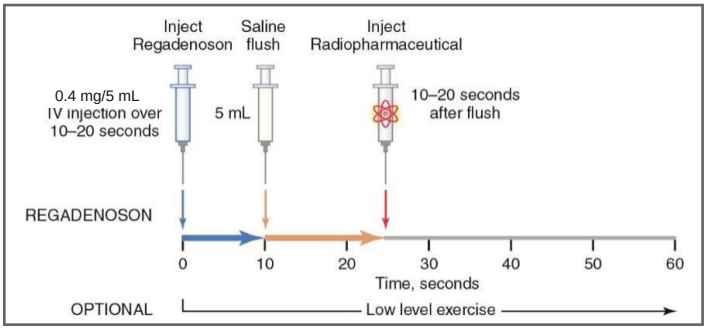


Figure 2: Regadenoson Protocol

HEMODYNAMIC EFFECTS AND SIDE EFFECTS

In clinical studies, the majority of patients had an increase in heart rate (HR) and a decrease in BP within 15 minutes after administration of regadenoson. Systolic BP decreased by 13 ± 14 mmHg and diastolic BP decreased by 10 ± 8 mmHg while the heart rate (HR) increased by 25 ± 11 bpm. Maximum hemodynamic effects after regadenoson administration were as follows:

Increase in HR of >40 bpm	5%
Decrease in systolic BP >35 mmHg	7%
Decrease in diastolic BP >25 mmHg	4%

Side effects of regadenoson include:

Common side effects	
Headaches	29%
Dyspnea	25%
Flushing	17%
Chest discomfort	11%
Chest pain	8%
Angina	8%
Dizziness	7%
Nausea	6%
Abdominal discomfort	6%
Rhythm or conduction abnormalities	
Overall	26%
First-degree AV block	3%
Second-degree AV block	0.1%
Asystole and QT interval prolongation	Reported
New onset or recurrent atrial fibrillation	Reported
New onset or recurrence of convulsive seizures	Reported
Refractory ischemia/myocardial infarction, hemorrhage and ischemic cerebrovascular accidents	Reported
Refractory ischemia and myocardial infarction	Reported

Most adverse reactions begin soon after doing and typically resolve within 15 minutes. Most headaches resolve in 30 minutes.

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

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PROCEDURE

- Patients should not eat be for at least 3 hours before to the test
- Consumption of food or beverage containing methylxanthines, or caffeine such as coffee, tea or other caffeinated beverages should be avoided. Additionally caffeine containing medications and theophylline should be avoided 12 hours prior to testing. Dipyridamole should be withheld for at least 48 hours prior to regadenoson administration.
- A 12-lead ECG should be recorded every minute after the injection.
- BP should be monitored every minute during infusion and 3 to 5 minutes into recovery or until stable.
- Regadenoson (5-mL, containing 0.4 mg of regadenoson) should be given as a rapid (~ 10 seconds) injection into a peripheral vein using a 22-gauge or larger catheter or needle.
- A 5-mL saline flush is administered immediately after the injection of regadenoson. The radionuclide tracer is injected 10-to-20 seconds after the saline flush using the same IV line.

COMBINATION OF EXERCISE AND REGADENOSON

- Patients who are ambulatory may undergo low-level exercise (e.g., treadmill 1.7 mph, 0% grade) for 90 seconds followed by regadenoson administration, tracer injection and an additional 2 minutes of exercise.
- Combination of low level exercise with regadenoson resulted in improved image quality, and was well tolerated without an increase in adverse events.
- Combination of low-level exercise with regadenoson is not recommended in patients with LBBB, WPW and ventricular pacing due to HR related imaging artifacts.
- In patients with uncertain functional capacity who do not attain their target HR during exercise stress testing, regadenoson may be used to supplement submaximal exercise stress with preserved image quality.

INDICATIONS FOR REVERSAL OF REGADENOSON

Indications for reversal of regadenoson, using 50-250mg of aminophylline intravenously at least 60 seconds after the radiotracer injection include:

Severe hypotension with systolic BP <80 mmHg
Development of symptomatic, persistent second degree or complete heart block
Other significant cardiac arrhythmia
Wheezing
Clinical evidence and/or ECG evidence of persistent ischemia.
Signs of poor perfusion (pallor, cyanosis, cold and clammy skin)

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CONTRAINDICATIONS

Patients with bronchospastic lung disease with active wheezing
Second degree AV block (Mobitz type 2) or third-degree AV block or sinus node dysfunction without a functioning pacemaker.
Sinus node disease such as sick sinus syndrome, symptomatic bradycardia without a functioning pacemaker
Systolic BP <90 mmHg. Patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericardial effusion or pericarditis, or carotid artery stenosis with cerebrovascular insufficiency may have a higher risk of serious hypotension.
Uncontrolled hypertension with systolic BP >200 mmHg and/or diastolic BP >110 mmHg
Use of dipyridamole or dipyridamole containing medications (e.g. Aggrenox) within 48 hours of testing
Known hypersensitivity to adenosine or regadenoson
Unstable angina, acute coronary syndrome, or <2-4 days after an acute myocardial infarction.

RELATIVE CONTRAINDICATIONS

Profound asymptomatic sinus bradycardia with heart rate <40 bpm.
Mobitz Type 1 second-degree AV block (Wenckebach).
Severe aortic stenosis
Ingestion of caffeinated beverages or food within the last 12 hours
Seizure disorder. Regadenoson may lower seizure threshold. Aminophylline is not recommended in cases of seizures associated with regadenoson.

Of note the seizures associated with the use of regadenoson may be either of new onset or may be recurrences. In addition, some seizures are prolonged and may require urgent anticonvulsant management.

SUGGESTED READING

Henzlova MJ, et al. ASNC Imaging Guidelines for SPECT nuclear cardiology procedures: Stress, protocols and tracers. J. Nucl Cardiol 2016;23:606-636.

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

Writing Group:
Dr. Richard Weinberg, MD, PhD
Dr. Renee Bullock-Palmer, MD

Reviewers:
Dr. Milena Henzlova, MD, PhD