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Pharmacologic Stress Testing with Myocardial Perfusion Imaging

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Abstract:

Stress testing with myocardial perfusion imaging can be performed with either physical exercise or pharmacologic methods. The preferred method is physical exercise however many patients are unable to reach an adequate endpoint. As an alternative, there are various pharmacologic optionsavailable.

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. There are many advantages physical exercise stress testing has over pharmacologic stress testing. Therefore, stress testing should be performed with exercise if an adequate endpoint can be reached. Additional information such as the patients exercise capacity, patient symptoms and their hemodynamic response to exercise is gained. Image quality is improved as there is less hepatic uptake of Tc-99m labeled tracers when injected during physical exercise. As stated in guidelines, patients should not be injected during a physical exercise stress test unless they reproduce symptoms such as SOB or CP 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 of preauthorization has resulted in the number of myocardial perfusion studies performed in the United States to decline. This guidance has more significantly reduced the number of "healthier" patients undergoing to procedure and 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 there should be 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 METS. 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. Reproducing a patients symptoms, even if under target heart rate, and if the patient reaches a level of 5 METS is an adequate stress endpoint.

With radionuclide MPI imaging, pharmacologic stress may be performed with an inotropic agent or vasodilator. Guidelines suggest vasodilators as the first option(*1*). There are currently three

vasodilators approved for MPI stress testing, dipyridamole, adenosine, and regadenoson. They are indicated for patients that are unable to reach an adequate endpoint with physical exercise stress testing. Vasodilators are adenosine receptor agonists. There are four 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 result in less desirable effects. Activation of the A_1 receptor results in decreased AV conduction. Activation of the A_{2B}, and A_3 receptors can result in bronchospasm.

DIPYRIDAMOLE

Dipyridamole was the first vasodilator used for MPI stress testing. Dipyridamole is an indirect coronary artery vasodilator. Its mechanism of action is building up adenosine in tissues by blocking the cellular reuptake of endogenous adenosine. This indirect process results in a slow onset. Dipyridamole is infused over 4 minutes, with the radiotracer injection 3-5 minutes following the completion of the dipyridamole infusion, which coincides with peak hyperemia. The dosage is 0.142 micrograms/kg/minute, or 0.57 micrograms/kg.(*2*) Patients generally have a modest increase in heart rate and a modest decrease in blood pressure. The infusion results in a 3.8-7 fold increase in coronary blood flow over baseline. Given that dipyridamole has a half-life of approximately 30-45 minutes, patients may experience side effects longer than 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 in the past 12 hours or a known hypersensitivity to dipyridamole. Relative contraindications include bradycardia (HR < 40 BPM), second or third degree AV block without a functioning pacemaker, severe aortic stenosis, or a seizure disorder.(*1*)

ADENOSINE

Adenosine is a direct coronary artery vasodilator. Adenosine acts upon the four known types of receptors. The indicated dose for adenosine is 0.14 micrograms/kg. By package insert recommendation, the drug is infused for 6 minutes with the radiotracer injection given at three minutes, or midpoint.(*3*) There is literature supporting that four-minute infusions with the radiotracer injection given at 2 minutes are as effective, with the benefit of reducing the pharmaceutical dose and the duration of side effects.(*4*) Like dipyridamole, patients generally have a modest increase in heart rate and a modest decrease in blood pressure. The infusion results in a 3.5-4 fold increase in coronary blood flow over baseline. Adenosine has a half-life of less than 10 seconds. Both the short half-life and its activation of the A_1 receptor and potential to cause heart block dictate that an infusion pump must be used to assure a sustained infusion. It is strongly recommended two IV lines be used. Should a single IV line be used, there is the potential to bolus adenosine with the radiotracer and flush, which will increase the chance of heart block. There is also the urge 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. As the adenosine half-life is very short, 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 AV block without a functioning pacemaker, sinus node disease without a functioning pacemaker, a systolic blood pressure of less than 90, uncontrolled hypertension (systolic pressure of over 200 mm/Hg or diastolic pressure of over 110 mm/Hg), caffeine in the past 12 hours, known hypersensitivity to adenosine or use of dipyridamole in the last 2 days. Adenosine is also contraindicated in patients with acute coronary syndrome, unstable angina or less than 2 days following a myocardial infarction. Relative

contraindications include bradycardia (HR < 40 BPM), Mobitz Type I (Wenckebach), caffeine within 12 hours, 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 ten times greater infinity for the A_{2A} receptor comparted to the A_1 receptor and little to no affinity for the A_{2B}, and A_3. Regadenoson is infused over 10 seconds. The dosing is not weight based like the other available vasodilators. All adult patients receive 0.4 mg, which is only available in a prefilled 5 ml syringe. The regadenoson dose is immediately followed by a saline flush. Ten to twenty seconds later, the radiotracer is administered 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 minutes. The half-life of regadenoson is triphasic. The first phase is 2-4 minutes, the intermediate phase is approximately 30 minutes and coincides with loss of effect, and the terminal elimination phase is approximately 2 hours 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 AV block without a functioning pacemaker, sinus node disease without a functioning pacemaker, a systolic blood pressure of less than 90, uncontrolled hypertension (systolic pressure of over 200 mm/Hg or diastolic pressure of over 110 mm/Hg), a known hypersensitivity to adenosine or regadenoson or use of dipyridamole in the last 2 days. Regadenoson is also contraindicated in patients with acute coronary syndrome, unstable angina or less than 2 days following a myocardial infarction. Relative contraindications include bradycardia (HR < 40 BPM), Mobitz Type I (Wenckebach), caffeine within 12 hours, 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 twelve hours prior to testing as they may lead to false negative results. Caffeine is commonly offered to patients following 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. As habitual caffeine drinkers hold their caffeine for the stress testing procedure, they will often have headaches and will benefit 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 one minute following radiotracer administration to preserve the sensitivity of the procedure. Typical dosing is 50 mg to 250 mg by slow intravenous injection over 30–60 seconds. Recent safety data suggests that methylxanthines not be used in patients who have a seizure related to vasodilator administration.(*3,5*)

Dobutamine is an inotropic option for myocardial perfusion stress testing. Dobutamine is not FDA 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, it is indicated for patients who cannot reach and adequate endpoint with exercise stress testing and have a contraindication to vasodilators. Dobutamine is a beta adrenergic agent that results in direct β_1 and β_2 stimulation. It is administered as anincremental infusion beginning at 5 or 10 micrograms/kg/minute for three minutes. It is increased to 20, 30, then 40 micrograms/kg/minute also for three-minute intervals for a maximum of 12 minutes or until the target heart rate is reached. Atropine may be given in

increments of .25 to .5 mg (up to 1-2 mg total) in addition if target heart rate is not reached with dobutamine alone.[1] The half-life of dobutamine is less than 3 minutes.(*6*) If necessary, a short acting beta-blocker, such as esmolol, can be administered as a reversal agent if necessary.

An infusion pump must be used for the infusion. Two separate IV lines or one with a Y-connector should be used to allow an uninterrupted flow of dobutamine to be infused during the radiotracer injection as well as to prevent a bolus of dobutamine.

Dobutamine is contraindicated in patients with unstable angina, acute coronary syndrome, less than 2 to 4 days after an acute myocardial infarction, hemodynamically significant left ventricular outflow tract obstruction, atrial tachyarrhythmias with uncontrolled ventricular response, prior history of ventricular tachycardia, uncontrolled hypertension (systolic BP > 200 mmHg or diastolic BP > 110 mm Hg), patients with aortic dissection, and known hypersensitivity to dobutamine. Relative contraindications include patients who are on beta-blockers where the heart rate and ionotropic responses will be attenuated, severe aortic stenosis, patients with a symptomatic or large aortic aneurysm, 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 including prognostic information gained from exercise.(*7,8,9*) There may be two components to the reduced side effects. The physical exercise may lessen the drop on 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 Tc-99m labeled myocardial perfusion tracer uptake in the liver. As a result, it is less likely to require a rescan a patient due to extracardiac activity. In fact, images can be acquired earlier, as they are with exercise stress protocols.

Although protocols slightly vary, often with adenosine and regadenoson, the patient undergoes low-level exercise (1.0-1.7 miles/hour) during the pharmacologic infusion and continuing until 1-2 minutes following the radiotracer administration. With dipyridamole, shortly following the four-minute infusion, the patient undergoes low-level exercise (1.0-1.7 miles/hour) until 1-2 minutes following the radiotracer administration.

Despite proper screening and conversation with patients, some will attempt physical exercise but not reach and adequate endpoint. Exercise should be aborted in these patients with conversation to pharmacologic stress. Recent data suggests that regadenoson stress can safely be performed three minutes following inadequate exercise. The most common events were similar in type and incidence for subjects stressed 3 minutes following inadequate exercise versus those stressed one hour following inadequate exercise.(*10*) It has been documented that the likelihood of a left bundle branch artifact, reduced 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*)

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.

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PHARMACOLOGIC AGENT	CLASS	MECHANISM OF ACTION	DOSE	DURATION	INFUSION PUMP REQUIRED	HALF LIFE	INCREASE IN CORONARY FLOW	INCIDENCE OF AV BLOCK (vasodilators)
ADENOSINE	Direct coronary artery vasodilator	Non-selective adenosine receptor agonist	140 µg/kg/min (up to 125 kg)	6 minutes with radiopharmaceutical injection at 3 minutes	Yes	< 10 seconds	3.5 – 4 times baseline	8% of studies
DIPYRIDAMOLE	Indirect coronary artery vasodilator	Non-selective adenosine receptor agonist	142 µg/kg/min (up to 125 kg)	4 minute infusion with radiopharmaceutical injection at 3-5 minutes post	No	30-45 minutes	3.8 – 7 times baseline	2% of studies
REGADENOSON	Direct coronary artery vasodilator	Selective A_{2A} receptor agonist	400 µg	10 second infusion with radiopharmaceutical injection 20-30 seconds post	No	Initial phase 2-4 min Intermediate phase 30 min Terminal phase 2 hours	2.5 times baseline	3% of studies
DOBUTAMINE	Inotropic agent	direct β_1 and β_2 stimulation	3 minute incremental stages 10, 20, 30, 40 µg/kg/min	Until THR or a 12 minutes maximum is reached	Yes	< 3 minutes	2-3 times baseline	N/A