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Title: Considerations for Stress Testing Performed in Conjunction with Myocardial Perfusion Imaging

Short running title: Considerations for Stress Testing

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Abstract:

When performing myocardial perfusion imaging (MPI) *(1-8),* the best test to evaluate hemodynamic changes during stress is an exercise treadmill test. It provides independent prognostic value including evaluation of total exercise time, performance and capacity, heart rate response during exercise, with ischemia, and in recovery, blood pressure response, myocardial oxygen demand and assessment of symptoms. Combining these exercise data with perfusion imaging provides the best prognostic value and risk stratification for patients.

While exercise stress testing accompanied with MPI is preferential, it is not always possible since an increasing number of patients are unable to exercise to a maximal (symptom limited) level. Further, there is much evidence in the literature demonstrating a sub-optimal, non-symptom limited (not achieving at least 4-6 minutes or < 85% of MPHR) exercise test performed as part of a MPI study may result in a false negative outcome. Therefore, pharmacologic stress agents provide an excellent alternative for those patients who are unable to achieve adequate heart rate response or adequately perform physical exercise.

This article was prepared to focus on considerations for performing stress (exercise and pharmacologic) testing in conjunction with MPI. It is meant to: 1) provide a basic overview of the principles of exercise stress testing, 2) discuss indications, contraindication, patient preparation and protocols for exercise stress testing, 3) discuss the contraindications administration protocols and side effects for performing vasodilator (adenosine, dipyridamole and regadenoson) stress testing and 4) discuss the contraindications, administration protocols, and side effects for performing dobutamine stress testing.

Key Words: Stress testing, exercise, dipyridamole, adenosine, regadenoson, dobutamine

When performing myocardial perfusion imaging, the best test to evaluate hemodynamic changes during stress is an exercise treadmill test *(1-8).* It provides independent prognostic value including evaluation of total exercise time, performance and capacity, heart rate response during exercise, with ischemia, and in recovery, blood pressure response, myocardial oxygen demand and assessment of symptoms. Combining these exercise data with perfusion imaging results is the best prognostic value and risk stratification for patients.

PRINCIPLES OF EXERCISE TESTING

Performing stress testing on individuals is a commonly used method to determine and assess the performance of the body and heart *(1-2,6).* When measuring engine performance, one may consider horsepower (the amount of work done) and fuel consumption (liters of gas consumed) as end-points. Similarly, in humans, performance can be measured as fuel consumption in terms of the amount of oxygen consumed (1,6). The two end-points used to measure oxygen consumption are External Work rate [Total Body Consumption (VO_2)] and Internal Work rate [Myocardial Consumption (MVO_2)].

VO_2 is a measure of volume (V) of oxygen (O_2) consumed by the body, also known as maximal oxygen uptake and reported as VO_{2max} *(1,6).* It is defined as the measurement of the maximum amount of oxygen a person can consume (metabolize) during physical exercise. VO_2 is measured by calculating Cardiac Output x A-V O_2 Differential (table 1). Normal $V0_2$ values are 35 to 40 mL/kg/min for sedentary males and 27 to 30 mL/kg/min for sedentary females. It is commonly used to measure aerobic endurance of athletes during their course of intensive training.

Cardiac output is defined as the volume of blood the heart pumps per minute *(1,6).* It is calculated by multiplying stroke volume by heart rate (Cardiac Output = Heart Rate x Stoke Volume) (table 1). Normal cardiac output in health patients ranges from 4.0 – 8.0 ml/min. Stroke volume is the amount of blood pumped from the left ventricle per beat and is determined by preload, contractility, and

afterload of the myocardium. It is calculated by subtracting end-systolic volume (ESV) from end-diastolic volume (EDV) (table 1). In healthy patients, standard normal values are 60 – 100 ml. A higher exercise tolerance results in a higher stroke volume providing a better VO_2 measurement. A-V O_2 differential is the measurement of arteriovenous (A-V) oxygen (O_2) difference (table 1) *(1,6)*. It is defined as the difference in the oxygen content between the arterial blood and the venous blood, and it is used to measure the amount of oxygen removed from the blood in capillaries as the blood circulates in the body. Normal value for A-V O_2 differential is 4.5 mL/100 mL/min.

Myocardial oxygen consumption (MVO_2) is equal to coronary blood flow multiplied by the arterial-venous oxygen difference (A-V O_2) *(1,6)*. During diastole, the ventricles receive blood before the systolic contraction occurs. This filling phase of the cardiac cycle allows the coronary arteries to provide maximum blood flow to the heart. MVO_2 consumption may also be calculated using heart rate x systolic blood pressure, which is referred to as rate pressure product (table 1) *(1,6)*. Normal MVO_2 is 30 to 35ml/min for an average sized (~300g) healthy heart.

During exercise testing, systolic blood pressure is expected to go up along with oxygen consumption. Systolic pressure equals flow x resistance of the vessels as cardiac output is increasing and peripheral resistance is decreasing. In healthy individuals, systolic blood pressure should increase during exercise in order to maintain an adequate cardiac output. A fall in blood pressure during exercise means a leveling or decrease in cardiac output. This decrease may be indicative of coronary artery disease (CAD). Therefore, an increase in systolic blood pressure is normal during exercise and a decrease may be indicative of a poor prognosis and outcomes *(1-2,6).*

Heart rate response to stress is also an important measure during exercise testing. Heart rate should increase during exercise, and patients should be able to achieve at least 85% of their maximum predicted heart rate (MPHR) *(1-2,6-8).* The MPHR should be calculated by subtracting the patient age from 220 (table 1) *(1-2,6-8)*. However, since the MPHR measure at the 95% confidence limit is 45 beats per

minute (bpm) (MPHR for a 60 year old patient ranges from 137 – 182 bpm making it difficult to accurately determine 85% MPHR target heart rate), it is important to always perform a symptom limited exercise test rather than use 85% MPHR achievement as a sole reason for termination of testing.

It is important to monitor heart rate recovery following exercise testing. Heart rates that are slow to respond back to baseline during recovery may be indicative of chronotropic incompetence. Chronotropic incompetence is the inability of the heart to adequately respond to increased demands during exercise, and also results in the heart's inability to recover from this demand post *exercise (1,6).* It most often occurs in patients with CAD and congestive heart failure (CHF), resulting in exercise intolerance and may impair quality-of-life. It is considered an independent predictor of risk for major adverse complications and cardiac events [death and myocardial infarction (MI)] in patients with CAD. In addition to chronotropic incompetence, low heart rates during stress may indicate large cardiac dimensions commonly seen is athletes who perform routine intense training. This condition does not present concern for future cardiac events, and is considered normal in those patients *(1-2,6).*

Metabolic equivalent (MET) is another measure achieved and recorded during exercise testing. One MET is equal to ~3.5ml Oxygen/Kg body weight/min^2 *(1,6).* It is well established most healthy, sedentary people seldom exercise beyond 10 to 11 METs *(1-2,6).* Further, in most patients with CAD, workloads of 8 METs are sufficient for angina evaluation. This measure is also used to determine functional classes of patients and assist with determination of treatment options *(1-2,6-8).* Class I is defined as patients able to exercise beyond 7 or 8 METs, Class II- patients becomes symptom-limited at 5 or 6 METs and Class III- patients usually becomes symptom-limited at 3 to 4 METs.

Exercise testing is a valid cardiac measure of performance and capacity. The heart extracts approximately 70% of the oxygen in the blood at rest, and increasing the extraction rate cannot significantly increase the delivery of oxygen. Therefore, coronary blood flow must increase in order to increase the myocardial oxygen supply *(1-2,6-8).* In healthy people, coronary blood flow increases

proportionally to the increased demand for oxygen by the myocardium. Myocardial ischemia is caused when coronary blood flow is unable to meet the demand for oxygen resulting in symptoms such as angina (chest pain) and shortness of breath. During an exercise test, ischemia may manifest itself as anginal pain, S-T segment/T-wave changes, ventricular dysfunction, arrhythmias or any combination of these findings *(1-2,6).*

PERFORMING AN EXERCISE STRESS TEST

Preparations, Indications and Contraindications

Standard stress protocols including patient preparation should be performed in compliance with American College of Cardiology (ACC)/American Heart Association (AHA)/American Society of Nuclear Cardiology (ASNC) guidelines for stress testing. Preparation includes having the patient fast [nul per os (NPO)] 3 hours and caffeine withheld for 12 hours prior to testing *(2-3,6-8).* In addition, a larger bore (> 24 gauge) intravenous (IV) cannula should be inserted and leads for 12-lead electrocardiogram (ECG) monitoring should be placed. Some cardiac medications have been demonstrated to diminish the diagnostic accuracy of exercise testing. However, some physicians may order the procedure to evaluate the efficacy of these medications in some patients *(3,6).* Therefore, discontinuation of cardiac medications should be at the discretion of the referring physician.

When performing stress tests in conjunction with MPI, it is necessary to have at least two qualified individuals present during the procedure, one person to monitor the patient and the other individual to perform the injection of the radiotracer *(3,6-8).* There are several reasons to perform an exercise stress test. However, standard clinical indications for testing include but are not limited to: 1) evaluation of patients with chest pain or other findings suggestive of coronary artery disease (CAD)**,** 2) determination of prognosis and severity of disease, 3) evaluation of effects from medical and surgical therapy, 4)

screening for latent CAD (only approx. 30% of pts. with ischemia have chest pain) and 5) evaluation of arrhythmias, functional capacity or congenital heart disease *(1-3,6-8).* More specifically, common clinical indications for stress MPI include but are not limited to: 1) diagnosis of suspected CAD, 2) risk stratification of known CAD, 3) assessment of medical or surgical therapies used to treat known CAD, 4) pre-operative assessment in patients with cardiac symptoms and 5) myocardial viability assessment *(2-3,6-8).*

Prior to an exercise test being performed, it is necessary to ensure the patient has no known contraindications for test performance. These contraindications are categorized into 2 types, relative and absolute. A relative contraindication refers to a clinical situation in which the test may be performed however, caution should be taken. These clinical situations include: 1) clinically significant non-cardiac disorders, 2) significant physical handicaps, 3) debilitated or elderly patients, 4) mentally unstable or uncooperative patients, 5) severe anemia or high fever, 6) moderate to severe hypertension, 7) pulmonary hypertension, 8) moderate aortic stenosis, 9) known significant left main disease, 9) asymptomatic severe aortic stenosis 10) other serious heart diseases, 11) tachy-arrhythmias, 12) brady-arrhythmias, and 13) if performed in conjunction with imaging, left bundle branch block (LBBB), permanent pacemaker or ventricular pre-excitation *(1-3,6-8).*

Absolute contraindications refer to clinical situations in which an exercise test should not be performed. These clinical situation include: 1) acute myocardial infarction (within 2 to 4 days), 2) unstable or crescendo angina, 3) serious cardiac arrhythmias, 4) acute myocarditis/pericarditis, 5) severe aortic stenosis, 6) acute or severe congestive heart failure, 7) cardiogenic shock, 8) acute pulmonary embolism/infarction, 9) aortic dissection, 10) any acute or serious non-cardiac disorder, 11) severe hyper/hypo tension, and 12) severe physical handicaps *(1-3,6-8).*

Protocols

There are various typed of protocols used to perform physical exercise tests including, Bruce, Modified Bruce, Naughton and Chung *(1-3,6-8).* Some practitioners may also decide to perform a manual test (customized at time of text for speed/grade/tine per stage and not automated) if there is a specific clinical scenario or situation they would like to reproduce or evaluate. However, performing a manual test should be performed in very limited situations and with extreme caution since there are no documented specific end-points for reference or comparison.

When performing MPI, the Bruce protocol is routinely performed in most laboratories (table 2). It is the recommended protocol for use in conjunction with MPI in various guidelines and is well validated in the published literature *(1,6-8).* During the procedure and as recommended in the guidelines, it is necessary to measure and document patient's heart rate and blood pressure at approximately two minutes into every stage, at peak exercise, and for at least 4 minutes into recovery phase. *(1-3,6-8).* The ECG should be monitored continuously during the test and for at least 4 minutes into the recovery phase, and recorded during each stage of exercise, at peak exercise, termination of recovery phase, and in cases of any abnormalities *(1-3,6-8).* The radiotracer should be injected as close to peak exercise as possible and approximately 1 minute prior to when the patient is no longer able to continue.

The end point of exercise should be symptom limited (moderate to severe chest pain, excessive shortness of breath, fatigue). The achievement of 85% MPHR, is not considered a sole indication for termination of the test *(3).* Of note, in patients with known CAD, and more specifically if the test is being performed for evaluating symptom management of medical therapies, the prognostic value of the test is preserved without reaching 85% MPHR *(3).* If patients are known to have limitation to exercise capacity, a modified Bruce protocol may be considered as an alternative (table 3).

Termination of Testing

As discussed earlier, during a MPI study, the radiotracer should be injected as close to peak exercise as possible and approximately 1 minute prior to when the patient is no longer able to continue. There are

however, several reasons to consider early termination of the exercise. The first and ***most important*** reason is the patient indicates the need to stop. Other reasons for termination of the test may include but is not limited to: 1) atrial tachycardia, atrial fibrillation, atrial flutter, 2) onset of 2nd or 3rd degree heart block, 3) progressive anginal pain, 4) severe ST depression (>3 mm), 5) ST elevation of >2 mm in precordial or inferior leads that do not have a resting Q wave, 6) development of pre-ventricular contractions (PVCs) in pairs or with increasing frequency as exercise increases, or when ventricular tachycardia develops (runs of 3 or more PVCs), 7) heart rate or systolic blood pressure drops progressively, 8) dyspnea, fatigue, faintness, 9) severe musculoskeletal pain, 10) extreme elevations in systolic or diastolic blood pressure associated with headache or blurred vision, 11) malfunctioning equipment, 12) uninterruptable ECG tracing, and 13) leads not being detected *(1-3,6-8).*

VASODILATOR AND IONOTROOPIC STRESS TESTING

While exercise stress testing accompanied with MPI is preferential, it is not always possible since an increasing number of patients are unable to exercise to a maximal level. Further, there is much evidence in the literature demonstrating a sub-optimal, non-symptom limited (not achieving at least 4-6 minutes or < 85% of MPHR) exercise test performed as part of a MPI study may result in a false negative outcome *(1,6-8).* Therefore, pharmacologic stress agents provide an excellent alternative for those patients who are unable to achieve adequate heart rate response or adequately perform physical exercise. Patient preparation, monitoring and clinical indications are similar to those for an exercise stress test.

Adenosine

Adenosine is a commonly used pharmaceutical for stress testing performed in conjunction with MPI. It is a potent coronary arteriolar vasodilator that acts by directly activating adenosine receptors on cell membrane surfaces. Adenosine occurs naturally in the body and induces vasodilation through specific

activation of the A2A receptor. During infusion, adenosine causes blood flow rates 4 -6 times resting blood flow. Peak vasodilation occurs at 1-2 minutes of continuous infusion, and adenosine has a 10 second half-life. In areas of the myocardium supplied by stenotic arteries, an attenuated hyperemic response can occur. Depending upon the coronary flow reserve limitations and severity of coronary stenosis, a relative fluctuation in flow may be induced. Similar to dipyridamole, adenosine used in conjunction with MPI is well validated in the literature *(3,6-9).*

Generally, adenosine does not cause myocardial ischemia as the myocardial blood flow increases to all coronary artery vascular beds with minimal or no rate increase in rate pressure product or myocardial oxygen demand. In a small percentage of patients with severe coronary artery disease, true ischemia may be induced due to coronary steal phenomenon. Coronary steal is an iatrogenic condition which is characterized by shunting of well oxygenated blood from a critical area of low perfusion, to an area of higher perfusion. Since tracer uptake in the myocardium is proportional to the regional myocardial blood flow, a heterogeneous distribution of radiotracer occurs in the myocardium when coronary steal occurs *(3,6-9).*

Adenosine is utilized in patients with baseline ECG abnormalities such as a LBBB, ventricular pacing, and Wolff-Parkinson-White syndrome. It is also employed with patients who are clinically stable and are less than 1-day following an acute MI but who are otherwise clinically stable and for patients who present in the emergency department following acute coronary syndrome *(3,6-9).* Adenosine is also used with patients who are not only unable to exercise due to pulmonary, peripheral vascular, musculoskeletal and mental conditions but also with patients who are unwilling to exercise. As with exercise stress testing, beta-blockers, nitrates and calcium antagonists have been reported to decrease accuracy in diagnosis with use of vasodilators prior to stress testing *(3,6-9).*

Contraindications for adenosine stress tests include: 1) second or third degree atrioventricular block in the absence of a pacemaker or sick sinus syndrome, 2) consumption of caffeine or aminophylline within 12 hours of administration, 3) systolic blood pressure less than 90 mm Hg, 4) recent use of dipyridamole or dipyridamole containing medications (i.e., Aggrenox™), 5) known hypersensitivity to adenosine, 6) unstable acute myocardial infarction or acute coronary artery syndrome, and 7) prior cardiac transplantation. Active wheezing and bronchospasm are clinical situations for which adenosine use is considered an absolute contraindication *(3,6-9).* However, there have been reports of patients, with adequately controlled asthma receiving adenosine after being pre-treated with 2 doses of albuterol or a comparable inhaler *(6-8).* Sinus bradycardia with a heart rate of less than 40 beats per minute is considered another relative contraindication for adenosine use.

Administration and Protocol

Adenosine is administered intravenously via an infusion pump over a 4 - 6 minutes period at a rate of 140 ug/kg/min. Due to the very short half -life of adenosine (10 seconds); the radiotracer is injected during the infusion of the adenosine (figure 1) *(3,6-9).* If a 4-minute protocol is being used, the radiotracer should be injected at 2 minutes, and a 6-minute protocol, at 3 minutes. Adenosine is supplied in 20mL and 30mL single-dose vials of 3mg/ml. To calculate the volume of adenosine to be drawn, the patient weight must be converted into kilograms (patient weight in pounds/2.2 = kilograms). This weight in kilograms is necessary to calculate the dose amount (ml) needed for infusion [(kg x 0.14 mg/kg) x 6 minutes/3.0 mg/mm = ml]. If a 4-minute protocol is being used, the time in the dose calculation should be changed accordingly *(3,6-9).*

In order to obtain additional data and improve image quality, patients who are ambulatory and do not have a LBBB or paced ventricular rhythm may walk on the treadmill at 1.7mph with 0% elevation during the adenosine infusion. When performing this protocol, the radiotracer should be administered at

2 minutes of walking (4-minute protocol) or 3 minutes of walking (6-minute protocol). Following injection of the radiotracer, patients should continue walking for an additional 2 minutes to allow for adequate vasodilation and uptake of the tracer *(3,6-9).*

During administration of adenosine, early termination should occur if any of the following clinical situation are present: 1) severe hypotension, 2) severe chest pain with ST depression of 2mm or greater, 3) complete heart block, 4) symptomatic second-degree heart block, 5) signs of poor perfusion, 6) upon patient request and 6) wheezing *(3,6-9).* In the event the patient has a seizure, adenosine infusion must be terminated immediately. Aminophylline should not be administered in this situation as it may increase seizure risk associated with adenosine. Methylxanthine use is also not recommended in patients who experience seizures in association with adenosine administration *(3,6-9).*

A large number of patients (80%) who receive adenosine may experience adverse reactions. However, since adenosine has a very short half-life (10 seconds), reversal methods are rarely needed because side effects dissipate within a few seconds of the infusion being terminated. Common reactions include: 1) flushing, 2) chest discomfort, 3) dyspnea, 4) headache, 5) dizziness, 6) throat or jaw discomfort, and 7) gastrointestinal discomfort *(3,6-9).* Atrioventricular blocks have been demonstrated to occur in 7.6% of patients but rarely require termination of the adenosine infusion. ST-segment depression may occur in 5 to 7% of the patients, and is indicative of coronary artery disease. Fatal and non-fatal MI are rare but have also been demonstrated to occur during administration of adenosine. If persistent symptoms or other clinical situations occur, aminophylline may be administered in a dose of 50 to 250 mg through a slow (50 to 100 mg over 30 to 60 seconds) IV injection *(3,6-9).*

Dipyridamole

Dipyridamole has the longest history of use of all the vasodilators and has the most data available in the literature related to MPI. It is a potent coronary vasodilator that acts by blocking intracellular reuptake and deamination of natural adenosine within the body *(3,6-8,10).* After the infusion of dipyridamole, the level of intrinsic adenosine is increased which causes vascular smooth muscle relaxation and coronary dilation. Blood flow is increased 3 - 5 times above baseline levels in normal coronary arteries. In the instance of coronary stenosis, blood flow may be restricted which would result in a decrease of tracer uptake in the area of the myocardium that correlates to the specific coronary artery territory. The half-life of dipyridamole is 30 to 45 minutes *(3,6-8,10).*

Dipyridamole is utilized in patients with baseline ECG abnormalities such as a LBBB, ventricular pacing, and Wolff-Parkinson-White syndrome. It is also employed in patients who are clinically stable and are less than 1-day following an acute MI and for patients who present in the emergency department following acute coronary syndrome. It is also used in patients who are not only unable to exercise due to pulmonary, peripheral vascular, musculoskeletal and mental conditions but also with patients who are unwilling to exercise. As with exercise stress testing, beta-blockers, nitrates and calcium antagonists have been reported to decrease accuracy in diagnosis with use of vasodilators in stress testing *(3,6-8,10).* The contraindications for dipyridamole include: 1) second and third degree atrioventricular block in the absence of a pacemaker or sick sinus syndrome, 2) consumption of caffeine or aminophylline within 12 hours prior to administration, 3) systolic blood pressure less than 90 mm Hg, 4) asthma with wheezing and 5) sinus bradycardia with a heart rate of less than 40 beats per minute *(3,6-8,10).*

Administration and Protocol

Dipyridamole is administered via infusion pump at 0.56mg/kg over a 4-minute period (142.0 ug/kg/min). It may also be administered manually through an IV at a rate of 10mL/min when a 40mL volume is utilized. The radiotracer is injected at 3 to 5 minutes post infusion (figure 2) *(3,6-8,10).* Low-level exercise performed in conjunction with dipyridamole has been demonstrated to decrease side effects and radiotracer uptake in non-target organs resulting in higher quality images. Patients who are ambulatory and do not have a LBBB or paced ventricular rhythm may walk on the treadmill at 1.7mph with 0% elevation for 4-6 minutes at the completion of the dipyridamole infusion. During this time the radiotracer should be injected (3-5 minutes post dipyridamole infusion) and the patient should walk an additional 2 minutes post injection to ensure adequate tracer uptake in the myocardium. Other suggested protocols for performing exercise in conjunction with dipyridamole include completion of a standard Bruce protocol following infusion. Like any other new or different procedure, a thorough investigation and research should occur prior to performing such protocols within the lab to ensure efficacy and safety to patients *(3,6-8,10).*

Common side effects of dipyridamole include: 1) flushing, 2) chest pain, 3) headache, 4) dizziness, 5) hypotension (~50% of patients), and 6) atrioventricular block (~2% of the patients). Side effects following dipyridamole may persist 15 to 25 minutes post infusion and may vary significantly from patient to patient. Patients may also experience a slight increase in heart rate and a modest decrease in both systolic and diastolic blood pressures. In patients with persistent side effects or clinical symptoms, aminophylline (125 to 250mg) may be administered intravenously 2 minutes post injection of the radiotracer. Aminophylline should also be injected if post-ischemic ECG changes occur. In patients who experience chest pain during or post infusion of dipyridamole and administration of aminophylline does not alleviate it, sublingual nitroglycerin at 0.4mg every 5 minutes for a total of 3 doses, may also be given (3,6-8,10). Early

termination of dipyridamole should occur in the instance of severe hypotension, severe chest pain with ST depression of 2mm or greater, complete heart block, symptomatic second-degree heart block, signs of poor perfusion, upon patient request, and in the event that the patient begins wheezing *(3, 6-8,10).*

Regadenoson

Regadenoson is an A2A agonist which causes vasodilation by activating the A2A receptors and increasing coronary blood flow in the same manner as adenosine and dipyridamole. Within 1 to 4 minutes post administration of regadenoson, the maximal plasma concentration is reached. Regadenoson has three half-lives. The initial phase is approximately 2 to 4 minutes and includes the onset of the pharmaco-dynamic response. The intermediate phase, with a half-life of approximately 30 minutes, coincides with the loss of the pharmaco-dynamic effect. The terminal phase has a half-life of around 2 hours and consists of a decline in plasma concentration *(3,6-8,11).*

Regadenoson is utilized in patients with baseline ECG abnormalities such as a LBBB, ventricular pacing, and Wolff-Parkinson-White syndrome. It is also employed with patients who are clinically stable and are less than 1-day following an acute MI and for patients who present in the emergency department following acute coronary syndrome. It is also used in patients who are not only unable to exercise due to pulmonary, peripheral vascular, musculoskeletal and mental conditions but also in patients who are unwilling to exercise. As with exercise stress testing, beta-blockers, nitrates and calcium antagonists have been reported to decrease accuracy in diagnosis with use of vasodilators in stress tests *(3,6-8,11).*

Contraindications for regadenoson stress testing include: 1) second or third degree atrioventricular block in the absence of a pacemaker or sick sinus syndrome, 2) consumption of caffeine within 12 hours of administration, 3) asthma with wheezing, 4) use of aminophylline with 24 hours, 5) systolic blood pressure less than 90 mm Hg, 6) recent use of dipyridamole or dipyridamole containing medications (i.e., Aggrenox™), 7) known hypersensitivity to adenosine, 8) unstable acute myocardial

infarction or acute coronary artery syndrome, 9) known hypersensitivity to regadenoson, and 10) sinus bradycardia with a heart rate of less than 40 beats per minute.

Administration and Protocol

Regadenoson is supplied as a single-use pre-filled syringe with a standard dose of 0.4mg/5mL (0.08 mg/mL). It should be administered intravenously over 10 second, immediately followed by a 5mL flush of normal saline. Twenty seconds post regadenoson administration, the radiotracer should be injected (figure 3) *(3,6-8,11).*

Exercise stress may be performed in conjunction with regadenoson in those patients unable to reach adequate (symptom limited) stress or 5-6 MET of exertion. However, exercise should be avoided in patients with a LBBB or paced ventricular rhythm. If exercise is performed in conjunction with regadenoson, a protocol should be chosen based on the patient's physical capabilities. Regadenoson should be injected following the standard protocol described above, and exercise should be terminated when the patient has become symptom limited and unable to continue *(3,6-8,11).*

Following regadenoson injection, if a patient experiences severe hypotension, severe chest pain with ST depression of 2mm or greater, complete heart block, new-onset atrial flutter or atrial fibrillation, symptomatic second degree heart block, signs of poor perfusion, or begins wheezing, administration of aminophylline (50 to 250 mg via intravenous injection of 50 to 100mg over 30 to 60 seconds) should be considered. In the event that the patient has a seizure, aminophylline should not be administered due to the increase seizure risk associated with regadenoson and its known risk to lower seizure threshold in certain patients *(3,6-8,11).* Common side effects of regadenoson include: 1) dyspnea, 2) headache, 3) flushing, 4) chest discomfort, 5) angina pectoris (chest pain) and 6) ST segment depression.

Adverse reactions associated with regadenoson are usually mild and resolve within 15 to 30 minutes post infusion. Headaches have been demonstrated to last the longest of all known side effects without treatment. If side effects persist, administration of aminophylline (50 to 250 mg via intravenous injection of 50 to 100mg over 30 to 60 seconds) should be considered. Approximately 3% of patients experience first-degree atrioventricular block with 0.1% experiencing second-degree atrioventricular block. In clinical trials of regadenoson, these rhythm changes did not need to be reversed. Hemorrhagic and ischemic cerebrovascular accidents have also been demonstrated to occur in some patients receiving regadenoson *(3, 6-8,11).*

Dobutamine

Dobutamine is primarily utilized for patients unable to exercise and who have contraindications to vasodilators used in conjunction with MPI. Dobutamine, unlike adenosine, dipyridamole, and regadenoson, is not a vasodilator. Dobutamine is a positive inotrope, resulting in direct B1 and B2 stimulation and has a half-life of approximately 2 minutes. Infusion of this agent results in a dose-related increase in heart rate, blood pressure and myocardial contractility which based on the principles of coronary flow reserve, increases regional myocardial blood flow. Similarly, subepicardial and subendocardial blood flow in vascular beds supplied by normal coronary arteries is increased and is dose-related. The increase of blood flow to vascular beds supplied by stenosed arteries is minimal with the majority of increase occurring within the sub-epicardium. This discrepancy in blood flow allows for the evaluation of myocardial ischemia when used in conjuntion with MPI *(3,6-8,12).*

The contraindications for dobutamine infusion include:1) MI less than one week, 2) unstable angina, 3) prior history of tachycardia, atrial tachyarrhythmia or uncontrolled ventricular response, 4) severe aortic stenosis, 5) significant left ventricular outflow tract obstruction, 5) severe hypertension and 6) significant aneurysm or dissection. Patients should not receive dobutamine if they are being treated with

beta-blockers (within 48–72 hour) or have a LBBB, permanent pacemaker or Wolfe-Parkinson White syndrome because a false positive result may occur.

Administration and Protocol

Dobutamine should be infused intravenously at a dose rate of 5-10 mcg/kg/min, and increased every 3 minutes to 20, 30 and 40 mcg/kg/min, respectively. The dose increase should be determined by the patient's heart rate and physical response to the medication. Target end-point for dobutamine is for the patient to achieve at least 85% of the patient's MPHR. Once this target is achieved, the radiotracer should be injected and dobutamine infusion terminated (figure 4) *(3,6-8,12).* If the patient does not reach target heart rate, administration of atropine or arm/leg exercises should be considered in order to increase heart rate. Following an attempt of either or both of these considerations, termination of the protocol should be considered if target heart rate in not achieved in order to avoid a false negative result *(3,6-8,12).*

Early termination of the dobutamine infusion should occur for ventricular tachycardia or ST-segment depression, which is more likely to occur with dobutamine than the other pharmacologic stress agents. Other indications for early termination include: 1) moderate to severe angina, 2) decrease in systolic blood pressure of greater than 20 mm Hg from baseline blood pressure when accompanied by other evidence of ischemia, 3) upon patient request, 4) signs of poor perfusion, 5) hypertensive response, 6) increasing chest pain, 7) ST or QRS changes, 8) development of a bundle branch block or intraventricular conduction delay not able to be differentiated from ventricular tachycardia, 9) ST elevation in leads without diagnostic Q waves, and 10) marked dyspnea *(3,6-8,12).*

Approximately 75% of patients have been demonstrated to experience an adverse reaction during infusion of dobutamine. The most common side effects are palpitations, chest pain, headache, flushing, dyspnea, and significant supraventricular or ventricular arrhythmias. Also, 1/3 of patients have been

demonstrated to experience ischemic ST-segment depressions. Side effects may be treated with a short acting beta-blocker administered intravenously over one minute *(3,6-8,12).*

CONCLUSION

Stress testing has been used for over 60 years in the evaluation of symptomatic patients (3). Both exercise and pharmacologic stress (vasodilator and ionotropic) are performed routinely in conjunction with single photon emission computer tomography (SPECT) and positron emission tomography (PET) MPI. Suboptimal or inadequate stress testing may lead to a false negative MPI and poorly impact clinical decision making and patient outcomes *(3,6-8).* Therefore, it is imperative technologists are well educated regarding the considerations for stress testing used in conjunction with MPI including; principles, indications, contraindication, patient preparation and protocols for exercise stress testing, contraindications, administration protocols and side effects for performing vasodilator (adenosine, dipyridamole and regadenoson) stress testing and contraindications, administration protocols, and side effects for performing dobutamine stress testing.

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Table 1: Cardiac measurement terms, equations and normal values.

TERM	FORMULA	RANGE
VO2/V02max	Cardiac Output x A-V O_2 Differential	35 to 40 mL/kg/min (male) 27 to 30 mL/kg/min (female)
Cardiac Output (CO)	Heart Rate x Stoke Volume	4.0 – 8.0 ml/min
Stroke Volume (SV)	End Diastolic Volume (EDV) - End Systolic Volume (ESV)	60 – 100 ml
A-V O_2 Differential	Oxygen Content of Pulmonary Blood - Oxygen Content in Mixed Venous Blood	4.5 mL/100 mL/min
MVO_2 /Rate Pressure Product	Coronary Blood Flow x A-V O2 differential/ heart rate x systolic blood pressure	30 to 35 ml/min
MPHR	220 - age	N/A

Table 2: Bruce Protocol

STAGE	MIN	SPEED (MPH)	GRADE (%)
1	3	1.7	10
2	6	2.5	12
3	9	3.4	14
4	12	4.2	16
5	15	5.0	18
6	18	5.5	20
7	21	6.0	22

Table 3: Modified Bruce Protocol

STAGE	MIN	SPEED (MPH)	GRADE (%)
0	3	1.7	0
1/2	6	1.7	5
1	9	1.7	10
2	12	2.5	12
3	15	3.4	14
4	18	4.2	16
5	21	5.0	18
6	24	5.5	20
7	27	6.0	22

Figure Legends:

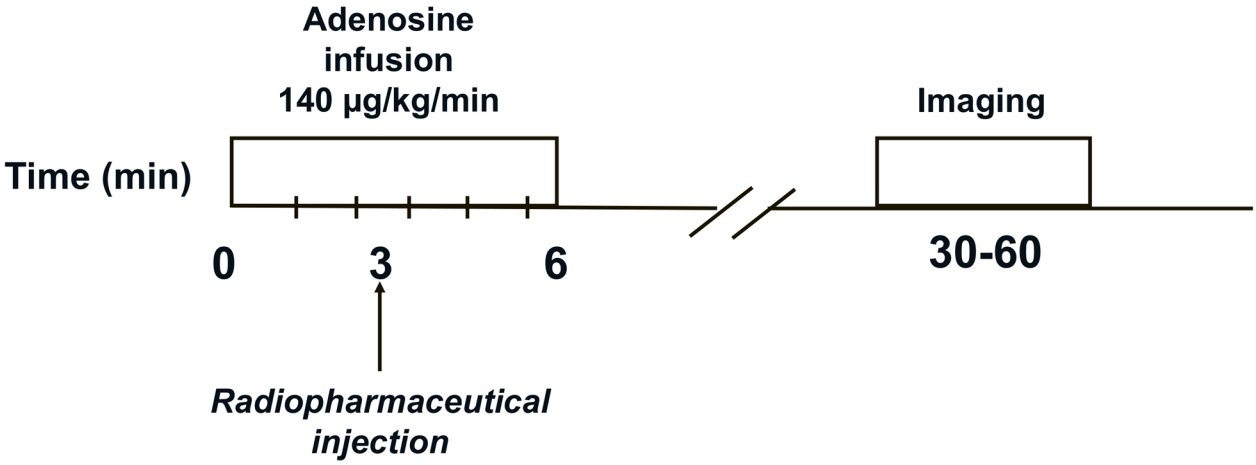

Figure 1: Adenosine Infusion Protocol

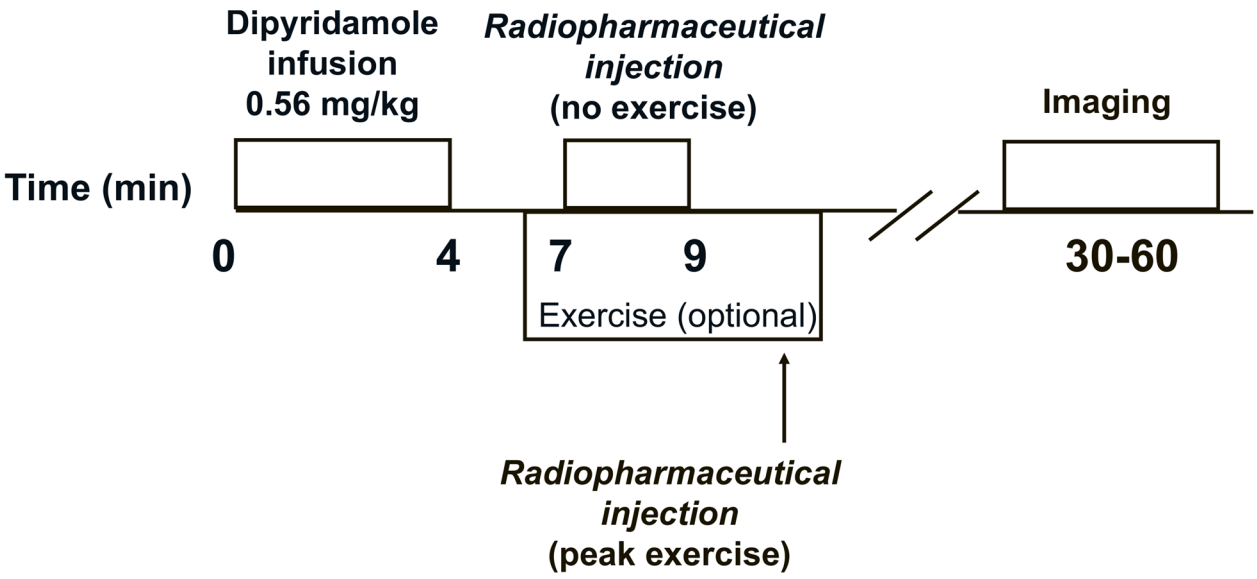

Figure 2: Dipyridamole Infusion Protocol

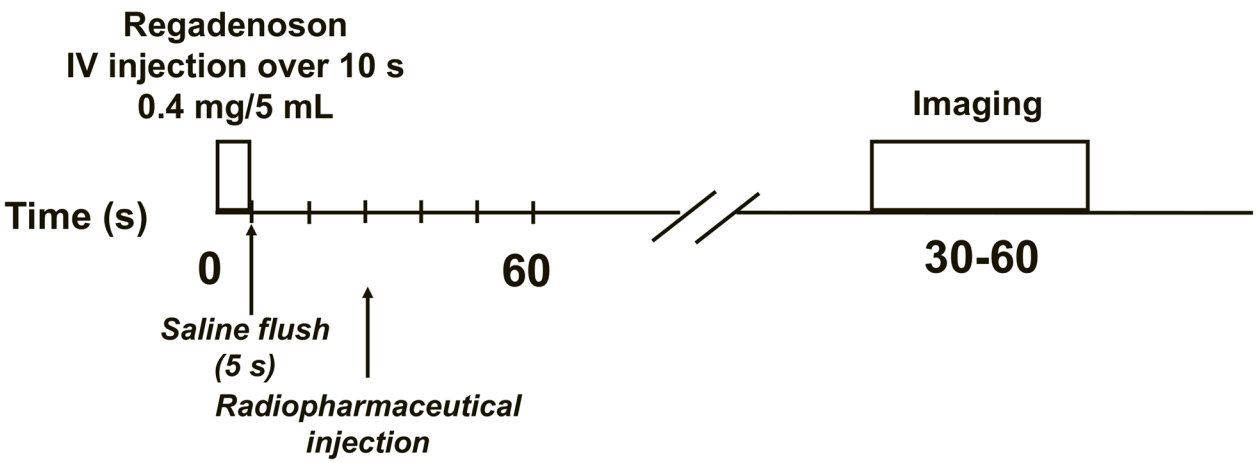

Figure 3: Regadenoson Infusion Protocol

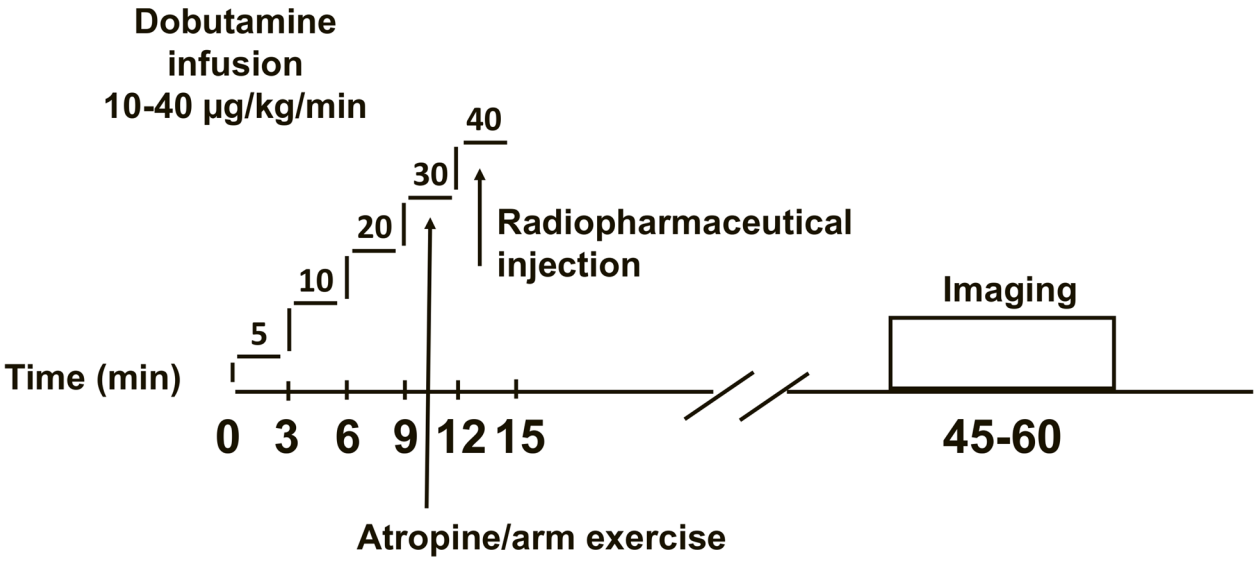

Figure 4: Dobutamine Infusion Protocol