

Pharmacologic Interventions in Nuclear Medicine Assessment of Cardiac Perfusion

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Abstract Drugs that are currently used for therapeutic purposes can also be used in diagnostic tests. This paper will review the use of such pharmacological interventions in cardiac assessment in Nuclear Medicine. To fully comprehend the effect of these drugs, a small review of diagnostic nuclear medicine as currently used to assess cardiac perfusion is included. This will allow pharmacists to understand the rationale behind the single administration of either vasodilator or inotropic agents and to review which drugs and food may interact with the test.

INTRODUCTION

Myocardial perfusion scintigraphy, a nuclear medicine technique, is one of the primary diagnostic techniques used to assess myocardial blood flow and function in patients with coronary artery disease. Following injection of an appropriate radiopharmaceutical, images acquired on a gamma camera provide information on both perfusion and contraction of the heart muscle. Treadmill exercise is the most commonly employed stressor in assessing these patient's hearts. Not all patients can exercise sufficiently to provide optimal test results, therefore pharmaceuticals that mimic the myocardial response to physical stress are often used.

Although diagnostic protocols vary among institutions, this paper provides an overview of how these studies are generally performed and how the information is acquired. Special emphasis will be given to the role of "pharmacologically induced stress" and the potential interactions that could occur with some common drugs and foods. These

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interactions can often necessitate diet restriction and cancellation of medication for patients prior to the test. This paper intends to summarize pertinent information that will allow a practising pharmacist to understand the procedure and properly inform patients referred for pharmacologically induced cardiac stress tests in nuclear medicine.

ASSESSMENT OF CARDIAC FUNCTION

Assessment of chronic coronary artery disease (CAD) and myocardial perfusion are routinely performed by stress electrocardiography (ECG), angiography, ultrasound and nuclear medicine. In recent years, the sub-specialty of nuclear cardiology has been the most rapidly growing area in nuclear medicine, due to an increasing influence of the test results on patient management (1) and advances in new radiopharmaceuticals (2). Unlike other imaging modalities, which are used to evaluate anatomical aspects of the heart, cardiac studies in nuclear medicine are used to assess myocardial function.

The nuclear medicine technique assesses three aspects of heart function: blood flow within the heart muscle (myocardial perfusion), motion of the ventricular walls of the heart (segmental ventricular function) and the efficiency of pump function through calculation of the ejection fraction (global ventricular function).

ROLE OF STRESS IN MYOCARDIAL FUNCTION STUDIES

A short review of the physiology of auto-regulation of coronary blood flow will allow a better understanding of the procedures. The auto-regulatory mechanism attempts to balance the supply and demand of oxygen for the heart. The heart rate, blood pressure, left ventricular contractility and left ventricular volume determine oxygen demand. The heart must consume more oxygen to do more work, but since it already extracts oxygen from the blood at nearly maximum efficiency at rest, it cannot simply

increase its oxygen extraction efficiency as it works harder. An increase in oxygen demand stimulated by exercise must be accommodated through increased blood flow to the heart. Since blood flow to the left ventricle occurs mainly in diastole, the aortic diastolic pressure defines the coronary perfusion pressure. The required increase in blood flow must arise from a decrease in vascular resistance, not through an increase in blood pressure (3). Under normal conditions, the resistance to blood flow occurs mainly at the level of the small arteries and arterioles and at the myocyte cell walls. These small vessels are normally capable of dilating and dropping their resistance (4).

Patients without flow limiting stenosis, can augment myocardial blood flow by a factor of around 3 to 4 during exercise(4).

The difference between the coronary blood flow observed at rest and during maximal vasodilatation is defined as the coronary vasodilator reserve. In the presence of a coronary artery stenosis, perfusion pressure is reduced distally to the stenosis and coronary autoregulation can be exhausted resulting in transmural myocardial blood flow maldistribution and eventually ischemia(5).

Even if the patient is asymptomatic at rest, when the stenosis reaches sub-critical levels, as low as 30-45% of the vessel diameter, auto-regulation becomes incapable of sustaining the blood flow required under stress conditions (6,7). Most patients with moderate occlusion remain asymptomatic at rest. In the presence of severe coronary occlusion (greater than 85% of vessel diameter), however, the ability of the auto-regulatory mechanism to provide an adequate oxygen supply is impaired, even at rest (6,7). It is important to define the extent of ischemia of the heart in coronary artery disease in order to explain the patient's symptoms, assess risk and select therapy. Cardiac nuclear medicine allows *in vivo* monitoring of the blood supply to the different areas of the heart. While under stress, those areas of the heart supplied by normal vessels will receive an increase in blood supply while the tissues perfused by the obstructed arteries will not increase as much. The difference in blood perfusion to the affected areas induced by the stress can be detected and quantified using nuclear medicine techniques.

It is important that patients reach a high enough oxygen demand level during the stress procedure in order to exceed the coronary vasodilator reserve, otherwise the

normal auto-regulatory response mechanisms may compensate sufficiently to mask significant stenosis. Upright aerobic or dynamic exercise (usually on a treadmill) using the large muscle groups stimulates the largest increase in coronary blood flow and cardiac output and remains the method of choice to induce stress for these studies. However, situations arise where it is not possible for patients to exercise sufficiently for optimal test results (Table 1).

Table 1: Contraindications to treadmill stressing

Conditions	
General	Specific
Inability to sustain physical activities	degenerative joint disease neuropathy spinal cord injury claudication obstructive lung disease liver or renal failure
Specific medication affecting response to exercise	Beta blockers Verapamil Diltiazem
Heart Intrinsic conduction disease	Acute MI Uncontrolled unstable angina decompensated Congestive heart failure Uncontrolled hypertension

From Imaging Guidelines for Nuclear Cardiology Procedures 1996

Alternatives designed to simulate the effects of exercise on the heart, such as cold pressor testing, have also been evaluated (8) but led to inconsistent results. Pharmacologic intervention has become the alternate method of choice.

IMAGING PROTOCOLS

All nuclear medicine radiopharmaceutical myocardial perfusion agents, following i.v. injection, accumulate within the cardiac muscle, as a function of the blood flow to the area. The patient is then scanned under a camera and tomographic images are acquired. Images of the heart are reconstructed on a computer and the data can be displayed as slices of the heart or as a 3 dimensional representation of the whole heart. The data can be analyzed both quantitatively and qualitatively to define the level of perfusion to each area of the heart.

The first cardiac perfusion imaging protocols used ²⁰¹Tl Thallium Chloride to evaluate myocardial blood flow. ²⁰¹Tl Thallous Chloride was adopted because thallium mimics the biochemical and physiological distribution of potas-

sium in the heart muscle. ^{201}Tl has the most useful imaging characteristics of the thallium radionuclides available. Later $^{99\text{m}}\text{Tc}$ complexes such as Sestamibi and Tetrofosmine were developed to exploit the better imaging characteristics of $^{99\text{m}}\text{Tc}$ compared to ^{201}Tl . $^{99\text{m}}\text{Tc}$ is bound to the molecule of either tetrofosmine or MIBI and decays with a physical half life of 6 hours by emission of a 140 Kev gamma ray. This particular photon energy can easily be detected by the standard gamma camera available in most hospitals. Although the $^{99\text{m}}\text{Tc}$ tracers are monovalent cations similar to potassium, they are distributed throughout the heart tissue by passive diffusion and do not mimic potassium or any naturally occurring molecule. Their exact mechanism of accumulation is still not fully understood but it has been suggested that $^{99\text{m}}\text{Tc}$ Sestamibi is trapped in the proximity of the mitochondria mostly due to its charge(2). Currently these three radiopharmaceuticals are the most commonly used. The distribution of these radiopharmaceuticals reflects the blood perfusion pattern within the heart muscle. After stress, an increase in perfusion is seen in normal tissue. More poorly perfused areas also accumulate the radiopharmaceutical but to a lesser extent when compared to the surrounding normal tissues. Typical myocardial perfusion procedures involve the acquisition of two sets of images following IV injection of the tracer. One set of images of the patient's heart is obtained with the patient in a resting state. A second set of images is obtained while the patient is under stress. The two sets of images are compared to obtain the diagnostic information.

Several imaging protocols, varying mostly in time between the stress and rest injections and injection dose (one day procedure, 2 days procedure, re-injection, etc.) are used. In order to illustrate the role of pharmaceutical induced stress, we will restrict our discussion to a widely accepted protocol which uses two injections of $^{99\text{m}}\text{Tc}$ Sestamibi on two separate days. Briefly, on the first day, the patient is stressed while being closely monitored by ECG. When the appropriate level of stress has been induced, $^{99\text{m}}\text{Tc}$ Sestamibi is injected into the patient where it rapidly accumulates in various tissues in proportion to blood flow.

One hour after injection the background activity will have cleared from the blood. The patient lies under a camera that rotates around them and acquires scintigraphic images representing the distribution of the radioactivity within the chest. On the second day, while at rest, the patient is injected a second time with $^{99\text{m}}\text{Tc}$ Sestamibi and imaged as before. By this time most of the radioactivity from the pre-

vious study has either decayed or been excreted by the patient.

This image data can then be displayed in various formats to analyse tissue perfusion from different views. These computer reconstructions visualize the ventricular wall of the normal heart as an area of relatively intense radioactivity. The ventricular cavity is represented as an area of very low radioactivity. Areas of low radioactivity in the rest image of the heart wall indicate the presence and extent of an infarct or scar tissue in the heart muscle that cannot be salvaged. In contrast, the presence of an area of low radioactivity in the stress image can indicate either ischemic tissue (which can be salvaged) or infarcted or scar tissue. Comparing the stress and rest images will reveal areas of the myocardium that are perfused while at rest but not while under stress. These areas are at risk but amenable to further treatment.

Figure 1 is a tomographic reconstruction of the heart of an individual both at stress and at rest.

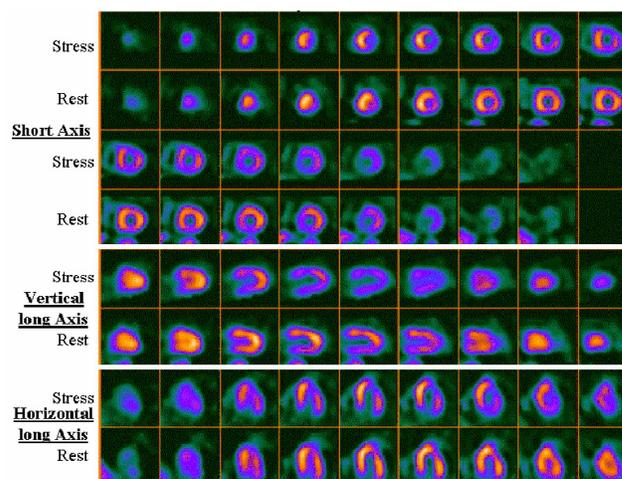


Figure 1: Scintigraphic pictures at rest and following pharmacological intervention in a patient with an 80% block of two of the major coronary arteries, a diagonal branch of the left anterior descending (LAD) and the right coronary artery (RCA).

The rest images show normal perfusion, the stress images, however, show lack of perfusion in the anterior and lateral walls when compared to the rest images. The computer display presents three orientations of the heart. The first orientation is the short axis. The heart is oriented with its apex toward the viewer and the series of images in that row represent parallel, sequential images or slices of tissue

starting at the tip of the apex and cutting across the left ventricle. The hole in all images represents the left ventricle cavity. The second and third representations are called vertical and horizontal long axis where the heart is oriented for the viewer to see both the apex and base of the left ventricle. In the vertical axis display the images are sliced from septum to lateral wall (and the horizontal axis displays the tissue with the slices from inferior to anterior wall).

PHARMACOLOGICAL STRESSING OF THE HEART

Pharmacologic stress techniques can be used either in conjunction with exercise to enhance response in patients who can exercise only sub-optimally or used alone in patients who cannot exercise at all. The agents (Table 2) used can be divided into two groups: those that directly result in coronary vasodilation (adenosine and dipyridamole) and those that stimulate myocardial oxygen demand (dobutamine and arbutamine). Table 2 also lists the major side effects of the “stressing” drugs and their contraindications.

VASODILATING AGENTS

Adenosine is a naturally occurring physiologic regulator (important in auto-regulation) of vascular blood flow. It

acts on specific cell surface receptors by either slowing the heart rate (A1 receptors) or inducing vasodilatation (A2 receptors). It is synthesized intracellularly (vascular smooth muscle cells) but acts extracellularly. Free adenosine is rapidly reabsorbed into the cells where it is metabolised, therefore its physiological half-life is very short. Adenosine production is activated locally in the presence of myocardial ischemia. It increases oxygen supply through coronary vasodilatation. Although adenosine also directly decreases both heart rate and myocardial oxygen demand, the subsequent drop in blood pressure usually results in an increase in myocardial oxygen demand. Adenosine (140 ug/kg/min) given intravenously has a short half-life (<10 sec.), which allows for good control of both vasodilation and side effects.

Dipyridamole was first introduced in the late 1970’s (9) and continues to be the most widely used agent in pharmacologic stress testing. Dipyridamole shares a common mechanism of action with adenosine, in that it indirectly increases the extra-cellular concentration of adenosine by blocking its cellular re-uptake. Dipyridamole increases cardiac output and heart rate while it decreases diastolic and mean blood pressure. The ejection fraction may increase

Table 2: Side effects and contraindications of the common pharmacologic stressors

Pharmaceutical	Dosage (i.v. infusion)	Mechanism	Side Effects (similar for all agents but different frequency)	Contraindications
Adenosine	0.140 mg/kg/min 0.84 mg/kg total	Direct Coronary Vasodilation	Asystole Myocardial infarction Pulmonary edema Ventricular tachycardia Flushing Chest pain Dyspnea	Ongoing wheezing High grade atrioventricular block Hypotension, 90mm Hg Recent use of dipyridamole or xanthine
Dipyridamole	0.142 mg/kg/min OR 0.568 mg/kg OR 60 mg total dose	Increase Blood Adenosine Levels Direct Coronary Vasodilation	ST-changes Headache Dizziness Nausea and vomiting Palpitations Arm, back, shoulder pain Parasthesia Arrhythmias	Theophylline therapy Active wheezing High-grade atrioventricular block
Dobutamine	0.04 mg/kg/min	Chronotropic Inotropic Beta agonist		Recent MI Unstable Angina Left ventricular outflow tract obstruction Critical aortic stenosis Atrial tachyarrhythmias with uncontrolled ventricular response Ventricular Tachycardia Uncontrolled hypertension Aortic dissections or large aortic aneurysm

Composite from Imaging guidelines for Nuclear Cardiology Procedures 1996

slightly in normal patients but it will decrease slightly in coronary artery disease. The standard clinical dose is 0.14 mg/kg/min over 4 minutes and total dose of 0.56 mg/kg.

Both dipyridamole and adenosine increase coronary blood flow up to 2–5 times rest levels. Their effect is greater than that achieved with exercise. The response to both drugs is very fast and has some advantages over physical exercise. Dipyridamole’s effects maximize approximately five minutes after infusion and last for 10 to 30 minutes, whereas adenosine’s effects occur within two minutes and last only during infusion (10,11).

Certain drugs and food which interfere with the production or metabolism of adenosine can affect the test and need to be discontinued prior to the test. In the case of dipyridamole and adenosine, methylxantines are typical of agents interacting with the binding of adenosine to its receptors. They are listed in Table 3. Table 4 lists the common sources of the most ubiquitous methylxantines.

Table 3: Pharmaceuticals to be discontinued before pharmacologic stress

Pharmaceutical	Rationale
Stress with Adenosine and Dipyridamole	
Caffeine	competitive inhibition
Theophylline	competitive inhibition
Aminophylline	competitive inhibition
Pentoxifylline (Trental)	competitive inhibition
Nitroglycerin	limits effect
Stress with Dobutamine	
Beta blocker	competitive inhibition
Calcium Blockers	channel Limits effects

POSITIVE INOTROPIC AGENTS

Positive inotropic agents, such as dobutamine and arbutamine, affect the force of the muscular contractions of the heart. They are usually used in a patient who cannot exercise adequately and has contraindications to dipyridamole or adenosine.

Positive inotropes increase myocardial oxygen demand by stimulating beta receptors in the heart. The resultant

increase in blood flow is in the order of two to three times rest levels. Their increase in blood flow is comparable to exercise but is less than that observed with dipyridamole or adenosine. They are considered to be the last line of stress testing as they do not produce as high a peak heart rate as physical exercise and do not yield exercise duration and capacity information. Therefore, they are used only in patients who cannot exercise and are contraindicated to dipyridamole and adenosine (12, 13).

Table 4: Common sources of caffeine and theophylline

Hot Beverages
Coffee, Tea, Cocoa, Hot Chocolate
Cold Beverages
Cola drinks i.e. Coke, Pepsi and others, Other Soft Drinks i.e. Tab, Mountain Dew, Mello Yellow
Foods
Generally limited to foods containing caffeine mostly chocolate
Drugs Containing Caffeine
Anacin, Cafergot, Darvon, Fiorinal, Wigraine
Drugs Containing Theophylline
Aerolate
Elixophyllin SR
Respbid
Sustaire
Theophylline SR
Theochron
Uniphyll
Bronkodyl S-R
LaBID
Slo-Bid Gyrocaps
Theo-24
Theospan SR
Theolair-SR
Constant-T
Lodrane
Slo-Phyllin Gyrocaps
Theoclear L.A.
Theobid (Jr.) Duracaps
Theo-Time
Duraphyll
Quibron-T S/R
Somophyllin-CRT
Theovent Long Acting
Theo-Dur and Sprinkle
Theophyl-SR

Patients with wheezing (requiring theophylline), patients with hypotension at baseline, and patients with high-grade atrioventricular block (without pacemaker) are contraindi-

cated to dipyridamole studies. Inotropic agents are selected over vasodilators for these patients. Patients with recent unstable angina or recent myocardial infarction should be carefully screened.

Dobutamine hydrochloride has a rapid onset of action (1 to 2 minutes i.v.). It increases stroke volume, cardiac output and inotropy substantially at low doses (5 to 20 µg/kg/min) but only modestly increases heart rate. Both heart rate and systolic blood pressure increase incrementally with dose. Coronary vascular resistance decreases distal to the stenosis but resistance increases at the stenotic site. The presence of coronary artery disease decreases the flow response to dobutamine relative to normal patients.

Arbutamine is similar to dobutamine with respect to inotropic and chronotropic activity, but is a mixed beta-1 and beta-2 agonist with mild alpha-1 affinity in contrast to the strong beta-1 but weak beta-2 and alpha-1 properties of dobutamine (14).

Table 3 lists the drugs that need to be stopped to prevent possible interference with the pharmacological action of Dobutamine. These include mostly beta blockers and calcium channel blockers; both decrease the response induced by the inotropic agents.

PHARMACOLOGIC STRESS PROTOCOLS

Pharmacologic stress is often combined with some form of physical exercise as evidence indicates this improves blood flow, tracer uptake and image quality while it decreases the incidence of side effects from dipyridamole and adenosine (15).

DIPYRIDAMOLE

With the dipyridamole protocol, dipyridamole is usually administered as an i.v. infusion at a rate of 0.14 mg/kg/min (total dose of 0.56 mg/kg or 60 mg) over 4 minutes. The radiotracer is injected when maximum vasodilatation is reached, usually after 3 minutes, which generally occurs approximately seven minutes from onset of infusion. When physical exercise is included in the protocol, it is generally initiated two minutes prior to injection of the tracer (13).

Non cardiac side effects are commonly reported with dipyridamole use, including headache (12%) and dizziness, nausea, vomiting and flushing (12%) while cardiac related

side effects such as chest pain (20%) and ST depression (7.5%) are less severe than with exercise stress (16). The risk of side effects increases with higher doses. Side effects can be easily reversed by administration of an i.v. bolus of 50 to 75 mg aminophylline or an infusion of 250 to 500 mg over 20 minutes. Nitroglycerin sublingual can be administered the rare time aminophylline is ineffective. Severe side effects are rare with non-fatal myocardial infarction estimated to occur in 0.1% of patients (17). A list of contraindications to vasodilator induced stress testing are given in Table 3.

ADENOSINE

Due to the short half-life of adenosine, its use differs from dipyridamole. The radiotracer is injected around three minutes after beginning the infusion (140 µg/kg/min) which lasts for six minutes (13).

In one study, side effects including chest, throat and jaw pain, headache and flushing and ischemic electrocardiogram changes were observed in up to 83% of patients. They include headaches (85%), flush (29%), chest, throat or jaw pains (57%) (18). Fortunately these side effects are readily and immediately reversed by termination of the infusion when necessary. Aminophylline and Esmolol can be useful to reverse the effects of adenosine but the need for their use is rare.

DOBUTAMINE

A standard dobutamine protocol starts at a low dose, in the order of 5 µg/kg/min and increments every three minutes to 10, 20, 30 and finally 40 µg/kg/min. The radiopharmaceutical is injected two to three minutes prior to the end of the highest dose level. (13). In some laboratories, atropine is used to help reach the desired heart rate with dobutamine. This latter protocol is similar except that 0.5 mg of atropine is injected approximately 9 minutes after the beginning of the dobutamine infusion (19).

Dobutamine increases heart rate, systolic blood pressure and the rate pressure product in patients. Although serious side effects are rare, minor effects are common, occurring in up to 75% of cases in one study (20). These included typical (26%) and atypical (5%) angina, palpitation (29%), flushing (14%), headache (14%) and dyspnea (14%). Other side effects include hypotension (3.4%), supraventricular (4.4%) and ventricular tachycardias (3.8%)(20,21). Table 3

lists the drugs required to be discontinued prior to using dobutamine.

Fig. 1 shows the images at rest and stress of a 65 y.o. male who gives vague history of intermittent upper sternal burning, usually provoked by effort, relieved by rest. The post dipyridamole images show a decrease in the anterior and lateral walls but no corresponding defect on the rest images. This demonstration of decreased coronary flow reserve in response to pharmacologic stimulation is due to 80% stenosis of two of the major coronary arteries, a diagonal branch of the Left anterior descending-LAD and the Right coronary artery-RCA.

PHARMACOLOGIC ENHANCEMENT OF MYOCARDIAL VIABILITY

There is some evidence to suggest that defects observed on the rest images in some patients overestimates the extent of irreversibly damaged myocardium. A second method to improve the differentiation of irreversibly damaged tissue from poorly perfused but still viable tissue exploits the vasodilating effects of nitrates such as nitroglycerin and isosorbide dinitrate. The rationale for their use is that nitrates also induce venous dilation as well as the epicardial arteries, including the stenosis site and may enhance collateral perfusion distal to the occlusion. Therefore the administration of a nitrate to the patient before injection of the radiopharmaceutical during the rest image may enhance uptake of radiopharmaceutical in the hypoperfused tissue which would increase detection of patients having treatable cardiac defects (22). Both nitroglycerin (23) and isosorbide dinitrate (24) can be used. Nitroglycerin (0.4 mg) is given sublingually and the radiopharmaceutical injected approximately five minutes after the appropriate hemodynamic response (blood pressure and heart rate) is observed. The isosorbide dinitrate protocol involves an infusion of the nitrate (10 mg in 100 mL saline) over 20 minutes and upon reaching the appropriate drop in blood pressure, the radiopharmaceutical is injected. The drop in blood pressure is expected and monitored. Sildenafil is reported to have a significant effect. Concomitant administration is contra-indicated (25). The likelihood for sildenafil to be administered prior to a major Nuclear Medicine exam is both limited and unlikely. Regardless, it cannot be ignored and patients should be properly counselled. Most protocols include installation of an IV line prior to the test to maintain intravenous access and fluid administration if needed.

PHARMACISTS ROLE

All nuclear medicine departments send information to patients when the appointment for the test is confirmed which includes restriction in both food and drugs. The patient, however, is not always familiar with either the procedures or the reasoning behind the interruption of some of the current medication or common food. The community-pharmacist's role becomes essential in both reassuring and helping patients to understand the procedure and its requirement. Hospital pharmacists monitoring patient therapy will also be able to understand therapy interruption and advise patients accordingly.

CONCLUSION

Pharmacological myocardial stressing is a common technique used extensively to assess heart perfusion. The diagnostic test can use a variety of fast acting vasodilators such as dipyridamole and adenosine or positive inotropes such as dobutamine depending on the patient. Their administration in these tests differs from their usual therapeutic use. This review should ensure pharmacists are familiar with the procedures, the drugs used during the stressing as well as the drugs that could interfere with the stressing procedures.

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