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PHARMACOLOGY PART 4: NUCLEAR CARDIOLOGY.

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Foot line: Pharmacology in nuclear cardiology

ABSTRACT

Pharmacology principles provide key understanding that underpins the clinical and research roles of nuclear medicine practitioners in nuclear cardiology. The scope of practice of the nuclear medicine technologist demands knowledge and understanding of indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used. This article is the fifth in a series of articles that aims to enhance the understanding of pharmacological principles relevant to nuclear medicine. This article will build on the introductory concepts, terminology and principles of pharmacology explored in the first two articles in the series. Specifically, this article will focus on the pharmacological principles and complex relationshiship associated with interventional, adjunctive and cessation medications in nuclear cardiology. Future articles will address the pharmacology related to the emergency trolley (crash cart) and contrast media associated with computed tomography (CT) and magnetic resonance imaging (MRI).

INTRODUCTION

The scope of practice for a nuclear medicine technologist (*1*) defines interventional (imaging) medications as those medications used to evoke a specific physiological or biochemical response used in conjunction with diagnostic imaging or therapeutic procedures (eg. adenosine and dipyridamole). The same document (*1*) defines adjunctive medications as those medications used to respond to a patient's condition during a nuclear medicine procedure (eg. salbutamol and aminophylline). Patients presenting to nuclear cardiology may be taking medication that can interfere with the nuclear medicine procedure, and in particular the stress test component of the procedure. These represent cessation medications and the period of cessation is largely dependent on the half life of the medication.

The scope of practice for a nuclear medicine technologist (*1*) requires that they display a thorough understanding and knowledge of indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used. That knowledge development needs a foundation understanding of the principles of pharmacology provided in earlier articles in this series (*2,3*); *Pharmacology part 1: introduction to pharmacology and pharmacodynamics*; and *Pharmacology part 2: introduction to pharmacokinetics*. Indeed, these previous articles should be considered assumed knowledge for this article and those that follow in the series. To that end, those foundation principles will not be redefined in this here.

PHARMACOLOGICAL STRESS TESTING

Stress myocardial perfusion imaging aims to create a disparity in blood flow between normal and stenosed arteries (*4,5*). This can be achieved by either increasing the myocardial oxygen demand or by vasodilation of coronary arteries (*6*) (figure 1). Exercise is generally considered the preferred method of stress testing but pharmacologic stress testing can overcome a number of limitations to exercise (*5-8*). There are essentially two approaches to pharmacological stress testing; vasodilators and positive inotropic agents (*7,8*). Vasodilators like adenosine and dipyridamole have a direct and potent impact on coronary flow reserve to accentuate the blood flow differences between normal and diseased vessels by factors in the order 3-4 (*5,7,8*) (figure 2). Positive inotropic agents like dobutamine increase cardiac workload, potentially inducing myocardial ischaemia (*5,7,8*) (figure 3). Vasodilatory and positive inotropic based interventional agents are discussed below and sumamrised in table 1.

Adenosine (Adenoscan or Adenocard)

General information / drug class:

Potent vasodilator endogenous adenine purine nucleoside that is a class V antidysrythmic drug due to its effect on the atrioventricular (AV) node (*9,10*).

Mode of action:

Adenosine is a natural regulator of blood flow and coronary demand, acting directly on adenosine cell surface receptors (*9-12*) (figure 2). Adenosine also modulates sympathetic neurotransmission (*11,12*). There are four main adenosine receptor sub-types (*9-11,13*):

1. A_1, blocks AV conduction, reduce force of cardiac contraction (negative inotropic and chronotropic action), decreased glomerular filtration rate, cardiac depression, renal vasoconstriction, decreased central nervous system (CNS) activity and bronchoconstriction.
2. A_{2A}, anti-inflammatory response, vasodilation, decreased blood pressure, decreased CNS activity, inhibition of platelet aggregation and bronchodilation.
3. A_{2B}, stimulates phospholipase activity, release of mast cell mediators, and actions on colon and bladder (contributes to bronchoconstriction).
4. A_3, stimulate phospholipase activity and release of mast cell mediators (contributes to bronchoconstriction).

Endogenous adenosine is produced in vascular smooth muscle cells and leaves the cell. In the extracellular space, endogenous and exogenous adenosine can couple with the 4 types of adenosine receptors outlined above. Receptors A_1 and A_3 couple with an adenylate cyclase inhibitory G protein (*9,11*). Receptor A_{2a} and A_{2b} couple with an adenylate cyclase stimulating G protein (*9-11*). Receptor A_{2a} specifically produces coronary and peripheral vasodilation by reducing intracellular calcium. Receptor A_{2A} stimulates adenylate cyclase activity which enhances the production of cyclic adenosine monophosphate (cAMP) to produce vasodilation and arterial smooth muscle relaxation (*9,10,14*). As a result, normal

arteries dilate while atheroschlerotic arteries do not (*9,10*). The resulting exaggeration in the difference between the blood flow in normal coronary arteries and the blood flow in atheroschlerotic coronary arteries causes differential perfusion patterns.

Pharmacokinetics:

Adenosine is rapidly transported inside the cell (erythrocytes and vascular endothelial cells) where it is rapidly metabolized to inosine via adenosine deaminase or to adenosine monophosphate (AMP) via adenosine kinase mediated phospholylation (*14,15*). This rapid transport and metabolism results in the very short half life of less than 10 seconds (*10,14,15*). Adenosine is also metabolized by xanthine oxidase in the intracellular space of endothelial, smooth muscle and red blood cells (*9-11*).

Usual indications:

The chronotropic, dromotropic and inotropic actions associated with the receptor A_1 allow adenosine to be used for managing sinoatrial (SA) node activity, AV node conductivity, and ventricular automaticity (*15*). The main indication of adenosine is to restore sinus rhythm in paroxysmal supraventricular tachycardia (*9,15*).

Use in nuclear medicine:

Adenosine is used as a vasodilatory agent for the performance of cardiac stress testing for those unable to exercise adequately (eg. vascular disease, respiratory disease, musculoskeletal limitations, calcium channel blockers, beta blockers, poor motivation) and in cardiac positron emission tomography (*4,7,16*). Adenosine increases coronary blood flow 4-5 times normal in normal blood vessels and to a lesser extent in stenosed vessels (*16*). This exaggeration in blood flow differences between normal and stenosed vessels is the basis for detecting hemodynamically significant disease.

Proper use and dose administration:

The dose is administered intravenously (IV) as 140 mcg/kg/min for 6 minutes with radiopharmaceutical injection at 3 minutes post commencement of infusion. Alternatively incremental doses each minute of 50 mcg/kg/min, then 75 mcg/kg/min, then 100mcg/kg/min and then 140mcg/kg/min until 7 minutes (*8,12,15,17*) (figure 4). The radiopharmaceutical is injected IV 3 minutes after commencement of the adenosine infusion. While the 6 minute method is recommended, common alternative is 140 mcg/kg/min IV for 4 minutes with radiopharmaceutical injection at 2 minutes post commencement of infusion.

Contraindications:

Adenosine is contraindicated in patients with sick sinus syndrome, second or third degree AV block, patients with asthma and a history of bronchospasm (*8,12,14,15*). Adenosine is relatively contraindicated in known hypersensitivity, unstable angina, oral dipyridamole use and hypotension (*8,14*).

Warnings and precautions:

Adenosine should be used with caution in patients on medications that suppress SA or AV nodes (additive or synergistic effects may result) (*14*).

Adverse reactions:

Adenosine itself is not selective for particular receptor sub-types. Consequently, a number of unwanted effects accompany adenosine stress. These are generally resolved rapidly by cessation of the infusion since adenosine has a duration of action less than 1 minute and it has a very short biological half life (<10 seconds) (*7,9-11,15*).

Commonly seen adverse reactions include chest pain, pain in the throat / jaw and arm, headache, flushing and dyspnea (*7,14-16*). Electrocardiogram (ECG) changes and AV block are also occassionaly noted (*10,16*). Some patients experience lightheadedness, gastrointestinal discomfort, paraesthesia and

hypotension (*14*). It is worth noting that 10.6% of patients experience these adverse effects several hours after cessation of the infusion; despite the very short half life (*14*).

Despite being an anti-arrhythmic medication, adenosine can potentiate arrhythmia (*15*). Bronchospasm, particularly in asthmatics, is a significant potential adverse reaction (*15*).

Common interactions:

Caffeine and similar xanthine products potentiate adenosine (*5,7,8*). Adenosine effects are potentiated by dipyridamole (*10,15*).

Dipyridamole (Persantin/Persantine)

General information / drug class:

Dipyridamole is an indirect potent vasodilator pyramidopyrimidine compound with adenosine reuptake inhibition and phosphodiesterase inhibition producing vasodilatory and antiplatelet activity (*10,15*).

Mode of action:

Dipyridamole is a pyramidopyrimidine compound with both vasodilatory and anti-thrombotic effects (*10,17*). Adenosine deaminase is an enzyme that catalyses the deamination of adenosine to inosine (*14,18*) (figure 2). Dipyridamole inhibits adenosine deaminase which is an enzyme involved in cellular uptake of adenosine. By blocking cellular uptake in myocardial, endothelial and blood cells, dipyridamole increases extracellular interstitial adenosine (*10,14*). Consequently, the increased adenosine has increased reactivity with adenosine receptors that regulate coronary blood flow which leads to vasodilation (*12,14,16,17*). In blood cells, inhibition of phosphodiesterase increases cAMP which reduces activation of cell aggregation (*10*).

Pharmacokinetics:

Dipyridamole is incompletely absorbed from gut, has 90-99% plasma protein binding and a 10-12 hour half life (*10,15*). It is metabolized in the liver and mostly eliminated in bile with a small fraction via urine (*15*).

Usual indications:

Dipyridamole is used as an anti-platelet medication for thromboembolism prophylaxis, especially after stroke or valve replacement (usually in oral dose form) (*10,15*).

Use in nuclear medicine:

Dipyridamole is used as an indirect vasoldilatory agent for the performance of cardiac stress testing for those unable to exercise adequately (eg. vascular

disease, respiratory disease, musculoskeletal limitations, calcium channel blockers, beta blockers, poor motivation) (*4,7,16*).

Proper use and dose administration:

A dose of 0.56mg/kg of dipyridamole diluted in 20-40ml of saline is infused over 4 min IV. The maximum vasodilatation occurs at 4 minutes after the end of the infusion but the radiopharmaceutical is administered at either 0 (zero) minutes or 2 minutes post infusion (*8,12,17*) (figure 4).

Contraindications:

Dipyridamole is contraindicated in patients with sick sinus syndrome, second or third degree AV block, patients with asthma and history of bronchospasm (*12,14,15*). Hypersensitivity to dipyridamole or aminophylline are also relative contraindications (*14*).

Warnings and precautions:

Since adenosine shunts endocardial blood flow to the epicardium, there may be a reduction in collateral blood supply or induction of ischemia (*12*). Severe ischemic symptoms may occur. Orthostatic hypotension may also occur. Severe hepatic dysfunction needs to be managed with caution due to liver metabolism (*16*). Caution should also be exercised in known hypotension, aortic stenosis, heart failure, recent myocardial infarction, coagulation disorders and angina (*15,16*). Careful consideration should be exercised in patients not abstaining from xanthine medications and products due to potential false negative (*14*).

Adverse reactions:

For dipyridamole, 47% of patients report adverse reactions, of which 0.26% are severe (*12*). Significant adverse reactions can be treated with IV adminophylline or nitroglycerine for chest pain (see below). Frequent adverse reactions include chest pain, headache, and dizziness. Less commonly, patients experience nausea, flushing, tachycardia, dyspnea, hypotension and ECG changes (*14-16*).

Patients with severe CAD or conduction abnormailities are at greater risk of adverse effects (*14*).

Common interactions:

Dipyridamole can potentiate the effects of anticoagulants and potentially inhibit fludarabine uptake, reducing efficacy (*15*). Interestingly, alcohol (ethanol) consumption has also been reported to increase adenosine levels by decreasing adenosine re-uptake (*19*). Thus, alcohol consumption might potentiate the effects of dipyridamole and decrease antagonism by xanthines (reduce the half life of caffeine).

Regadenoson (Lexiscan)

General information / drug class:

Regadenoson is a potent adenosine derivative vasodilator with selectivety for receptor A_{2a}.

Mode of action:

Regadenoson is an adenosine derivative that is a selective A_{2a} agonist and extends several potential advantages over adenosine (*8,20,21*) (figure 2):

- It is given as an IV bolus at a fixed dose which 'uncomplicates' the infusion process.
- It produces less undesirable side effects (eg. AV block and bronchospasm) due to the A_{2a} selectivity.
- It could be used in patients with mild-to-moderate reactive airways disease.

Most clinical evaluations tend to focus on it being 'not inferior' to adenosine rather than on any specific tangible benefits over adenosine (*8*).

Pharmacokinetics:

Regadenoson is given by IV bolus injection with onset of action (increased coronary blood flow) occurring at 0.5-2.3 minutes post IV with 2.3 minutes being the recognized duration of action (*22*). Approximately 20-30% of regadenosine is plasma protein bound and it is not rapidly metabolized like adenosine (*22*). Regadenoson undergoes tri-phasic elimination with half lives of 2-4 minutes, 30 minutes and 2 hours repectviely (*22*).

Usual indications:

Regadenoson was developed specifically for stress testing.

Use in nuclear medicine:

Regadenoson is a vasodilatory pharmacological stress with specific application in patients with mild to moderate airways disease.

Proper use and dose administration:

The standard dose is 0.4mg in 5mL by IV injection over 10 seconds followed by a 5mL bolus saline flush after which, the radiopharmaceutical dose is injected (figure 4).

Contraindications:

As for adenosine with some flexibility in mild-moderate airways disease.

Warnings and precautions:

As for adenosine, however, regadenoson also decreases the seizure threshold so should be used with caution in those with history of seizures.

Adverse reactions:

Regadenoson has a 13 fold lower affinity for A_1 receptors than A_{2A} but is 10 times more potent than adenosine (*23*). Despite the selective A_{2A} agonistism designed to eliminate bronchoconstriction, there is a surpirisingly high incidence of dyspnea reported (*8*). The most common adverse reactions include dyspnea, headache, nausea, abdominal discomfort and ventricular conduction abnormalities; all occurring more frequently than with adenosine (*8*). Less frequently than adenosine, flushing, chest pain, angina, and AV block can occur (*8*). The use of regadenoson has an increased risk of seizures not evident with adenosine (*22*).

Common interactions:

As for adenosine.

Dobutamine (Dobutrex)

General information / drug class:

Dobutamine is a sympathomimetic beta-1 (β_1) agonist with positive inotropic (increased contractility) and chronotropic (increased heart rate) effects (*9,10,14,15*).

Mode of action:

Adrenergic β receptors are important to understand in cardiac pharmacology and will be discussed further below under β-blockers. There are three sub types for β adrenergic receptors designed to respond to catecholamines:

- β_1 receptors are found in the heart and kidneys with responsibility for increasing the rate and force of cardiac contraction, and renin secretion respectively.
- β_2 receptors are found in the lungs, liver and skeletal muscle causing, when activated by an agonist, vasodilation, bronchodilation, glycogenolysis and glucagon release.
- β_3 receptors are found in adipose tissue with responsibility for lipolysis.

Dobutamine is a powerful positive inotropic and chronotropic sympathomimetic drug with a primary mechanism of action through direct stimulation of β_1-receptors of the sympathetic nervous system (*9,10,16*). Dobutamine also demonstrates weak β_2 agonist activity (vasodilation) and α_1 activity (increases intracellular calcium concentrations) (*10*). In the extracellular space, endogenous norepinephrine and exogenous dobutamine can couple with β_1 receptors (figure 3). Receptor β_1 couples with an adenylate cyclase stimulating G protein to drive increased intracellular calcium which facilitates formation of actin - myosin cross bridges and produces an increased force and rate of contraction (*9-11*). Arbutamine has been used as an alternative to dobutamine with similar inotropic and chronotropic actions but less peripheral vasodilation (*4*).

Pharmacokinetics:

Dobutamine is inactive orally (*15*). The onset of action is 1-2 minutes after IV injection and the duration of action is 10 minutes (*10,11*). The half life post IV injection is just 2-3 minutes (*10,11,15*). Dobutamine is rapidly metabolized in the liver and conjugates with glucuronic acid before being mainly excreted in urine with a small fraction in feces (*11,15*).

Usual indications:

Dobutamine is used to treat acute heart failure and septic shock by increasing cardiac output (*11,15*).

Use in nuclear medicine:

The primary advantage of dobutamine in nuclear cardiology is the minimal β_2 activity which significantly reduces the risks in those with respiratory compromise (*7,14*). The absence of bronchospasm makes dobutamine the pharmacological stress agent of choice (over dipyridamole, adenosine and regadenosine) for patients with asthma or obstructive airways disease (*7,14,16*). From a practical sense, dobutamine can be employed in patients who have consumed caffeine and is ideal in those patients who are limited physically from undertaking exercise stress.

Proper use and dose administration:

The dose is administered as an incremental dose of 10 mcg/kg/min up tp 40 mcg/kg/min every 3 minutes (*15,17*) (figure 4). The radiopharmaceutical is administered when the target heart rate is reached.

Contraindications:

Hypersensitivity to dobutamine, hypertrophic cardiomyopathy, non-cessation of beta blockers, uncontrolled hypertension, unstable angina, atrial fibrillation, aortic stenosis, ventricular arrhythmias and pheochromocytomas are the main contraindications (*11,14,15*).

Warnings and precautions:

Caution should be exercised when using dobutamine in patients with acute myocardial infarction and cardiogenic shock (*15*). It is possible that dobutamine can interfere with the uptake of the radiopharmaceutical in myocardial perfusion imaging and, therefore, vasodilators are preferred (*7*).

Adverse reactions:

A wide range of adverse effects are possible with sympathomimetics and this reflects sympathetic nervous system stimulation (*11,15*). Dose related increases in heart rate, blood pressure, angina, and palpitation can occur (*11,15*). There is a greater risk of arrhythmia and decreased blood pressure (*12*). Angina, palpitations, headache, nausea, tachycardia are seen in 31-70% of patients (*11,14-16*). While a short half life allows adverse reaction resolution with infusion cessation, a fast acting β-blocker (eg. esmolol) may be used to reverse dobutamine (*14,16*).

Common interactions:

Dobutamine will interact with medications that affect blood pressure and with β-blockers (*15*). Severe interactions to be avoided can occur with monoamine oxidase inhibitors, tricyclic antidepressants, CNS stimulants, and drugs that deplete potassium (eg. diuretics, corticosteroids, aminophylline) (*15*).

ADJUNCTIVE MEDICATIONS

Adjunctive medications are those medications that may be used to directly respond to the patient's status during a nuclear medicine procedure. Given the emergency / crash trolley will be discussed in a separate article, this section will limit discussion to the reversal of pharmacologic interventions, and the use of salbutamol and nitroglycerin to manage acute adverse reactions. These adjunctive medications are discussed below and sumamrised in table 2.

Aminophylline

General information / drug class:

Aminophylline is a methylxanthine that is described as a xanthine based anti-asthma class medication (*11,15*). Aminophylline itself is a prodrug which, after administration, rapidly releases theophylline as its active bronchodilating constituent (*15*). Aminophylline is also a phosphodiesterase inhibitor, antagonizes CNS adenosine receptors causing stimulation, and has diuretic action stronger than caffeine (*15*).

Mode of action:

While theophylline antagonises all adenosine receptors, it has a greater effect on A_2 receptors (*9-11*). Antagonism of A_1 receptors reduces bronchoconstriction, increases CNS activity and increases cardiac contraction force while A_{2A} receptors antagonism blocks vasodilation, blocks anti-platelet activity and increases CNS activity (figure 2) (*10,11*). Theophylline also inhibits phosphodiesterase causing an increase in cAMP which in turn leads to smooth muscle relaxation and stimulation of cardiac muscles (*9-11*). Inhibition of phosphodiesterase, in theory at least, results in bronchodilation and increased cardiac contraction rate and force but this generally requires therapeutic doses (*9,10*).

Aminophylline is the *prodrug* ester derivative of theophylline. Aminophylline (or theophylline invivo) has higher affinity for adenosine receptors than does

adenosine itself and, thus, provides effective blockade (*9,11*). Aminophylline does not reduce the amount of either dipyridamole or adenosine but simply displaces them due to preferential binding.

Pharmacokinetics:

Theophylline gut absorption is unpredictable and can cause gastric irritation (*10,11*). Consequently, theophylline is given as the more soluble aminophylline which is rapidly hydrolyzed into theophylline and ethlenediamine at a ratio of 2:1 and a half life of several minutes (*10,15*). Theophylline is 50-70% plasma protein bound, is metabolized in the liver with urinary excretion, and 10% excretion in urine unchanged (*11,15*).

Theophylline and caffeine are metabolized in liver by CYP450 with elimination half lives of 8 and 4-6 hours respectively (*9,15*). The half lives do, however, vary significantly amongst individuals and in particular; nicotine smoking decreases half life by 50%, oral contraceptive use doubles the half life, the last trimester of pregnancy substantially increases half life (15 hours), liver disease increases half life, alcohol concumption decreases half life, and age increases half life (*9,15*).

Usual indications:

As an anti-asthmatic medication, aminophylline is not the first line therapy but rather is reserved for unresponsive life-threatening acute asthma (*15*). It can be used as a general bronchodilator in asthma and chronic obstructive airways disease management (*15*).

Use in nuclear medicine:

Theophylline competitively antagonizes adenosine at all adenosine receptor sub-types to reverse the effects of dipyridamole infusion. There is no need to reverse adenosine infusion due to the short half life of less than 10 seconds, however, the prolonged activity of dipyriadamole in increasing availability of extracellular adenosine requires antagonism.

Proper use and dose administration:

The standard reversal dose is 50-250mg of aminophylline by slow IV infusion to avoid adverse CNS and cardiovascular stimulant effects (*15*). There are several approaches including reversal only when patient symptoms warrant, and aminophylline reversal in all patients immediately following the stress test. An alternative approach adopted in some sites is to only use aminophylline reversal in severe symptoms or mild symptoms not resolved by a strong cup of coffee.

Warnings and precautions:

There are no specific contraindications but caution should be exercised in patients already taking xanthine medications, peptic ulcer disease (oral dose), porphyria, hyperthyroidism, hypertension, cardiac arrhythmia, heart failure, liver dysfunction and epilepsy (*11,15*).

Adverse reactions:

Hypersensitivity to the ethylenediamine component of aminophylline is possible (*15*). Tolerance can occur (*15*). Dose dependent adverse effects include CNS stimulation, gut disturbances (even IV), nausea, vomiting, diarrhea, abdominal pain, headache, insomnia, anxiety, irritability, tremor, and palpitations (*11,15*). Over dosage can cause excessive diuresis, dehydration, tachycardia, hypotension and metabolic acidosis (*11,15*). Overdosage can be treated with activated charcoal to increase elimination / decrease absorption of oral doses or β-blockers (*15*).

Common interactions:

Theophylline can interact with other medications that can enhance or reduce liver metabolism (*15*). Xanthine effects are additive with aminophylline (*9,15*). The effects of aminophylline can be potentiated by β_1 agonists and diuretics (*11*). Clearance of aminophylline can be reduced by acyclovir, allopurinol, some antiarrhythmics, antidepressants, cimetidine, disulfiram, fluvoxamine, interferon

α, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, and viloxazine (*11,15*). Clearance can be increased by phenytoin and antiepileptics, phenobarbitone, ritonavir, rifampicin and sulfinpyrazone (*11,15*). Theophylline can reduce the concentrations of lithium, macrolides, pancuronium and phenytoin (*11*).

Nitroglycerin (Glyceryl Trinitrate)

General information / drug class:

Nitrovasodilator / organic nitrate.

Mode of action:

Essentially nitroglycerin enhances oxygen delivery and reduces oxygen demand (*9-11*). Nitrites and nitrogen compounds enter the endothelial cell and are converted from arginine to nitric oxide (and citrulline) which in turn stimulates guanylate cyclase metabolism in smooth muscle cells (*9-11,15*) (figure 5). The resultant cyclic guanosine monophosphate (cGMP) activates a protein kinase causing protein phosphorylation (*9-11,15*). Vasodilation is associated with the reduction in calcium concentration and dephosphorylation of myosin (*9-11,15*). Nitroglycerin results in pooling of blood in veins and by reducing the amount of blood returned to the heart, decreases preload (left ventricular end diastolic volume) and decreases myocardial oxygen demand (*10,11,15*).

At low doses, nitroglycerin produces venodilation and reduced preload (*9,11,15*). Higher doses produce arterial dilation which reduces afterload (resistence against contraction). Reducing both preload and afterload effectively reduces the primary determinants of myocardial oxygen demand (*15*). Nitroglycerin also causes dilation of coronary (and collateral) vessels to more efficiently distribute blood and oxygen to ischemic tissues (*9-11,15*).

Two important relationships need to be outlined for nitroglycerin. Firstly, nitric oxide reacts with metals, thiols and oxygen and as such can modify proteins, lipids and DNA (*9*). Secondly, phosphodiesterase 5 inhibitors used for erectile dysfunction, like sildenafil (Viagra), function by potentiating the effects of nitric oxide in the corposa cavernosa (*9,10*).

Pharmacokinetics:

Nitroglycerin is rapidly absorbed from oral mucosa but bioavailability is reduced by extensive first pass metabolism in the liver (*9-11,15*). Other routes of administration see rapid activation by liver metabolism (*9*). Effects are therapeutic immediately after IV administration, after 1-3 minutes post sublingual or buccal administration, and 30-60 min after transdermal or ointment application (*9-11,15*). Duration of effect varies from 3-5 min for IV, 30-60 min for sublingual to 3-5 hours for buccal and 24 hours for transdermal (*9-11,15*). Nitroglycerin is metabolized in the liver and eliminated via the kidneys with a plasma half life of 2-3 minutes (*9-11*).

Usual indications:

Nitroglycerin is the initial therapy for treating ischemia and angina pectoris (*9-11,15*). It has also been used for treatment of heart failure and myocardial infarction (*9-11,15*).

Use in nuclear medicine:

Nitroglycerin is used to treat acute angina in response to stress testing and is generally administered in the form of sublingual spray/tablet or buccal tablets for rapid onset and relief of symptoms (*15*).

Proper use and dose administration:

For application in nuclear medicine in response to acute angina (*11,15*):

- One 300 to 600 mcg sublingual tablet under the tongue.
- One or two sprays of 400 mcg each directed onto or under the tongue.
- 2-3mg buccal tablet placed btween the upper lip and gum.
- Sublingual tablet or spray doses can be repeated if necessary at 5 minutes intervals but failure to respond to a maximum of 3 repeated doses requires medical intervention.
- Do not rinse mouth for 5 minutes after administration.

Contraindications:

Nitroglycerin is contraindicated with phenytoin, alteplase and levofloxacin (*15*). Concurrent use with phosphodiesterase type 5 inhibitors like sildenafil (Viagra) is also contraindicated (*9,11,15*). Nitrates are contraindicated in cardiomyopathy, hypotension, hypovolemia, aortic or mitral stenosis, severe anemia and increased intracranial pressure (*11,15*).

Warnings and precautions:

Caution should be exercised in renal and liver dysfunction, and in hypothyroidism (*15*). Sublingual and buccal preparations can reduce effectiveness associated with changes to oral moisture (*15*). Tolerance can develop (*10,11*).

Adverse reactions:

Flushing, dizziness, tachycardia, headache are common (*10,11,15*). Larger doses can lead to vomiting, restlessness, vision disturbances, hypotension and syncope (*10,15*). On rare occasions it may lead to cyanosis, respiratory dysfunction and bradycardia (*15*).

Common interactions:

Alcohol, antihypertensives and other vasodilators enhance hypotension (*11*).

Salbutamol / Albuterol

General information / drug class:

Direct acting sympathomimetic β_2 agonist.

Mode of action:

β_2 agonists like salbutamol dilate the bronchi by direct action (figure 6). Salbutamol mimics the effects of endogenous norepinephrine by coupling with bronchial smooth muscle cell surface β_2 receptors. Receptor β_2 couples with a G protein, stimulating adenylate cyclase to decrease intracellular calcium (*9,11*). This leads to calcium efflux from the cell and uptake in the sarcoplasmic reticulum stripping calcium from actin - myosin bridges to produce smooth muscle relaxation and bronchodilation (*9,11*). Short acting salbutamol is given by inhalation for direct action and symptom relief (*9*). Salmeterol is a longer acting β_2 agonist used regularly as a symptom preventer (*9*).

Pharmacokinetics:

After inhalation, 10-20% of the dose reaches the lower airways for direct action on smooth muscle (*15*). The direct action and rapid onset combined with the half life makes salbutamol a short acting bronchodilator suitable as a symptom reliever (*11*). It is not metabolized in the lung but does undergo first pass metabolism in the liver (*11,15*). Of the remainder not inhaled, that component swallowed will be readily absorbed from the gut (*15*). Salbutamol and its metabolites are rapidly excreted in urine with a small amount of fecal elimination. Plasma half life is 4-6 hours (*15*).

Rapid onset of action following inhalation (less than 5 min) with peak effect at 1 hour and duration of action lasting 3-6 hours (*9,11,15*). If given orally, onset of action is 30 min, peak 2-3 hours and duration 6 hours (*15*).

Usual indications:

High IV doses have been used to delay labour (*15*). Salbutamol is a bronchodilator for reversible airways obstruction (eg. asthma and chronic obstructive airways disease) (*9,15*).

Use in nuclear medicine:

In nuclear medicine patients having reversible respiratory difficulties including during or after stress testing, including exercise, may have symptom relief with salbutamol.

Proper use and dose administration:

For relief of acute bronchospasm, 1-2 inhalations of 100mcg each with a third inhalation if necessary 1 minute after the second (*11,15*). This same dose can be given prophylactically before stress testing (*15*).

Contraindications:

Hypotension.

Warnings and precautions:

Hyperthyroidism, myocardial insufficiency, hypertension, arrhythmia and diabetes mellitus are the main precautions (*11,15*). Plasma potassium levels should be monitored in severe asthma to minimize synergistic effects of medications causing hypokalemia (*15*).

Adverse reactions:

Adverse effects are reduced through inhalation and selectivity for β_2 (*15*). Tremor, palpitations, tachycardia, anxiety, headaches, peripheral vasodilation, muscle cramps, hyperglycemia are the main adverse reactions (*11,15*). Hypersensitivity has occurred which may manifest as paradoxical bronchospasm, angioedema, urticaria and hypotension (*15*).

Common interactions:

An increased risk of hypokalemia is associated with concurrent use with other β_2 agonists, corticosteroids, diuretics and xanthines (*11,15*). Concurrent use with other sympathomimetcis may cause sympathetic excitation while β-blockers antagonise effects (*11*). Antidepressant medications may potentiate cardiovascular effects (eg. tachycardia) (*11*).

CESSATION MEDICATIONS

There are a number of medications a patient may be taking that can interfere with nuclear cardiology studies, directly or through interference with the stress component of the study. A blanket cessation rule may be in place to uncomplicate patient preparation but three considerations need to be mentioned. First, the nuclear medicine study may be attempting to assess patient status on the medication. Second, withholding the medication may compromise the patient, including their ability to have the nuclear medicine study. Thirdly, not all cessation medications apply to each stress testing approach. How long medications are withheld should be determined by their half life; typically 5 half lives is adequate. Prescribed medications should only be ceased on consultation with the patient's physician. Medications that are generally ceased for a nuclear cardiology study are discussed below and summarised in table 3.

Xanthines

Xanthines are purines found throughout the body and structurally resemble adenine and guanine. The basic xanthine structure is, therefore, similar to the adenine portion of adenosine and this similarity allows antagonism of adenosine (*11*). *Methylation* (CH_3) of the xanthine produces a number of methylxanthines including caffeine, theobromine and theophylline. Caffeine is typically found in coffee, tea, guarana and yerba mate, theobromine in chocolate and yerba mate, and theophylline mostly in tea (and aminophylline).

While theophylline antagonizes all adenosine receptors (figure 2), it has a greater effect on A_2 receptors. Caffeine tends to be more selective for A_1 and A_{2A} and theobromine has higher activity for A_1 (*19*). Generally speaking, a single cup of strong coffee provides sufficient caffeine to block less than 20% of A_1 and A_{2A} receptors (*5,19*). To achieve 50% antagonism would require five times higher plasma concentrations and 80% antagonism would need 25 times high plasma concentrations (*5,19*).

Methylxanthines also inhibit phosphodiesterase causing an increase in cAMP which in turn leads to smooth muscle relaxation (figure 6) and stimulation of cardiac muscles (figure 3) (*9-11*). While this potentially results in bronchodilation and increased cardiac contraction rate and force, therapeutic range doses might be required (*9,10*).

Structurally, xanthine is a weak antagonist and the simple addition of a methyl (CH_3) group in theobromine increases receptor affinity by a factor of 40 (*24*). A further methyl group (theophylline and caffeine) provides affinity 80 times that of xanthine (*24*). Adenosine has significantly lower affinity than theophylline; allowing theophylline to displace adenosine at receptors. The NH_3 or CH_3 groups on various xanthines also change their potency. While caffeine has high affinity, it has poor potency, theobromine has low affinity and low potency, and theophylline has high affinity and high potency. This does question whether chocolate (theobromine) should be ceased prior to a myocardial perfusion stress test.

<u>Caffeine</u>

Caffeine is almost completely absorbed (99%) in the gastrointestinal tract within 45 minutes of consumption, however, plasma concentrations resulting from the same caffeine ingestion can vary from one person to the next by as much as 16 fold (*19*). Caffeine is metabolized in liver by CYP450 with an elimination half life of 4-6 hours but this can increase with oral contraceptive use, pregnancy, and liver disease, or decrease with nicotine and alcohol use (*9,19*). The major metabolites of caffeine include paraxanthine which approximates caffeine in potency, theobromine (low potency), and theophylline (3-5 times more potent) (*19*).

Managing methylxanthine cessation, therefore, requires an understanding of the affinity and potency, and the sources of caffeine (*5,19*):

- 150ml of coffee contains 40-180mg of caffeine.
- 150ml of decaffeinated coffee contains 2-8mg of caffeine.

- 150ml of tea, including iced tea, contains 24-50mg of caffeine.
- 150ml of cocoa only contains 2-7mg of caffeine.
- 28g of milk chocolate contains 1-15mg of caffeine.
- 28g of dark chocolate contains 5-36g of caffeine.
- 180ml of soft drink contain 15-24mg of caffeine.
- 180ml of energy drinks like red bull contain 80mg of caffeine.

Caffeine is also contained (100mg or more) in some medications including, but not limited to, migraine medications, pain relievers, diuretics, cold remedies, menstrual products, weight control medications and stimulants.

A single cup of coffee produces serum caffeine levels of 0.004mM, blocking 18% of adenosine receptors while toxicity occurs at 0.25mM (90% blockade) (*19*). In the unlikely scenario of caffeine toxicity in a stress test patient, 6 half lives (30 hours) would return serum caffeine levels to the equivalent of 1 cup of coffee. Also unlikely is 50% receptor blockade (0.02 mM) but this would only require 2 half lives (10 hours) to return to the equivalent of a single cup. Thus, the first 12 hours of caffeine abstinence provides a tangible benefit to patient preparation (dipyridamole and adenosine stress patients) while the marginal benefit beyond 24 hours is very small. A more intuitive approach might lead to greater compliance with both patient preparation and scanning.

Beta Blockers

As previously outlined, there are three sub types for β adrenergic receptors with the two of interest being (*9-11*):

- β_1 receptors are found in the heart and kidneys with responsibility for increasing the rate and force of cardiac contraction, and renin secretion respectively.
- β_2 receptors are found in the lungs, liver and skeletal muscle causing vasodilation, bronchodilation, glycogenolysis and glucagon release.

Anatgonists of the β adrenergic receptors are referred to as β-blockers and function by competitive blockade of the actions of catecholamines (*9-11,17*) (figure 3 and 5). β-blockers can be selective for either β_1 (atenolol, bisoprolol, esmolol and metroprolol) or β_2 (butoxamine), however, it is common for β-blockers to be non-selective (propranolol, sotalol, oxyprenolol and pindolol) or non selective for α and β receptors (labetalol and carvedilol) although they do not generally act on β_3 (*9*). A clinically important role of β-blockers is to limit the response to exercise or other excitatory stimuli (*9-11,17*). Thus, at exercise or excitation, β_1-blockers (or cardioselective blockers) work to reduce heart rate, cardiac output and arterial pressure (*9-11,17*). At high doses, selective β_1 blockers can also inhibit the action of β_2 receptors (*11*). This is particularly important in nuclear cardiology because β-blockers limit maximal response to exercise and, thus, pharmacologic vasodilation stress is required for patients on a β-blocker whose medication cannot be withheld for the purpose of stress testing. Furthermore, β-blockers in those with asthma can inhibit bronchodilation (*9-11*). Dobutamine stress, as a β agonist, is unsuitable in patients on β-blockers for obvious reasons. Furthermore, β-blockers limit vasodilation of skeletal muscles and can potentially reduce exercise capacity (*9,10*). As a selective β_2 blocker, butoxamine would not require cessation prior to an exercise or dobutamine stress test.

Using the 5 half life rule of thumb for cessation of medications prior to exercise or dobutamine stress testing, the following cessation times apply (*11*):

- Atenolol for 30-35 hours (half life 6-7 hours, 50% bioavailability, 85-100% renal elimination).
- Bisoprolol for 50-60 hours (half life 10-12 hours, 80% bioavailability, 50% renal elimination / 50% hepatic elimination).
- Metroprolol for 15-25 hours (half life 3-5 hours, 40% bioavailability, 90% hepatic elimination).
- Propranolol for 15-30 hours (half life 3-6 hours, 25% bioavailability, 99% hepatic elimination).
- Sotalol for 35-90 hours (half life 7-18 hours, 100% bioavailability, 90% renal elimination).
- Oxyprenolol for 5-15 hours (half life 1-3 hours, 24-60% bioavailability, 95% hepatic elimination).
- Pindolol for 15-20 hours (half life 3-4 hours, 75% bioavailability, 50% renal elimination / 50% hepatic elimination).
- Labetalol for 30-40 hours (half life 6-8 hours, 20% bioavailability, 95% hepatic elimination).
- Carvedilol for 30-50 hours (half life 6-10 hours, 25% bioavailability, 75% hepatic elimination).

Calcium Channel Blockers

Calcium channel blockers stop the influx of calcium through the calcium channel of cell membranes in both cardiac myocytes and smooth muscle cells (*9-11*). Calcium channel blockers decrease the intracellular calcium concentration, reducing the release of calcium from the sarcoplasmic reticulum and thus blunting the calcium driven excitation-contraction coupling of actin - myosin cross bridges (*9-11*). Consequently, calcium channel blockers reduce cardiac contraction force (negative inotrope) which make them incompatible with effective exercise or pharmacological stress testing (figure 2 and 3). Calcium channel blockers can be used to treat angina, tachyarrythmias and hypertension (*9-11*).

Calcium channel blockers are metabolized in the liver (CYP3A4) to metabolites that tend to have their own activity (*9-11*). Given the CYP3A4 metabolism, a wide variety of drug interactions can occur and this will vary from one medication to another, however, generally calcium channel blockers interact with β-blockers, carbamazepine, cyclosporin, digoxin and inhibitors of CYP3A4 (eg. grape fruit juice).

Using the 5 half life rule of thumb for cessation of medications prior to exercise or pharmacological stress testing, the following cessation times apply (*11*):

- Amlodipine for 175-225 hours (half life 35-45 hours, 65% bioavailability).
- Diltiazem for 20 hours (half life 4 hours, 40-50% bioavailability).
- Felodipine for 75-100 hours (half life 15-20 hours, 15-20% bioavailability).
- Nifedipine for 10 hours (half life 2 hours, 50% bioavailability).
- Verapomil for 20 hours (half life 4 hours, 20% bioavailability).

Nitrates

Organic nitrates, like glyceryl trinitrate, have been discussed in detail above and outlined in figure 6. As a cessation medication, the aformentioned vasodilatory effects in reducing both cardiac preload and afterload has the potential to interfere with the effectiveness of exercise, vasodilatory and dobutamine stress testing. Unlike adenosine and dipyridamole, importantly nitrates dilate collateral blood supply (*9*).

When considering the period of cessation prior to a myocardial perfusion stress test, consideration to both the medication half life and dose form needs to be given. The relatively rapid action of sublingual and buccal dose forms can reduce the cessation period compared controlled release dose forms (tablet or patches). More importantly is the elimination half life. Short duration nitrates like glyceryl trinitrate with a plasma half life of 2-3 minutes taken in the hours immediately preceeding the stress test are unlikely to be prohibitive of performing the stress test; especially if delivered via sublingual or buccal routes. Conversely, longer acting nitrates like isosorbide mononitrate with its 5 hour plasma half life, regardless of the route of administration, will require cessation for 24 hours. Cessation commencement is when the last dose was administered or when the patch was removed.

Digoxin

Digoxin is a cardiac glycoside that originates from the foxglove plant (digitalis). Digoxin is used to treat heart failure and cardiac arrythmias (*9-11*). The action of digoxin is associated with the inhibition of the sodium / potassium pump (figure 3). Inhibition of the sodium potassium pump increases intracellular sodium and this inhibits the efflux of calcium, increasing uptake of calcium in the sarcoplasmic reticulum (*9-11*). In turn, this provides more calcium ions for release to form actin - myosin bridges which produce the excitation / contraction coupling and an increased cardiac contraction force (inotrope) (*9-11*). It should be noted that the increased contraction force and cardiac output are achieved without increased oxygen demand (*9,11,25*). Digoxin produces a paradoxical negative chronotropic action (decreased rate of contraction) and slows AV conduction velocity (negative dromotropic) (*9,11,25*). This is achieved by increasing resting membrane potentials leading to decreasing the sensitivity of the SA and AV nodes to sympathetic and catecholamine stimuli (*9,11*). The plasma half life of digoxin is 20-50 hour which increases to 3-5 days in renal dysfunction (*9,11*). Digoxin is primarily eliminated unchanged by the kidneys (80%) with the remainder being eliminated by the biliary system without liver metabolism (*11*). Clearly these actions interfere with exercise or dobutamine stress testing and require cessation for 2 weeks; longer in patients with renal dysfunction.

Digoxin has a narrow therapeutic index and extensive list of drug interactions, perhaps the most important of which are those that increase digoxin serum levels (increased absorption or delayed elimination) and risk toxicity (eg. amiodarone, calcium channel blockers, quinine, and spironolactone) (*11*). Digoxin is also associated with significant adverse effects including nausea, vomiting, diarrhea, anorexia, visual disturbances, confusion, agitation, sleep disturnaces and less commonly, arrythmias (*11*). Caution should be exercised when used with patients having renal or thyroid dysfunction, electrolyte imbalances, and acute myocardial infarction (*11*). It is contraindicated in patients with heart block, ventricular

arrythmia, obstructive cardiomyopathy, cor pulmonale, constrictive pericarditis and known hypersitivity to digoxin (*11*).

CONCLUSION

Nuclear cardiology demands an understanding of basic pharmacology for interventional, adjunctive and cessation medications. An insight into the complex interaction between interventional, adjunctive and cessation medications in nuclear cardiology enhances practice and patient safety, and ensures the nuclear medicine technologist meets the minimum capabilities for their scope of practice (*1*).

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Figure 1: Schematic representation of the general principle of pharmacological stress in myocardial perfusion imaging. Ischemic myocardium may maintain resting blood supply with collateral vessels and resting vasodilation. Under pharmacologic vasodilation or increased oxygen demand (exercise or inotropic), the blood flow difference between normal and stenosed vessels will exaggerate the blood flow difference and expose coronary flow reserve (the difference between maximum and resting flow rates). This may be further influenced by coronary steal.

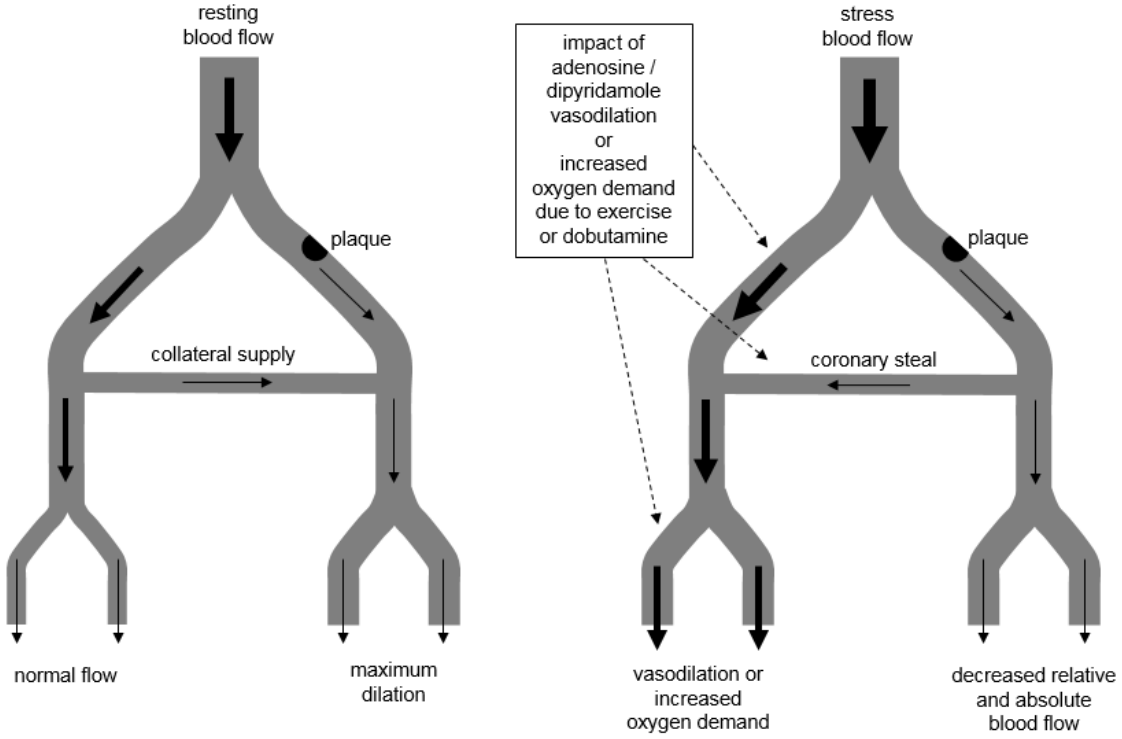

Figure 2: Schematic representation of the action of vasodilating agents in a vascular smooth muscle cell. Endogenous adenosine is produced in vascular smooth muscle cells and leaves the cell. In the extracellular space, endogenous and exogenous adenosine can couple with the 4 types of adenosine receptors. Receptor A_1 couples with an adenylate cyclase inhibitory G protein to produce atrioventricular (AV) block and some bronchoconstriction. Receptor A_3 couples with an adenylate cyclase inhibitory G protein to produce bronchoconstriction. Receptor A_{2b} couples with an adenylate cyclase stimulating G protein to produce mast cell degranulation, peripheral vasodilation and anti-platelet activity. Receptor A_{2a} couples with an adenylate cyclase stimulating G protein to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) and produce coronary and peripheral vasodilation. Regadenosine is selective for receptor A_{2a} to produce vasodilation. Caffeine has greater selectivity for receptors A_1 and A_{2a} to antagonize those actions. Theophylline (aminophylline and tea) has 3-5 times higher potency than caffeine in antagonizing receptors A_1 and A_{2a} while theobromine (typical of chocolate) has lower potency than caffeine. Dipyridamole antagonizes adenosine deaminase which reduces adenosine metabolism and thus increases availability of adenosine in the extracellular space. Dipyridamole is also a phosphodiesterase inhibitor so blocks conversion of cAMP to adenosine monophosphate (AMP), further increasing vasodilation. Calcium channel blockers act to antagonize the voltage dependent calcium channel to block vasodilation.

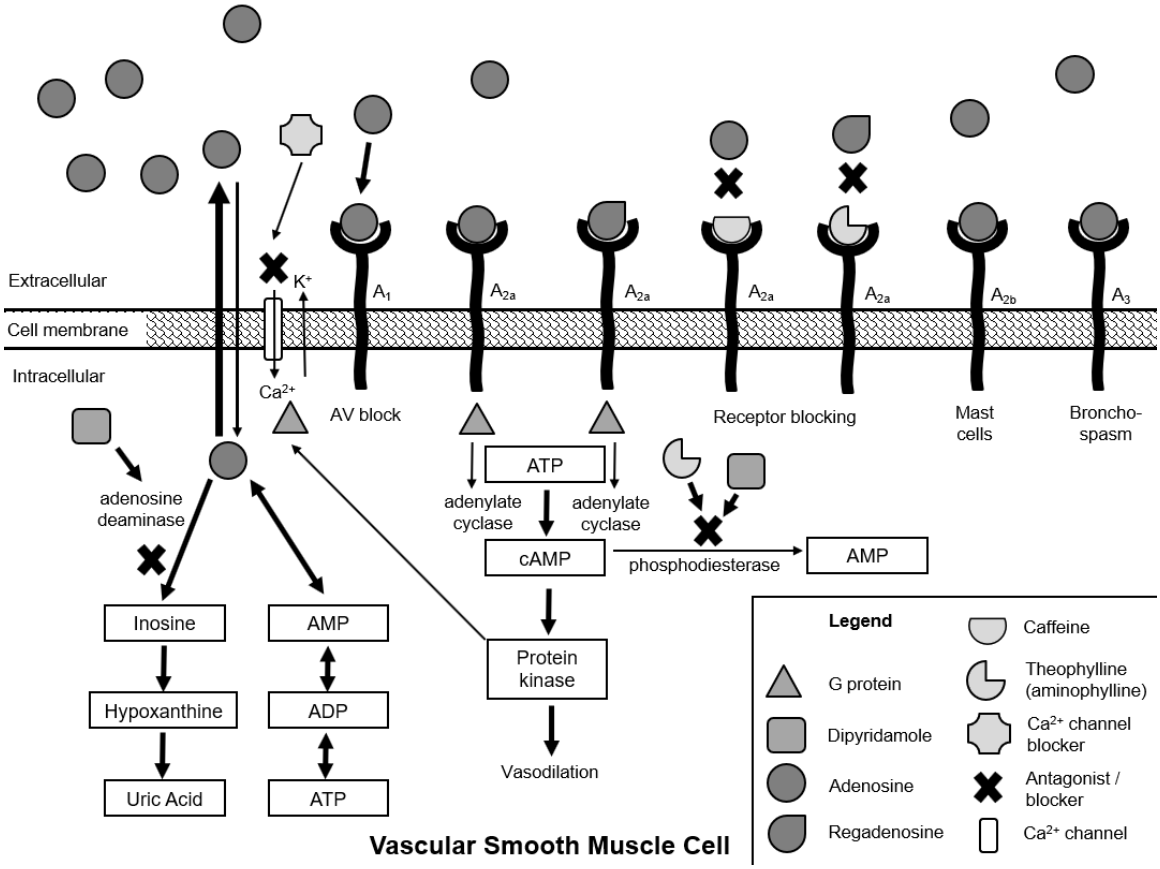

Figure 3: Schematic representation of the action of inotropic / chronotropic agents in a cardiac myocyte. Endogenous norepinephrine is released from the sympathetic nerve. Note that in a re-uptake mechanism failure (eg. heart failure), excess norepinephrine is available for beta-1 (β_1) activation. In the extracellular space, endogenous norepinephrine and exogenous dobutamine can couple with β_1 receptors. Receptor β_1 couples with an adenylate cyclase stimulating G protein to drive increased intracellular calcium which facilitates formation of actin - myosin cross bridges and produces an increased force and rate of contraction. This response can be antagonized by a beta blocker either non-selective (eg. propranolol) or selective for β_1 (eg. atenolol). Calcium channel blockers act to antagonize the voltage dependent calcium channel to block the inotropic and chronotropic contraction response. Likewise, cardiac glycosides like digoxin antagonize the sodium / potassium pump to increase intracellular calcium via the calcium exchanger, increasing the force of contraction.

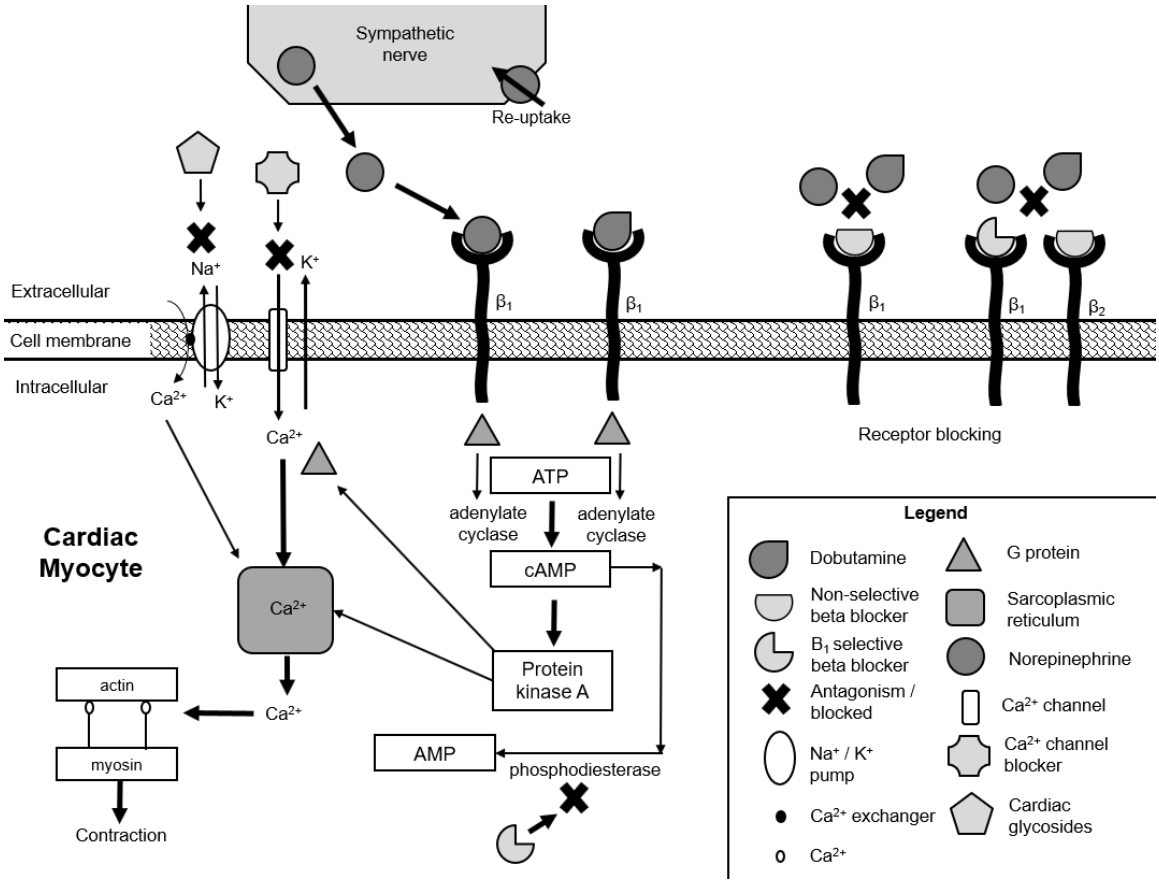

Figure 4: Comparison of the infusion techniques for the main pharmacological stress agents.

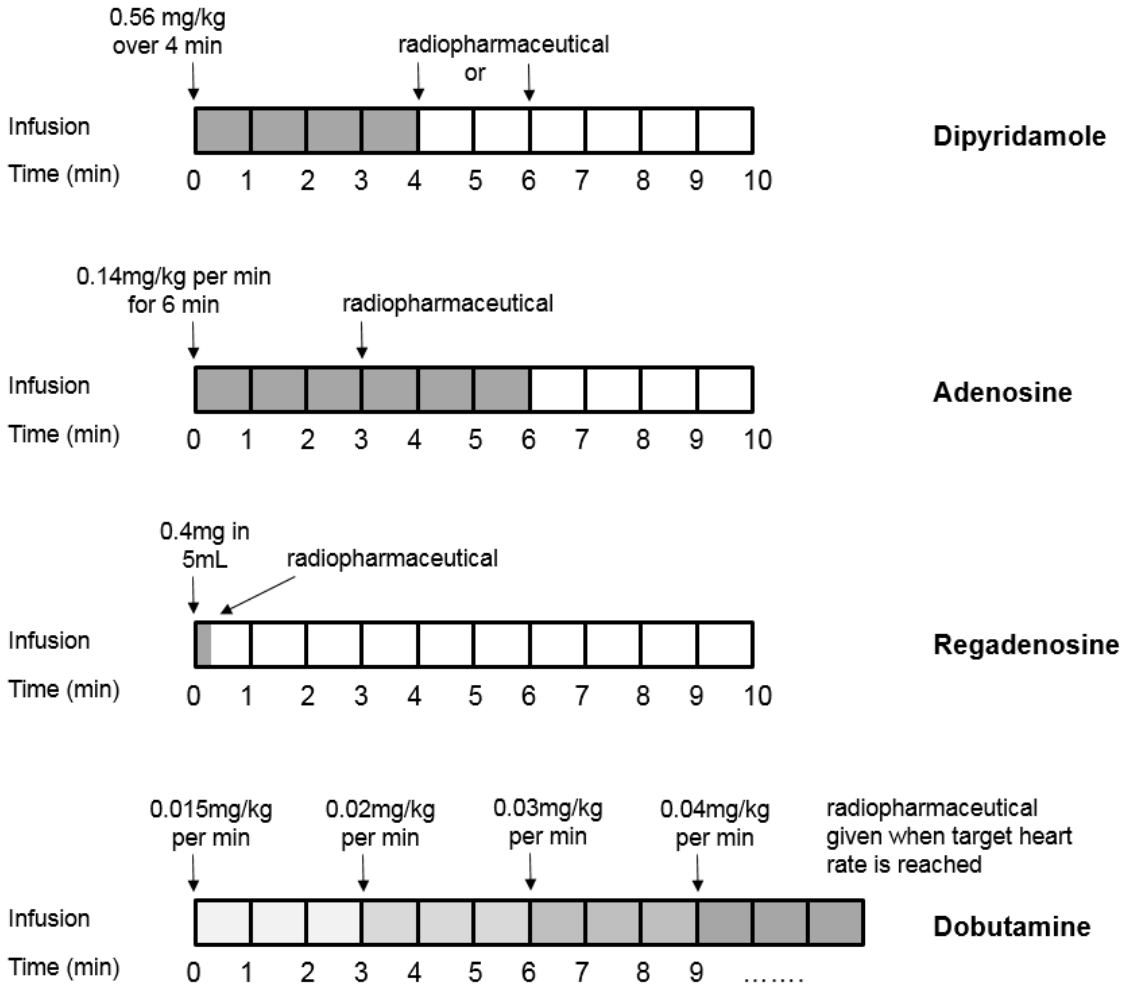

Figure 5: Schematic representation of the production of nitric oxide in endothelial cells with subsequent activation of guanylate cyclase in smooth muscle cells. This facilitates the conversion of guanine triphosphate (GTP) to cGMP, activating protein kinase G which leads to smooth muscle relaxation and vasodilation. It is worth noting that cGMP is converted to GMP by phosphodiesterase 5. Thus, the use of phosphodiesterase inhibitors like sildenafil (Viagra) block this conversion, potentiating the effects of cGMP. It is essential, therefore, to be aware of potential sildenafil use in patients who may receive cardiac medications and, in particular, nitroglycerin.

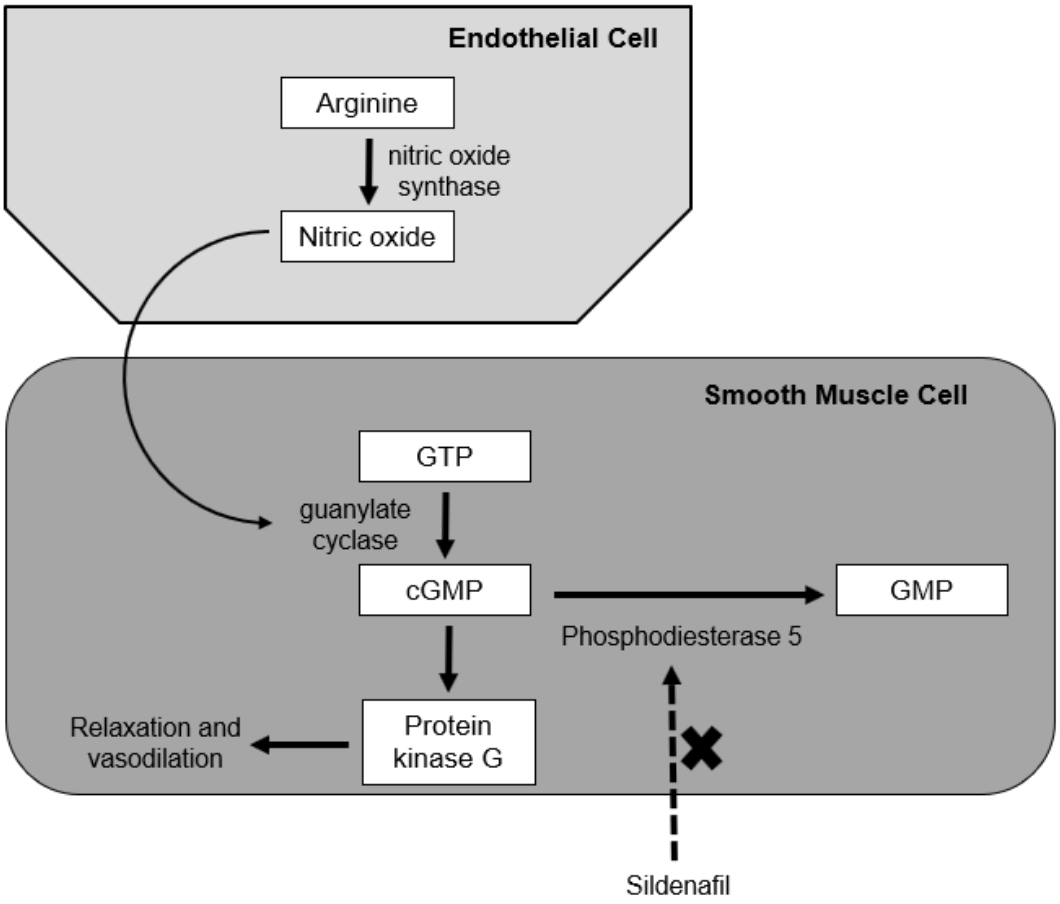

Figure 6: Schematic representation of the action of β agonism in a bronchial smooth muscle. Endogenous norepinephrine is released from the sympathetic nerve. In the extracellular space, endogenous norepinephrine and exogenous salbutamol can couple with β_2 receptors. Receptor β_2 couples with an adenylate cyclase stimulating G protein to produce decreased intracellular calcium through calcium efflux and uptake in the sarcoplasmic reticulum leading a reduction in actin - myosin bridge formation producing smooth muscle relaxation and bronchodilation. Inhibition of phosphodiesterase conversion of cAMP to AMP by methylxanthines (eg. caffeine, theobromine, theophylline) further decreases intracellular calcium. This response can be antagonized by a β-blocker either non-selective (eg. labetalol) or selective for β_2 (eg. butoxamine).

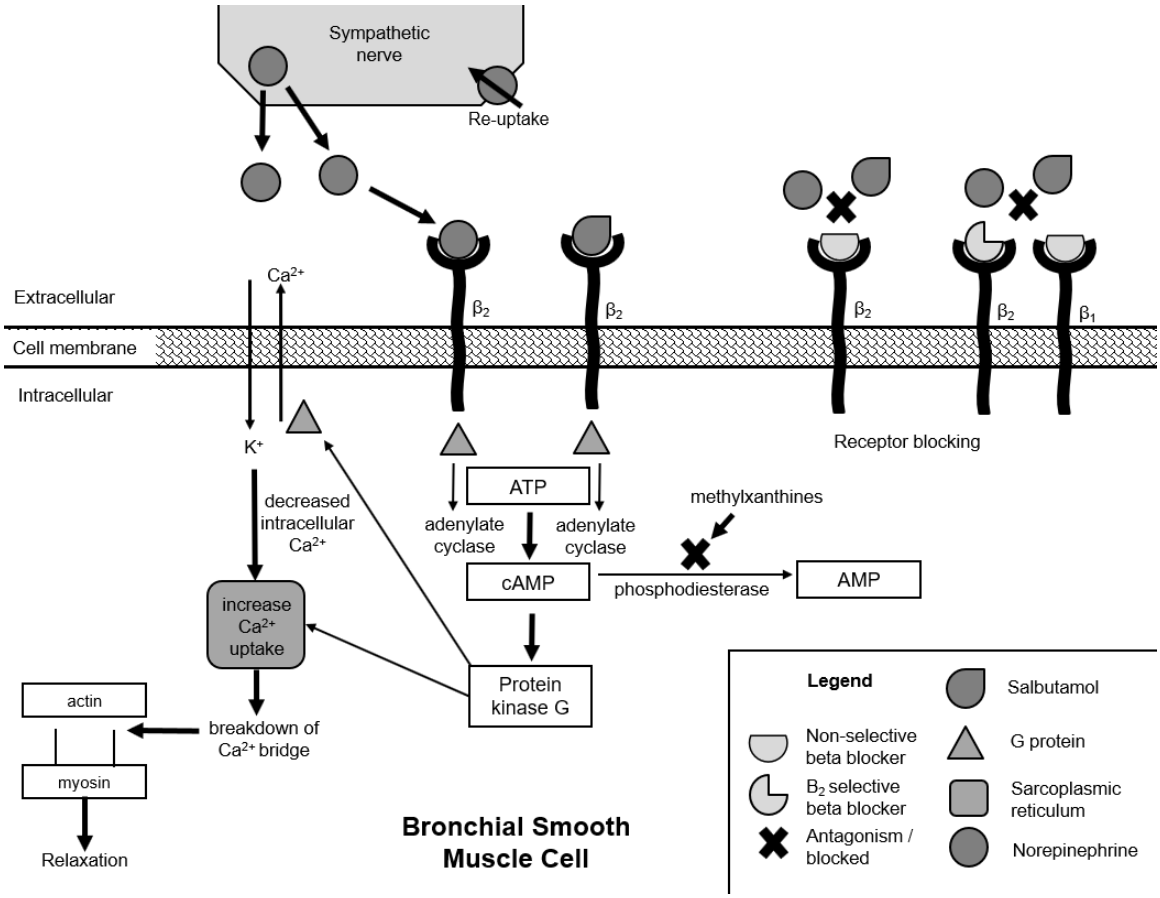

Table 1: Interventional medications used for cardiac stress testing (*7-12,15-17*). Duration is the period of significant or measurable effect. Some adverse effects are more likely when used therapeutically than in single interventional doses.

Drug	Indication	Dose	Pharmacokinetics	Mechanism of Action	Contraindications / Cautions	Adverse Effects / Interactions
Adenosine	Vasodilator stress	Alternative approach is 140 mcg/kg/min for 6 min with radiopharmaceutical administered at 3 min. Alternative approach is 140 mcg/kg/min for 4 min with radiopharmaceutical administered at 2 min.	• Rapid onset • Peak < 1 min • Half life < 10 sec • Duration < min constant infusion • No plasma protein bound	Vasodilation through activation of adenosine receptor A_{2a}.	Contraindicated in AV block, severe bronchospasm or asthma, known hypersensitivity. Use with caution in hypotension, unstable angina, oral dipyridamole therapy and medications that suppress SA or AV nodes. Long standing methyxanthines need cessation for 5 half lives.	Adverse reactions include chest, neck, jaw or arm pain, headache, flushing, dyspnea and ECG changes. Bronchospasm is possible, especially in asthmatics. Adverse reactions reversed with cessation of infusion. Interactions include caffeine / xanthine drugs or foods.
Dipyridamole	Vasodilator stress	0.56 mg/kg IV in 20-40 mL of saline over 4 min with radiopharmaceutical administered at the end of 4 min infusion or 2 min after completion of infusion.	• 1-2 min onset • Peak 4 min • Half life 10-12 hours • Duration can be prolonged without reversal • 90-99% plasma protein bound	Inhibits cellular uptake of adenosine to increase availability of endogenous adenosine. Vasodilation through activation of adenosine receptor A_{2a}.	As for adenosine.	As for adenosine except adverse reactions reversed with aminophylline.
Regadenosine	Vasodilator stress	0.4mg in 5mL IV bolus followed by 5mL saline flush and	• 0.5-2.3 min onset • Duration 2.3 min • Half life is	Vasodilation through selective activation of	As for adenosine except potentially more flexible in mild	As for adenosine except less bronchoconstriction

		immediate administration of the radiopharmaceutical.	triphasic with 2-4, 30, and 120 min respectively • 20-30% plasma protein bound	adenosine receptor A_{2a}.	to moderate airways disease.	but does have risk of seizures.
Dobutamine	Stress testing through increasing oxygen demand	10 mcg/kg/min IV increasing to 20 mcg/kg/min, 30 mcg/kg/min, and 40 mcg/kg/min every 3 minutes.	• 1-2 min onset • Duration 10 min • Half life 2-3 min • 40% plasma protein bound	Syntheitc catecholamine beta-2 adrenoreceptor agonist that produces increased rate and force of contraction.	Contraindicated in hypertrophic cardiomyopathy, uncontrolled hypertension, unstable angina, atrial fibrillation, beta blocker use, and known hypersensitivity. Use with caution in myocardial infarction and cardiogenic shock. Beta blockers need cessation for 5 half lives.	Adverse reactions include angina, palpitations, headache, nausea, tachycardia. Adverse reactions reversed with cessation of infusion or beta blockers. Interactions include blood pressure medications, beta blockers, triclyclic antidepressants, MAOIs, CNS stimulants, potassium depleting drugs.

Table 2: Adjunctive medications commonly used in nuclear cardiology (*7-12,15-17*). Some adverse effects are more likely when used therapeutically than in single adjunctive doses.

Drug / Indication / Dose	Pharmacokinetics / Mechanism of Action	Contraindications / Cautions	Adverse Effects / Interactions
Aminophylline Reverse dipyridamole 125-250mg by slow IV	• Rapid onset and peak • Half life 8 hours • 50-70% plasma protein bound Antagonises all adenosine receptors.	No absolute contraindication, however, caution in patients with porphyria, hyperthyroidism, hypertension, arrhythmia, heart failure and liver dysfunction.	Adverse effects include CNS stimulation, gut disturbances, headache and palpitations. Interactions include xanthine products and medications, medications altering liver metabolism, acyclovir, allopurinol, some antiarrhythmics, antidepressants, cimetidine, disulfiram, fluvoxamine, interferon alfa, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, viloxazine, phenytoin and antiepileptics, phenobarbitone, ritonavir, rifampicin, sulfinpyrazone, lithium, macrolides, pancuronium and phenytoin.
Nitroglycerin Relieve acute angina 300-600mcg sublingual tablet or 1-2 sprays of 400mcg each onto or under the toingue or 2-3mg buccal tablet	• 1-3 min onset • Half life 2-3 min • Duration 30-60 min Facilitates nitric oxide metabolism which causes vasodilation and reduced preload and afterload.	Contraindicated in hypotension, hypovolemia and increase intracranial pressure. Contraindicated with the use of phenytoin, alteplase, levofloxacin and sildeniafil. Caution in renal and liver dysfunction, and hypothyroidism.	Adverse reactions include flushing, dizziness, tachycardia and headache. Interaction include alcohol, antihypertensives and vasodilators.
Salbutamol Relieve dyspnea and bronchospasm 1-2 inhalations of 100mcg each with a third inhalation if necessary 1 minute after the second	• 5 min onset • Peak 60 min • Half life 4-6 hours • Duration 3-6 hours Direct acting β_2 agonist to dilate bronchi	Contraindicated in hypotension. Caution in hyperthyroidism, myocardial insufficiency, hypertension, arrhythmia and diabetes mellitus.	Adverse reactions include tremor, palpitations, tachycardia, anxiety, headaches, peripheral vasodilation, muscle cramps, hyperglycemia and hypersensitivity. Interactions with other β_2 agonists, corticosteroids, diuretics, xanthines, beta blockers and antidepressants.

Table 3: Cessation medications commonly used in nuclear cardiology should be stopped for 5 half lives of the medication but only in consultation with the primary care physician.

Drug	Cessation window	Comment
Nitrates	12-24 hours for exercise, vasodilator and dobutamine stress testing.	24 hours of cessation should be used for long acting nitrates. 1 hour cessation could be used for short acting nitrates delivered in sublingual forms. For patches, cessation commences at the time the patch is removed.
Beta blockers	48 hours for exercise and dobutamine stress testing.	24 hours is sufficient for those with shorter half lives but longer than 48 hours may be required for longer half lives. Refer to specific half life of β-blocker is use for potential variations.
Calcium channel antagonists	48 hours for exercise, vasodilator and dobutamine stress testing.	24 hours is sufficient for those with shorter half lives but longer than 48 hours may be required for longer half lives. Refer to specific half life of calcium channel blocker is use for potential variations.
Methylxanthine food and drinks including caffeine	12-24 hours for vasodilator stress testing.	There is unlikely to be a marginal benefit beyond 24 hours cessation, however, 6 hours could be sufficient for those with mild consumption. Caffeine and theophylline products (coffee, tea etc) are of importance while theobromine (chocolate) is less likely to have benefits from cessation.
Methylxanthine medications	1-5 days for vasodilator stress testing depending on formulation.	Refer to the specific half life of the medication to determine appropriate cessation period. Most medications are theophylline based or caffeine containing and thus, 24 hours is adequate for most (unless in a controlled release form).
Dipyridamole	12-24 hours for vasodilator stress testing.	The half clearance time for dipyridamole should allow a cessation period of 12 hours to be used if urgent.
Digoxin	2 weeks for exercise and dobutamine stress testing.	Longer should be considered in known renal dysfunction.