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PHARMACOLOGY IN NUCLEAR CARDIOLOGY.

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Abstract

While exercise remains the preferred method of cardiac stress testing, pharmacological stress plays an important role in nuclear cardiology. The globally aging population will see an expansion of the application of pharmacological stress testing and with that, comes the need to understand the pharmacologic basis, mechanisms of action, potential interactions and adverse effects to inform use in less than ideal circumstances. This article aims to enhance the decision-making process in day-to-day clinical nuclear cardiology practice through a better understanding of nuances relevant to the pharmacological agents employed for cardiac stress testing.

Introduction

The protocols and procedures employed in nuclear cardiology several decades ago were quite different to those of today. While the underlying principles have not changed, the radiopharmaceuticals, imaging equipment and imaging protocols have evolved. The basic principle of myocardial perfusion imaging is to create a disparity in blood flow between normal and stenosed arteries which can be achieved by either increasing the myocardial oxygen demand or by vasodilation of coronary arteries (*1*). While exercise remains the preferred method of stress testing due to added physiologic and ECG information, pharmacological stress overcomes a number of barriers to exercise stress testing including physical disability, peripheral vascular disease, neurological dysfunction, respiratory disease, degenerative joint disease and negative chronotropic cardiac medications (*1-4*). Pharmacological stress testing also plays an important role in avoiding the anteroseptal perfusion artefact associated with exercise in left bundle branch block (*3,5*). To date, pharmacologic agents are used in lieu of exercise in half of the stress myocardial perfusion studies performed in the United States (*6-10*) and its popularity is likely to increase with the aging of the world population.

With the expanding application of pharmacological stress comes the need to understand the pharmacologic basis, mechanisms of action, potential interactions and adverse effects of the various agents relevant in today's nuclear cardiology practice. A detailed understanding of the pharmacology of stress agents extends advantage, particularly when circumstances vary from ideal. For example, nuclear medicine departments vary their patient preparation regarding caffeine cessation from 6 hours, 12 hours, 24 hours and 48 hours. Generally all patients are asked to cease caffeine 'in case' they are required to have pharmacological stress and as a general rule each department has a 'one size fits all' policy. Such distinct lack of 'flexibility' in the protocols might be avoided with a better pharmacological understanding.

This article aims to enhance the decision-making process in day-to-day clinical nuclear cardiology practice through a better understanding of nuances relevant to the pharmacological agents employed for stress testing.

Introduction to Pharmacology

Pharmacology is the study of the action of drugs on living systems and the interactions of drugs with living systems (*11-14*). Generally speaking, pharmacology is divided into *pharmacodynamics* and *pharmacokinetics* (*11-14*). A *drug* is a chemical substance that produces a biological effect and can be either synthetic or derived from plant, animal or mineral sources (*11-14*). Generally a drug is *exogenous* although *endogenous* sources might also exist (*11-13*); for example, adenosine is an endogenous drug produced by the body while dipyridamole is an exogenous drug introduced to the body.

Receptors are proteins (macromolecules) that mediate drug activity (*11-13*). The chemical signal (*ligand*) binds to a specific site (receptor) and triggers a response in the cells (*11-13*). The intra-cellular changes initiated by the ligand-receptor complex can be through direct or indirect action, however, the ligand generally functions as an agonist or an antagonist (*11-13*). An *agonist* will mimic the endogenous ligand to produce a similar response while an *antagonist* blocks the usual ligand and, thus, inhibits the physiological response (*11-13*).

Specificity is the measure of a receptors ability to respond to a single ligand (*11-14*). Low specificity generally results in physiological responses not targeted or intended by the drug; side effects provide a good example. *Selectivity* defines the ability of the receptor to distinguish between drugs and has the same implications as specificity; indeed the terms are often used interchangeably (*11-14*). *Affinity* defines the strength of attraction between the drug and its receptor (*11-13*). A high affinity is generally associated with a lower dose requirement (compared to low affinity for the same receptor). *Potency* describes the relationship between the drug dose and the magnitude of the effect (*11-14*). High potency induces a maximum effect with a minimum of drug. *Efficacy* is the invivo potency (*11-13*). The interaction (eg. absorption, metabolism, excretion) of the drug in the body may alter the relative *bioavailability* and thus, change the theoretical effect of the drug.

Vasodilators Stress Agents

Vasodilators have a direct and potent impact on blood flow through coronary arteries to accentuate the blood flow differences between normal and diseased vessels. While vasodilators do not cause ischaemia, they are effective in evaluating coronary flow reserve.

Adenosine

Adenosine is an *endogenous* purine nucleoside (Figure 1) composed of a molecule of adenine (*azole* and *pyrimidine* ring complex) and a molecule of ribose sugar (*furan* ring complex) (*11,12,14*). It is produced in vascular smooth muscle and endothelial cells from adenosine triphosphate (ATP) or the S-adenosyl methionine pathway before entering the extracellular space where it interacts with adenosine receptors (*6*). Adenosine is recognised most commonly for its role in energy transfer; ATP and adenosine diphosphate (ADP) (*3,11,12*). It also plays a key role in intracellular signal transduction in the form of cyclic adenosine monophosphate (cAMP) which is a second messenger for substrates unable to cross the cell wall (*3,11,12*). Adenosine is rapidly metabolised by adenosine deaminase or xanthine oxidase in the intracellular space of endothelial, smooth muscle and red blood cells (*6*). Metabolism provides a clue to activity with conversion of the NH_2 to a double bond oxygen (O) by adenosine deaminase resulting in a loss of activity but not affinity. The hydrogen (H) substituent on the pyrimidine ring provides bonding to the lipophilic pocket of the adenosine receptor. The structure-activity relationship will be further described in the discussion of methylxanthines below.

There are four main adenosine receptor sub-types (*3,6,11,12*):
1. A_1, block atrioventricular (AV) conduction, reduce force of cardiac contraction, 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}, stimulate phospholipase activity, release of mast cell mediators, and actions on colon and bladder.

4. A_3, stimulate phospholipase activity and release of mast cell mediators (contributes to bronchoconstriction).

Furthermore, adenylate cyclase is a lyase enzyme that forms an important part of the cAMP pathway (*11,12*). A_{2A} and A_{2B} stimulate adenylate cyclase activity while A_1 and A_3 inhibit it. A_2 receptors stimulate nociceptive afferent neurons in the heart which is part of the pain mechanism in ischaemic angina (*11*). A_1 receptors inhibit glutamate release to provide a neuroprotective effect in cerebral ischaemia (*11*). It is worth noting that some authors indicate that bronchospasm is caused by the A_{2B} and / or A_3 receptor (*7,9,10*). This is likely to relate to the secondary effect of phospholipase stimulation (A_{2B} and A_3) causing some degree of bronchoconstriction, however, the major pharmacological bronchoconstriction arises from the A_1 receptor. This is supported by caffeine interfering with A_1 and A_{2A} in the main and having known bronchodilatory actions. Nonetheless, the effects of A_{2B} and A_3 receptors on histamine release from mast cells has a significant bearing on respiratory compromise in asthmatics.

The role adenosine plays in promoting sleep and suppressing excitement (inhibitory neurotransmitter) is beyond the scope of this article, however, A_1 and A_{2A} receptors play a crucial role in regulating sleep (*15*). Caffeine and other drugs that share a similar purine structure with adenosine (theobromine, theophylline, xanthine) are adenonsine receptor anatgonists (*11,14*). After intravenous (IV) administration, adenosine has immediate onset of action and is rapidly metabolised to inosine and AMP (*14*). The negative impact of caffeine on sleep relates to antagonsim of the adenosine receptor (*15*).

From a cardiovascular perspective the A_1 and A_{2A} receptors are the most important. Adenosine receptors are found in cardiac myocytes, sinus node and AV node (*3*). Inhibition of adenylate cyclase and the resulting reduction in cAMP causes hyperpolarisation by increasing potassium conduction in the heart (*3,11,12*). This action is responsible for the transient heart block associated with adenosine and is related to the A_1 receptor (*3,11,12*). Adenosine is a class V antidysrythmic drug due to its effect on the

AV node (*3,11,12*). With respect to pharmacological stress in myocardial perfusion imaging, adenosine (A_{2A} receptor) causes arterial smooth muscle relaxation (*11,12*). As a result, normal arteries dilate while atherosclerotic arteries do not (*11,12*). The resulting exaggeration in the difference between the blood flow in normal coronary arteries and the blood flow in atherosclerotic coronary arteries causes differential perfusion patterns. The general principle appears sound and certainly the perfusion images have been successful, whether single photon emission computed tomography (SPECT) or positron emission tomography (PET). The goal of myocardial perfusion imaging regardless of the method of stress, however, is to assess the haemodynamic status of the coronary arteries by assessing hyperaemic response and coronary flow reserve (*10*). If stress were to induce ischaemia (exercise or dobutamine), the resulting perfusion patterns would indicate the vascular territories associated with a functionally significant stenosis. In contrast, adenosine exaggerates the blood flow difference between normal and stenosed coronary arteries and a resulting perfusion deficit may indicate more about the anatomy of the plaque than the physiology. Furthermore, the the percentage of patients who experience adenosine induced ischaemia due to *coronary steal*, may be experiencing non physiological ischaemia unattainable with exercise alone (Figure 2). This may explain the unclear significance of adenosine induced ischaemia.

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) due to being broken down by adenosine deaminase (*11,12*). Adenosine deaminase is found in red blood cells and the blood vessel wall (*11,12*). The action of dipyridamole (discussed below) is to inhibit adenosine deaminase, increasing bioavailability of adenosine and causing coronary vasodilation (*11,12*). The most important adverse effect of adenosine is bronchospasm. Alcohol consumption has been reported to increase adenosine levels by decreasing adenosine re-uptake (*15*). Adenosine is reletively contraindicated in those with asthma due to associated bronchospasm and should be avoided in those with adenosine hypersensitivity, AV block or sick sinus syndrome (*14*).

Kubo (*16*) reported using ATP (adenosine triphosphate), which is a precurrosr to adenosine, for pharmacologic stress. ATP is rapidly hydrolysed to adenosine, however, most of the bodies adenosine is not sourced from ATP (*15*). Extracellular adenosine increases when there is a discrepancy between the rates of consumptions and synthesis (*15*). In the context of this discussion, adenosine refers to adenosine ($C_{10}H_{13}N_5O_4$) rather than ATP ($C_{10}H_{16}N_5Na_2O_{13}P_3$).

Dipyridamole

Dipyridamole (Figure 3) is a pyramidopyrimidine compound with both vasodilatory and antithrombotic effects (*3*). Adenosine deaminase is an enzyme that catalyses the deamination of adenosine to inosine (converting NH_2 to a double bond O and the adjacent cyclic N to an NH) (*17*). Adenosine deaminase metabolism results in a *transition state* (tetrahedral intermediate) rather than converting directly to inosine (*17,18*). These transition states are transient, however, they do bind to the active site of the enzyme. Adenosine deaminase inhibition is achieved by inactive structures that sufficiently resemble the tetrahedral intermediate so that they bind to the active enzyme site; effectively competitively blocking enzyme action (*17,18*).

Dipyridamole causes vasodilation by inhibiting adenosine deaminase and thereby blocking the re-uptake of adenosine (*3*). Dipyridamole inhibits the action of adenosine deaminase and as a result causes a build up of cellular dATP (Figure 2). This increased cellular dATP then inhibits ribonucleotide reductase which converts ADP to dADP (*3,18*). Interestingly, alcohol (ethanol) consumption has also been reported to increase adenosine levels by decreasing adenosine re-uptake (*15*). Thus, alcohol consumption might potentiate the effects of dipyridamole and decrease antagonism by xanthine (reduce the half life of caffeine).

Regadenoson (Lexiscan)

Regadenoson is an adenosine derivative that is a selective A_{2A} agonist and extends several advantages over adenosine (*7,19*):

- It is given as an intravenous bolus at a fixed dose which 'uncomplicates' the infusion process. This relates to the longer half life of regadenoson compared to the very short half life of adenosine. The latter requires a constant infusion to maintain vasodilation.

- It produces less undesirable side effects (eg. atrioventricular block and bronchospasm) due to the A_{2A} selectivity and the bolus administration, although the severity of some symptoms has been reported to be exacerbated by the bolus administration.

- It might be able to be used in patients with mild-to-moderate reactive airway disease.

Most clinical evaluations tend to focus on it 'non inferiority' to adenosine rather than on any specific tangible benefits over it (*9,20,21*).

The structure-activity relationship is important for regadenoson because there are three subtypes of A_{2A} adenosine receptor agonists depending on the benzene ring substituent (*19*). For regadenoson (Figure 4), the *pi system* (type of bond involving pyrazole ring) substituting for the hydrogen (H) of adenosine (Figure 1) has a *heteroatom* (NH) *alkyl* (CH_3) linker at a 152 degree trajectory providing a suitable hydrophobic group that allows lipophilic pocket binding for A_{2A} receptor affinity (*19*). The substituent on the pyrazole ring provides for A_{2A} receptor activity (*19*). Regadenoson has a plasma half life of 5 minutes and shows good potency (*19*).

The apparent advantages of regadenoson over adenosine include less side effects due to selectivity, however, a large trial has shown an event rate of 79% in both adenosine and regadenoson groups (*10,20*). Adenosine had statistically higher rates for flushing and chest pain while headache, abdominal discomfort and interestingly dyspnea (25% versus 18%) were statistically higher for regadenoson (*10,20*). Given that selective A_{2A} agonists are designed to circumvent the bronchoconstriction associated with non selective agonists, the high incidence of dyspnea (*9,10,20*) is of concern and certainly undermines the previously cited potential advantages over adenosine. Nonetheless, regadenoson has a 13 fold lower affinity for A_1 receptors than A_{2A} but is 10 times more potent than adenosine

(*22*). This allows a lower theoretical dose to elicit A_{2A} effects but will still have some A_1 activity. Moreover, some of the side effects may be explained by the bolus administration of regadenoson. Regadenoson can be readily administered as a slower infusion, however, the validation data has been done with a bolus and the 'uncomplication' of the infusion protocol is a major marketing factor.

Methylxanthine

Xanthine is a purine found throughout the body. Indeed, two of the building blocks of DNA itself are structural analogues; adenine and guanine. In figure 5 the basic xanthine structure is shown and the close relationship to the adenine portion of adenosine (Figure 1) can be seen. This structural similarity means that there is potential antagonism of adenosine by xanthine based drugs. There are a number of xanthine derivatives that offer bronchodilation and mild CNS stimulation by virtue of antagonisms of adenosine. *Methylation* (substitution of H with CH_3) of the xanthine produces a number of variants called methylxanthines; caffeine, theobromine and theophylline will be the focus of this discussion. As shown in figure 6, the structural difference has methylation at positions 1, 3 and 7 for caffeine; 3 and 7 for theobromine; and 1 and 3 for theophylline. Caffeine is typically found in coffee, tea, guarana and yerba mate. Theobromine is typically found in chocolate and yerba mate. Theophylline is mostly found in tea.

Methyxanthines are generally recognised as having complex and controversial mechanisms of action (*12*). Methylxanthines are A_1, A_2 and A_3 receptor antagonists although there is some selectivity (*11,12*). While theophylline antagonises all adenosine receptors, it has a greater effect on A_2 receptors. Caffeine has greater selectivity for A_1 and A_{2A} (*15*). 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 (*12*). The main action of antagonism of A_{2B} and A_3 receptors is to inhibit the release of histamine and leukotrienes from mast cells which may also reduce vasoconstriction (*12*). A single cup of strong coffee provides sufficient caffeine to block less than 20% of A_1 and A_{2A}

adenosine receptors and plasma concentrations 5 and 25 times higher are required to elicit 50% and 80% A_1 and A_{2A} adenosine receptor blockade respectively ([15]).

Methylxanthines also inhibit phosphodiesterase causing an increase in cAMP which in turn leads to smooth muscle relaxation and stimulation of cardiac muscles ([11,12]). Inhibition of phosphodiesterase, in theory at least, results in bronchodilation and increased cardiac contraction rate and force but this generally requires therapeutic doses ([11,12]), thus, dietary consumption of methylxanthines is unlikely to be useful in this regard. Moreover, even therapeutic doses of theophylline only result in bronchodilation in the absence of strong bronchoconstriction drugs (eg. dipyridamole). The A_1 receptor antagonism can also block bronchoconstriction.

Structurally, xanthine is a weak antagonist and the simple addition of a methyl group at position 1 increases receptor affinity by a factor of 40 ([23]). This CH_3 group represents the hydrogen (H) substituent in adenosine that binds to the lipophilic receptor pocket (ie. 3xH provides greater affinity than 1xH). Methyl groups at 1 and 3 positions (theophylline) provides affinity 80 times that of xanthine ([23]). This is important to consider in the context of the structure of adenosine with the purine substituent of adenosine offering significantly lower affinity than theophylline. The 1,methyl is essential for affinity while the 3,methyl contributes to potency ([23]). The NH_3 of adenosine and the substituted CH_3 of caffeine and theophylline contribute to their respective potency. While caffeine has high affinity, it has poor potency due to the 7,methyl (site of furan substituent on adenosine). Theobromine has low affinity by virtue of the absent 1,methyl group and low potency due to the 7,methyl. This raises debate about withholding chocolate for myocardial perfusion patients. Firstly, the caffeine content is a little mythical and secondly the theobromine does not have the same affinity and potency as even caffeine.

Apart from antagonism of adenosine receptors, caffeine has other cardiac effects including an increase in heart rate and blood pressure although the actual impact is blunted because tolerance develops within several weeks ([15,24]). Caffeine improves coronary oxygen and glucose supply and, thus, can increase the ischaemic threshold. This

is unlikely to affect vasodilation stress but could theoretically reduce the detection of ischaemia using exercise and dobutamine stress. In practice, the effect would require excessive caffeine doses. Antagonism of the A_{2A} receptor increases the vasomotor tone in the heart but also indirectly by stimulating catecholamine release (eg. dopamine) leading to coronary vasoconstriction (*24*). The impact of this alteration to vasomotor tone might lower the ischaemic threshold in those with CAD, increasing the event rate (*24*). One suspects that this would extend advantage to myocardial perfusion SPECT by increasing the detection rate of CAD in patients undergoing exercise or dobutamine based stress by reducing coronary flow reserve (*24*). Nonetheless, this effect is counter-intuitive with the previously reported property of caffeine to offer cardio-protection in ischaemia related to more efficient utilisation of available oxygen and glucose.

While 99% of caffeine is absorbed in the gastrointestinal tract within 45 minutes of consumption, plasma concentrations following the same caffeine ingestion can vary amongst individuals by as much as a factor of 16 (*15*). Pharmacokinetics is further complicated by significant variations in caffeine sensitivity (*15*). Theophylline and caffeine are metabolised in the liver by CYP450 with elimination half lives of 8 and 4-6 hours respectively (*11,15,25*). The half lives do, however, vary significantly 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 and alcohol consumption decreases half life (*11,15*). The metabolites of caffeine (dimethylxanthines) have their own activity; the major metabolite is paraxanthine (1,7-dimethylxanthine) which approximates caffeine in potency, theobromine (3,7-dimethylxanthine) has very low potency, and the minor metabolite theophylline (1,3-dimethylxanthine) is 3-5 times more potent than caffeine for inhibition of A_1 and A_{2A} receptors (*15*).

Protocol for cessation of methylxanthines is quite variable but generally in the range 12-48 hours (*4,8,10,25*). The following cited advice for myocardial perfusion stress preparation probably best highlights the need for clarity "*patients must be off caffeine, aminophylline, theophylline, chocolate, and nicotine for 24 hours before the test*" (*4*).

Firstly, chocolate is largely comprised of theobromine rather than caffeine and thus has very little effect on adenosine receptor blockade (*15,23*). Secondly, the statement suggests that nicotine is a methylxanthine or, at least, similar in effect. Indeed, nicotine is not generally considered a contraindication for performing pharmacological stress. In fact, nictotine does not antagonise adenosine but rather adenosine potentiates the effects of nicotine (*26*). More importantly, the half life of caffeine is halved in nicotine smokers and, thus, nicotine will reduce the antagonistic effect of caffeine on adenosine (*15*). Furthermore, with only a 2 hour half life for nicotine, 24 hours is probably excessive.

Caffeine

Managing methylxanthine cessation prior to myocardial perfusion imaging requires more than just an understanding of the affinity and potency of structural variations. It is important that sources of caffeine are understood and conveyed to patients. It would serve little benefit to have the patient cease coffee and chocolate for 24 hours if they instead consumed medication containing caffeine. Per 150ml, coffee contains between 40-180mg of caffeine or 2-8mg for decaffeinated coffee (*15*). Tea, including iced tea, contains 24-50mg of caffeine per 150ml while cocoa only contains 2-7mg; similar to decaffeinated coffee (*15*). Milk chocolate only contains 1-15mg of caffeine per 28g serving while dark chocolate contains 5-36g (*15*). Soft drink ranges from 15-24mg per 180ml up to 80mg for energy drinks like red bull (*15*). Interestingly, soft drinks like Mellow Yellow, Mountain Dew and Sunkist orange have much greater caffeine content than Coca Cola and Pepsi per volume equivalent. Caffeine is also contained in large amounts (100mg or more) in numerous medications including some migraine medications, pain relievers, diuretics, cold remedies, menstrual products, weight control medications and stimulants.

Failure to abstain from caffeine often results in the cancellation or rescheduling of the myocardial perfusion study (*8,27*) which clearly has implications for workflow, resource management and patient satisfaction. The variability in protocol employed for caffeine cessation, apparently without deleterious effects on diagnostic integrity, and an understanding of the pharmacology questions the rigor required for caffeine abstention. Several recent reports suggest a lack of clinically significant effect for caffeine on

vasodilator stress myocardial perfusion SPECT (*8,27*). A serum caffeine level less than 4 mg/L does not interfere with CAD detection (*27*). Generally speaking, this would suggest a single cup of coffee does not justify rescheduling of the procedure, however, the 16 fold variation in serum caffeine levels associated with a single cup of coffee between individuals would make a general rule unreliable. Furthermore, metabolism variations associated with nicotine, alcohol, oral contraceptive pill and liver disease make a single rule unsuitable. We recommend an intuitive approach to determining whether caffeine consumption prior to vasodilator stress should necessitate cancellation or rescheduling of the stress test.

Aminophylline

Aminophylline is the *prodrug* ester derivative of theophylline (discussed above) (*12*). Theophylline gut absorption is unpredictable and can cause gastric irritation (*12*). Consequently, theophylline is given as the more soluble aminophylline which is rapidly hydrolysed into theophylline and ethlenediamine at a ratio of 2:1 and a half life of several minutes (*12*). Like other methylxanthines, aminophylline (or theophylline invivo) has higher affinity for adenosine receptors than does adenosine itself and, thus, provides effective blockade. Aminophylline does not reduce the amount of either dipyridamole or adenosine but simply displaces them due to preferential binding (*10*). Like other methylxanthines, aminophylline is both a competitive non-selective phosphodiesterase inhibitor and non-selective adenosine receptor antagonist. The action of A_1 antagonism makes aminophylline a bronchodilator. Structure-activity relationships have been discussed previously (above).

Catecholamines as Stress Agents

Catecholamines increase cardiac workload due to positive inotropic and chronotropic actions. Since they increase cardiac workload, it is possible that catecholamines can induce myocardial ischaemia. Dobutamine is the principal catecholamine used for myocardial stress testing while arbutamine has reported use.

Dobutamine

Dobutamine is a powerful positive *inotropic* (increased force of contraction) sympathomimetic drug with a primary mechanism of action through direct stimulation of β_1-receptors of the sympathetic nervous system (*3,11,12,14*). It (Figure 7) is an analogue of dopamine (Figure 7) and offers good receptor selectivity (*3,11,12*). Both dobutamine and dopamine are metabolised in a similar fashion to noradrenaline; monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) with metabolites excreted in the urine (*14,18*). Dobutamine, however, does not interact with dopamine receptors so does not result in the release of noradrenaline from sympathetic nerve terminals and as a consequence, dobutamine does not elicit the same side effects as dopamine (eg. hypertension) (*11,12*). The onset of action for dobutamine is rapid, within 1-2 minutes following intravenous administration and the plasma half clearance time is 3 minutes. Of potential clinical relevance in pharmacological stress, however, it is to be noted that the duration of action is 10 minutes (*14*). Thus cessation of intravenous infusion during pharmacological stress testing using Dobutamine is not necessarily associated with rapid abatement of its physiologic cardiovascular or arrhythmic effects.

Though classically referred to as a selective β_1 agonist, dobutamine also demonstrates weak β_2 agonist activity (vasodilation) and α_1 activity (*12,14,18*), hence the structural similarity to labetalol. Dobutamine is a *chiral* molecule (no symmetrical internal plane) and thus the two mirror images (*enantiomers*) can not be superimposed on one another. The enantiomers (or optical isomers) are usually referred to as either right and left or positive (R) and negative (S). In the case of dobutamine, the (S) enantiomer is a β_1 agonist and a powerful α_1 agonist (*15*). Conversely, the (R) enantiomer is an α_1 antagonist. Dobutamine is administered as a *racemic* mixture [equal amounts of (R) and (S) enantiomers] resulting in overall β_1 agonism (*11,18*).

The structure of dobutamine and labetalol are similar but functionally very different. The first ring in dobutamine is a *catechol* (aromatic ring with two hydroxyl groups). The bottom *phenol* (OH) substituent (*para*) on the first ring is essential for adenoreceptor affinity (*17*). The top phenol substituent (*meta*) can improve affinity but is not essential

and, indeed, can be effectively replaced by other groups capable of hydrogen bonding (*17*). Nonetheless, loss of a phenol substituent will have a greater negative impact on β activity than that of α activity (*17*). Compared to other catecholamines, dobutamine and dopamine lack a secondary alcohol. A hydroxyl group attached to the first carbon in the side chain is involved in hydrogen bonding at the receptor and its presence is not essential but contributes to activity (*17*). The amine (N group) is essential for α activity and the number of substituents will vary that activity. Good α activity is associated with primary and secondary amines while tertiary amines and quaternary ammonium have poor activity (*17*). N-Alkyl substitution (CH_3) in the side chain reduces α activity but increases β activity and the larger the N-alkyl substituent the greater the loss in α activity and the greater the increase β activity which suggests that β adenoreceptors have a *hydrophobic* pocket (*17*). Extending the side chain offers no particular benefit except when the end has a polar functional group like a phenol (*17*); as is the case with arbutamine. The second ring is a phenol (aromatic ring with a single hydroxyl group) which causes a dramatic rise in the activity (*17*). The methyl group in dobutamine does not inhibit $β_1$ receptor binding (affinity) but does reduce activity.

The primary advantage of dobutamine in nuclear cardiology is the minimal $β_2$ activity which significantly reduces the risks in those with respiratory compromise. The absence of bronchospasm makes dobutamine the pharmacological stress agent of choice (over dipyridamole and adenosine) for patients with asthma or obstructive airways disease. In nuclear cardiology, dobutamine tends to be the 'fall back' agent when patients present with respiratory problems. Conversely, in stress echocardiography it tends to be the 'agent of choice'. This is likely to relate to its ability to not only increase myocardial contractility and cardiac output, but also its ability to increase oxygen demand and actually induce ischaemia for the detection of ischaemically stunned myocardium (Figure 2). Consequently, there are conflicting position statements relating to pharmacological stress in echocardiography. The European Society of Cardiology, on the basis of matching accuracy, sensitivity and specificalty in CAD between dipyridamole and dobutamine, recommend either agent depending on local expertise (*28*). Conversely, The American Heart Association and American College of Cardiology recommend

dobutamine for stress echocardiography because it has higher sensitivity for the assessment of wall motion changes (*28*). Thus, ischaemically stunned myocardium is not as reliably achieved with adenosine and dipyridamole as it is with dobutamine.

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. As a β agonist, dobutamine does not provide the ideal pharmacological agent for use in patients who are prohibited from undertaking exercise adequately due to β blockade. Patient preparation should include 48 hours without β-blockers (*29*).

Arbutamine

Arbutamine is a synthetic catecholamine that was specifically developed to simulate exercise and is a positive *inotropic* and *chronotropic* agent, although inotropic activity is somewhat lower than that of dobutamine (*30,31*). Arbutamine has β_1 and β_2 agonism and weak α_1 affinity (agonist). The main advantage of arbutamine over dobutamine is that there is a more linear response of heart rate increase and increased myocardial contraction (*31*). Clearly, the main disadvantage of arbutamine compared to dobutamine is the effects of β_2 agonism; bronchodilation, peripheral vasodilation and decreased GUT activity. Arbutamine is no longer widely used. Structurally, arbutamine is similar to dobutamine with the following variations (refer to Figure 7):

- Omission of the N-Alkyl (CH_3) side chain.
- Addition of a hydroxyl (OH) at the first carbon of the chain (catechol end).
- Extension of the carbon chain by 1 carbon at the phenol end.

Beta Blockers

Antagonists of the beta (β) adrenergic receptors are referred to as β-blockers and function by competitive blockade of the actions of catecholamines (*3,14*). Beta-blockers can be selective for either β_1 or β_2, however, it is common for β-blockers to be non-selective. Nonetheless, most β-blockers do not act on β_3 (*11*). The most important pharmacological actions of β-blockers relate to cardiovascular and bronchial actions (Table 1). Cardioselective β-blockers are those that act on β_1-receptors in the myocardium, such as metoprolol (*14*).

A clinically important role of β-blockers is to limit the response to exercise or other excitatory stimuli (*3,11,12,14*). Thus, at exercise or excitation, β-blockers work to reduce heart rate, cardiac output and arterial pressure (*3,11,12,14*). This is particularly important in nuclear cardiology because β-blockers limit maximal response to exercise and, thus, pharmacologic stress is required for patients on a β-blocker whose medication cannot be withheld for the purpose of stress testing. Furthermore, β-blockers limit vasodilation of skeletal muscles and can potentially reduce exercise capacity (*11,12*). Another important consideration regarding β-blockers in nuclear cardiology is that coronary blood flow is reduced disproportionately to oxygen consumption which actually improves oxygenation of myocardium (*11,12*). The implication of this action is that stress induced ischaemia may be attenuated in the presence of β-blockade.

Figure 8 shows the structure of a model β-blocker (propranolol) and also shows the structure of labetalol. While labetalol is not the *prototype* β-blocker, it is non-selective for β_1 and β_2 and also antagonises α_1 which provides an opportunity to highlight the structure-activity relationships. It has also been selected as a case example because of its resemblance to dobutamine (Figure 7). While labetalol lacks the *oxymethyl* bridge (additional 2 carbon with oxygen bond) one position counter clockwise from current chain insertion on ring 1 that is typical of most β-blockers, this only reduces the potency (*3,18*). The *hydroxyl* (OH) and *amine* (NH) groups on the carbon chain adopt a conformation that allows binding regardless of the oxymethyl bridge (*3,18*). The *methyl* group (CH_3) is also necessary for receptor binding, however, typical β-blockers would

have a second methyl group substituted for the second *benzine ring* as illustrated in figure 8 (*18*). The other key feature is the first benzine ring (left) which is typically a *naphthalene* (dual aromatic rings) configuration for non selective β-blockers (*3,18*). The single aromatic ring with dual methyl groups is typical of β_1 selectivity. The naphthalene ring can also increase *lipophilicity* and this is an important consideration for patients with potential liver or kidney dysfunction because increased lipophilicity means increased liver metabolism and decreased lipophilicity means increased renal excretion (*18*). In labetalol, the second ring (right) and methyl group combine (aryl alkyl group) to produce α_1 affinity with no actual activity (antagonism) (*18*).

Summary

In a similar fashion to the lack of interchangability of myocardial perfusion radiopharmaceuticals (without implications for diagnostic integrity in CAD), stress methods are also not interchangeable without careful consideration (Table 2). CAD is best detected using vasodilator stress while haemodynamic significance is best assessed using dobutamine or exercise.

A single cup of coffee results in serum caffeine levels of 0.004mM which blocks 18% of adenosine receptors (*15*). Toxicity occurs at 0.25 mM and is associated with approximately 90% blockade (*15*). From toxicity, 6 half lives (30 hours) will return serum levels to the equivalent of 1 cup. But few patients are likely to present with caffeine toxicity. Even 50% receptor blockade (0.02 mM) would require enormous caffeine consumption yet only 2 half lives (10 hours) are required to return that to the equivalent of a single cup. Thus, the first 12 hours of caffeine abstinence provides a tangible benefit while the marginal benefit beyond 24 hours is very small. We recommend no caffeine for 12 hours prior to the stress procedure with the concession of permitting a single serving (50mg) of caffeine 3 hours prior to the stress test to improve patient compliance. To determine whether to cancel or reschedule a patient, we recommend using a point system (corresponding to hour units). Start at 6 hours and add or subtract based on the following factors:

- Moderate or heavy smoker, minus 3 hours.

- Heavy alcohol consumption, minus 3 hours.
- Adenosine stress, minus 3 hours.
- Dipyridamole stress, plus 6 hours.
- Liver disease, plus 6 hours.
- Oral contraceptive pill, plus 6 hours.
- Less than 100mg daily intake, minus 6 hours.
- 100-300mg daily intake, no change.
- 300-500mg daily intake, plus 6 hours.
- More than 500mg daily intake, plus 12 hours.

If the patient presents with a caffeine consumption of less than 100mg in the previous 24 hours then there is no need to reschedule. If the patient presents having consumed more than 100mg of caffeine in the preceding 24 hours and above total is 3 hours or less, then the stress procedure need not be rescheduled. For an hour total greater than 3 hours in the presence of greater than 100mg of caffeine in the preceding 24 hours, the patient should be rescheduled unless one of the following options is suitable (noting that a plus 3 total might be reduced to less than 3 if dipyridamole stress were changed to adenosine):

1). Perform rest / stress protocol (same day possible).

2). Partial exercise (total less than 12 hours).

3). Dobutamine.

Conclusion

CAD is best detected using vasodilator stress. Adenosine provides superiority over dipyridamole while regadenoson does not appear to extend theoretical benefits into tangible clinical benefits. Haemodynamic significance is best assessed using dobutamine or exercise. Caffeine ingestion may not necessitate cancellation or rescheduling of the procedure if an understanding of pharmacology can be employed to adopt an intuitive approach to case based decision making.

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Figure legends

Figure 1: Adenosine is comprised of adenine (azole and pyrimidine ring complex) and a molecule of ribose sugar (furan ring complex). Adenosine is conventionally displayed in the format on the left, however, it has been displayed rotated 180 degrees (image on the right) for ease of comparison with antagonists. The hydrogen on the aromatic ring is generally not displayed but it provides a useful illustration for comparison with regadenoson later in this discussion.

Figure 2: Schematic representation of coronary blood flow in normal and stenosed arterie at rest and under stress. The diagram highlights the increased oxygen demand that drives exercise and dobutamine stress which translates to an evaluation of ischaemia. It also highlights the action of adenosine and dipyridamole in vasodilation and subsequent assessment of coronary flow reserve. The schematic on the far right offers a demonstration of the concept of coronary steal.

Figure 3: The structure of dipyridamole.

Figure 4: The chemical structure of regadenoson closely resembles adenosine. The azole (pyrazole) substituent provides A_{2A} selectivity, the hydrophobic alkyl (CH_3) provides binding at the lipophilic pocket and the pyrazole substituent (O=C-NH-) provides agonist activity.

Figure 5: Xanthine is characterised by the purine structure and hydrogen at carbons 1, 3 and 7.

Figure 6: Caffeine (left), theobromine (middle) and theophylline (right).

Figure 7: Dobutamine is a β_1 agonist (top). Dopamine indirectly induces similar effects as a β_1 agonist (bottom).

Figure 8: Propranolol (top) as a model β blocker showing the naphthalene ring configuration, oxymethyl bridge (-O-) and dual methyl groups. Labetalol (bottom) is a non-selective β_1 and β_2 blocker with α_1 antagonism.

Table legends

Table 1: Summary of β receptors and agonist / antagonist actions.

Table 2: Summary of characteristics associated with various methods of stress for myocardial perfusion studies.

Table 1: Summary of β receptors and agonist / antagonist actions.

Receptor Sub-Type	Agonist Action	Antagonist Action
β_1	Increase contraction force. Increase rate of cardiac contraction. Increase oxygen consumption. Can induce ischaemia.	Decrease contraction force. Decrease rate of cardiac contraction. Decrease oxygen consumption.
β_2	Broncho-dilation. Peripheral vasodilation. Decrease contraction in gut.	Broncho-constriction. Peripheral vasoconstriction. Smooth muscle contraction.
β_3	Increase lypolysis.	Decrease lypolysis.

Table 2: Summary of characteristics associated with various methods of stress for myocardial perfusion studies.

	Exercise	Dobutamine	Adenosine	Dipyridamole	Regadenoson
Increased flow	2-2.5 x	2.4-2.9	4.4	4.3	2.5-3.0
Plasma half life	-	3 min	< 10 s	30-45 min	5 min
Duration	-	2.4-10 min	< 1min	90min	3 min
Onset	-	rapid	immediate	slow	rapid
Mechanism	True ischaemia	True ischaemia	Coronary flow reserve	Coronary flow reserve	Coronary flow reserve
Action on CFR	direct	indirect	direct	indirect	direct
Adverse effects	+	+++	++ but short lived	++	++
Reversal		Stop infusion or beta blocker	Stop infusion	Aminophylline required in 12%*	Stop infusion / ? aminophylline
Caffeine a problem	no	no	yes	yes	yes
Beta blocker a problem	yes	yes	? decreased sensitivity but increased prognostic information	? decreased sensitivity but increased prognostic information	? decreased sensitivity but increased prognostic information
Non-dihydropyridine calcium channel blockers a problem	yes	yes	? decreased sensitivity but increased prognostic information	? decreased sensitivity but increased prognostic information	? decreased sensitivity but increased prognostic information
In asthma	yes	yes	no	no	maybe
Coronary vasodilation	↑	↑	↑↑↑	↑↑	↑↑↑
Heart rate	↑↑↑	↑↑	↑	↑	↑
BP	↑↑	↑↑	↓	↓	↓
Ischaemia	↑↑↑	↑↑↑	↑	↑	↑
Perfusion	yes	yes	yes	yes	yes
Wall motion	yes	yes	no	no	no

* Anecdotally, some departments routinely give aminophylline to all dipyridamole patients.