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Interventional Agents in Stress Myocardial Perfusion Imaging

Continuing Education for Nuclear Pharmacists and
Nuclear Medicine Professionals

By

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INTERVENTIONAL AGENTS IN STRESS MYOCARDIAL PERFUSION IMAGING

STATEMENT OF OBJECTIVES:

1. Discuss the pharmacology, patient selection/preparation, adverse events and clinical use of cardiovascular vasodilator agents (dipyridamole, adenosine) in myocardial perfusion imaging.

2. Discuss the pharmacology, patient selection/preparation, adverse events and clinical use of inotropic/chronotropic adrenergic agents (dobutamine, dobutamine/atropine combination) in myocardial perfusion imaging.

3. Discuss the pharmacology, patient selection/preparation and clinical use of agents to reverse adverse effects of chemical stress agents used in myocardial perfusion imaging.

4. Discuss new developments associated with the second generation vasodilator agents and the improvements these agents bring to myocardial perfusion imaging.

COURSE OUTLINE

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CARDIOVASCULAR SYSTEM

The cardiovascular system consists of the heart and blood vessels responsible for circulating blood throughout the body. The adult heart weighing 300g and holding 500mL of blood when full, is located in the lower portion of the thoracic cavity and is divided into 4 chambers: the right atrium, left atrium, right ventricle and the left ventricle.

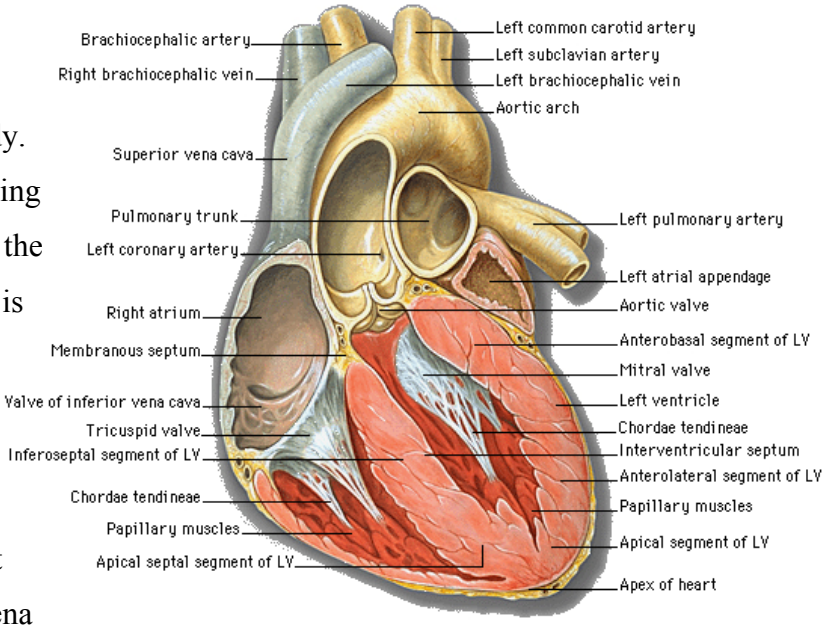

Figure 1. The Heart (Hwww.med.yale.eduH)

Deoxygenated blood returns to the heart via the right atrium from the superior vena cava. From the right atrium, blood then passes into the right ventricle through the tricuspid valve. Blood leaves the right ventricle through the pulmonary artery in order to re-oxygenate. Once gas exchange takes place, blood leaves the lungs through the pulmonary veins into the left atrium. Lastly, the blood leaves the left atrium through the mitral valve and is distributed to the body from the left ventricle.

Each beat of the heart represents one cardiac cycle consisting of ventricular contraction (systole) and relaxation (diastole). During diastole the left atrium and left ventricle are relaxed, which allows for passage of blood through the mitral valve. Once the filling of the left ventricle is complete, the ventricular pressure rises and the mitral valve closes. Once the ventricular pressure exceeds the aortic pressure, the aortic valve opens causing expulsion of blood from the ventricles into the vessels.

MYOCARDIAL PERFUSION IMAGING IN NUCLEAR MEDICINE

Nuclear medicine imaging of the heart is used to evaluate a number of cardiovascular factors including: myocardial perfusion, myocardial function, assessing myocardial infarction and assessing myocardial metabolism and viability. Radiopharmaceuticals used in myocardial imaging can be separated into 2 categories: SPECT and PET as shown in Table 1.

Table 1

Cardiovascular Radiopharmaceuticals	
SPECT Agents	**PET Agents**
Ventricular Function Agent ▪ technetium Tc-99m RBCs Infarct Localizing Agent ▪ technetium Tc-99m pyrophosphate Myocardial Perfusion Agents ▪ thallium Tl-201 thallous chloride ▪ technetium Tc-99m sestamibi ▪ technetium Tc-99m tetrofosmin	Myocardial Perfusion Agents ▪ rubidium Rb-82 chloride ▪ oxygen-15 water ▪ nitrogen-13 ammonia Myocardial Metabolism Agents ▪ carbon-11 acetate ▪ carbon-11 palmitate ▪ fluorine-18 fludeoxyglucose (FDG)

The most commonly performed nuclear medicine study; **myocardial perfusion imaging** is used to detect coronary blood flow deficits caused by myocardial ischemia. Currently, 7 million perfusion studies are completed each year. In order to determine perfusion deficits, maximum coronary blood flow must be established. Ideally, coronary dilation is achieved through exercise. Patients who are unable to exercise may undergo pharmacologic agents that dilate the vessels and "mimic" the heart under exercise conditions.

- 7 million stress myocardial perfusion studies each year
- 50% of the patients are unable to undergo exercise stress
- Drug induced (chemical) stress is a viable alternative

EXERCISE STRESS

Exercise increases workload and metabolic demand on the heart. During myocardial perfusion imaging, the radiopharmaceutical is injected when the heart is at maximum workload in order to demonstrate stress induced ischemia. When arteries are stenosed, ischemia results from a lack of oxygen to the area, causing chest pain and shortness of breath. Ischemic cells lack oxygen due to

reduced blood supply. This results in a reduction in the uptake of the radiopharmaceutical. In diagnosed cases of ischemia the images reveal an area of decreased or no perfusion to the area of the myocardium perfused by the stenosed vessel.

Treadmill exercise is the most commonly used method in stress testing. In order to achieve maximum stress, patients walk on the treadmill under increasing speed and incline until 85% maximum heart rate is achieved. Once the endpoint is established, the patient receives an intravenous injection of the radiopharmaceutical for imaging.

PHARMACOLOGIC (CHEMICAL) STRESS

This type of stress test is used in patients who are unable to exercise on a treadmill. Patients with claudication, CVA, arthritis, amputation, anxiety, or current use of beta blockers would be candidates for this type of test. Several interventional pharmaceutical agents have been used for this study, including dipyridamole, adenosine, dobutamine, and adenosine receptor subtypes..

Dipyridamole, USP (various suppliers)

Dipyridamole is a coronary vasodilator drug that causes marked dilation of the coronary vascular bed thereby causing an increase in myocardial perfusion. Its mechanism of vasodilatation is thought to result from inhibition of metabolism of adenosine, an important mediator of coronary vasodilatation. Circulating levels of adenosine increase 2x with the use of dipyridamole. Dipyridamole is supplied in ampules containing 50mg and 10mL vials containing 50mg.

Recommended dosage is 142μg/kg/min (0.57mg/kg) to be infused over 4 minutes with peak pharmacologic effects occurring 6-8 minutes following initiation of the infusion. The biological effects persist for 10-20 minutes following infusion with myocardial perfusion imaging agent typically administered 2-4 minutes following completion of the infusion [1]. Maximum dosage of dipyridamole should not exceed 60mg regardless of weight.

Patients who are on maintenance therapy with theophylline for COPD or have taken caffeine prior to injection will not experience the coronary vasodilatation induced by dipyridamole leading to a false negative myocardial perfusion study. Methylxanthine containing medications (theophylline); beverages and food containing caffeine should be discontinued 24- 48 hours before study. Caffeine can reduce the hyperemic effect of dipyridamole by as much as 70% [2].

Table 2

Drugs/Foods Containing Caffeine [3]	
Drug/Food Category	Caffeine Content (per dosage)
Prescription Analgesics	40-100mg
OTC Analgesics	32-65mg
Energy/Alertness Aids	100-300mg
Beverages	15-100mg
Herbal Preparations	50-200mg

Typically, one-half of patients complain of side effects, but they are generally benign and related to dipyridamole's peripheral vasodilatory effect. Chest pain, flushing, lightheadedness, headache, nausea and mild hypotension are most often experienced. More serious side effects include bronchospasm, severe cardiac ischemia, severe hypotension and stroke.

The effects of dipyridamole are rapidly (within minutes) reversed by administration of the adenosine receptor antagonist aminophylline. Slow IV infusion of 1-2mg/kg (100mg typically is used) is adequate. Aminophylline competitively blocks endothelial adenosine receptors [4]. Administration of nitroglycerine simultaneously helps reduce ischemia.

Adenosine (Adenoscan®, Astellas)

Intravenous adenosine was originally approved for use in the treatment of paroxysmal supraventricular tachycardia. One of the main effects of this drug is peripheral and coronary artery vasodilatation. Since the principal action of dipyridamole is to inhibit the metabolism of adenosine, giving the agent directly leads to a similar physiologic response. Since this agent has the ability to maximally vasodilate coronary arteries, increase blood flow and increase radiopharmaceutical delivery, diagnostic images acquired are similar to those obtained following exercise. Adenosine produces coronary vasodilatation by activation of the A2 receptors reportedly producing more consistent coronary vasodilatation compared with dipyridamole [1].

In addition, adenosine has a short T_B (2-10 seconds) resulting in quick reversal of the drug's effects in cases of severe reactions. This quality is a benefit in comparison to dipyridamole which requires administration of aminophylline to reverse its effects due to its longer T_B.

Adenosine is administered IV at a rate of 140μg/kg/min for 6 minutes (max dose is 0.84mg/kg). Maximal vasodilatation is realized sooner than with dipyridamole generally occurring within 2

minutes of initiation of infusion. Myocardial perfusion agent is given midway through the infusion.

Side effects are common, occurring in 80% of patients. Side effects also tend to be more intense than with dipyridamole with 5-7% of patients requiring discontinuation of the infusion because of complaints of severe side effects. Common side effects include hypotension, increased heart rate, chest pain, flushing, headache and shortness of breath leading to dyspnea. More serious side effects include arrhythmias, A-V nodal block and bronchospasm.

Dobutamine (various suppliers)

This agent is a synthetic catecholamine with direct acting inotropic activity resulting from stimulation of the beta-1 receptors of the heart leading to increased coronary output. At high doses used for pharmacologic stress perfusion imaging, both inotropic and chronotropic action of the heart are increased with resulting increase in myocardial contractility and heart rate. This leads to an increased oxygen demand and increased blood flow in normal coronary arteries similar to that seen with exercise [5].

Dobutamine is not used routinely for pharmacologic stress myocardial perfusion imaging because the increase in coronary blood flow is less than that observed with dipyridamole or adenosine. Dobutamine is usually used in patients who cannot exercise and have contraindications to dipyridamole or adenosine (airway disease, high grade A-V block, arterial hypotension or currently using methylxanthine drugs for control of COPD.

The effects of dobutamine are also short term (T_B of 2 minutes) with onset of action at 1-2 minutes. Recommended dosage of dobutamine needed to increase cardiac output ranges from 2.5 to 40µg/kg/min (which is a small dose commonly used for renal patients). This dose should be adjusted according to the patient's response as determined by heart rate, presence of ectopic activity, blood pressure and cardiac output. Dobutamine is given IV using a graded infusion beginning at 10µg/kg/min and increased by 10µg every 3 minutes to a maximum of 40µg/kg/min. The myocardial perfusion imaging agent is infused 1 minute after the last increase in dosage of dobutamine and the dobutamine infusion continued for another 2 minutes. Dobutamine is supplied in vials containing 250mg/20mL.

It is recommended that patients taking calcium channel blockers and beta-blockers discontinue their medications for 48 hours prior to study. These agents will reduce the effects of dobutamine [5].

Side effects frequently occur (80% of patients) and often require lowering of dose rate. Non-cardiac side effects include nausea, headache, flushing, chills and dyspnea. Common cardiac side effects seen are chest pain, palpatations, angina, PVCs and other ECG changes and hypotension. If side effects persist after stopping the infusion, they can be reversed by administering a short acting IV beta blocker such as metoprolol (1-5mg) or esmolol [5].

Adenosine receptor – subtype 2A (A_{2A})

Studies have shown the naturally occurring ligand, adenosine, activates all four known receptor subtypes including A_1, A_{2A}, A_{2B} and A_3. Although binding to receptor A_{2A} is known to cause the preferred coronary vasodilatation in stress myocardial perfusion studies, many of the undesirable side effects are due to binding to other receptor subtypes; flushing/dizziness (A_{2B}), A-V block (A_1 receptors in A-V node), bronchoconstriction/dyspnea (A_{2B} & A_3). Several potent, high affinity and selective A_{2A} receptor agonists have been synthesized and currently undergoing clinical studies for their use as chemical stress agents in myocardial perfusion studies [6-8]. Although the coronary vasodilatation effects are similar to those associated with dipyridamole and adenosine, the selective A_{2A} agonist receptor agents should have minimal to no side effects.

Table 3

Interventional Agents for Stress Myocardial Perfusion Studies			
Interventional Agent	Dosage	Common Side Effects	Side Effects Tx
Dipyridamole	0.142mg/kg/min infused over 4 min (60mg max)	Chest pain (30%) Headache (15%) Dizziness (15%)	50-100mg IV aminophylline
Adenosine	0.140mg/kg/min infused over 6 min (0.84mg/kg max)	Chest pain (50%) Headache (35%) Dyspnea (15%)	Stop infusion
Dobutamine	5-40µg/kg/min infused with 5µg increments p3min	Headache (15%) Nausea (20%) Chest pain (30%)	1-5mg IV metoprolol or esmolol
A_{2A} receptor agonist	1-2µg/kg IV bolus	Chest pain (15%) Dyspnea (15%) Dizziness (10%) Headache (5%)	Stop infusion

SUMMARY

Pharmacologic stress using vasodilator agents is a viable alternative in those patients who cannot exercise. Patients with normal pharmacologic stress myocardial perfusion studies have a good prognosis with less than 2% annual risk of cardiac event. The introduction of selective A_{2A} agonist receptor agents should improve the incidence of undesirable side effects while insuring adequate coronary vasodilatation similar to exercise stress.

REFERENCES

1. Hendel RC, et al, J Nucl Cardiol, 10:197-204, 2003.
2. Bottcher M, et al, J Nucl Med, 36:2016-21, 1995.
3. Durrant KL, J Am Pharm Assoc, 42:625-637, 2002.
4. Leppo JA, J Nucl Med, 30:281-287, 1989.
5. Elhendy A, et al, J Nucl Med, 43:1634-1646, 2002.
6. Glover DK, et al, Circulation, 94:1726-1732, 1996.
7. He ZX, et al, Circulation, 102:438-444, 2000.
8. Glover DK, et al, Circulation, 100:1-311, 1999.

ASSESSMENT QUESTIONS

1. The most common side effect associated with ANY pharmacological stress agent is:

    a. Dizziness
    b. Headache
    c. Chest Pain
    d. Nausea

2. The most commonly performed cardiac nuclear medicine study is

    a. Myocardial metabolism
    b. Myocardial perfusion
    c. Infarct localizing
    d. Ventricular function

3. Patients unable to undergo exercise stress are estimated at

    a. 25%
    b. 50%
    c. 10%
    d. 30%

4. Aminophylline will rapidly reverse the side-effects of

    a. Dipyridamole
    b. Adenosine
    c. DobutamineA_{2A} receptor agonist

5. The more consistent coronary vasodilatation occurs with

    a. Dobutamine
    b. Dipyridamole
    c. Adenosine
    d. A_{2A} receptor agonist

6. Patients who cannot exercise due to severe COPD or otherwise airway disease are best stressed pharmacologically with.

    a. Adenosine
    b. Dobutamine
    c. Dipyridamole
    d. A_{2A} receptor agonist