Pharmacologic Cardiac Intervention: Comparison of Adenosine, Dipyridamole, and Dobutamine

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This is the second article in a four-part series on interventional nuclear medicine. Upon completion of this article, the technologist will be able to (1) describe the purpose of interventional stress imaging, (2) explain the mechanism by which each pharmacologic stress agent works, and (3) list advantages and disadvantages of each for different patient conditions.

The cardiovascular nuclear medicine armamentarium has recently expanded to include pharmacologic stress testing coupled with perfusion imaging for the evaluation of coronary artery disease (CAD). Adenosine, dipyridamole, and dobutamine are becoming widely used alternatives for those patients who, due to drug therapy, physical limitations, or motivational impairment, cannot achieve desired stress levels with conventional exercise tests. An understanding of the functions of these agents is essential in determining which methods a nuclear medicine department should use for cardiac stress testing. While adenosine and dipyridamole are both vasodilators, the differences in their parameters for patient selection, pharmaceutical administration, and duration of action should be carefully considered when choosing the agent to be used for scintigraphy in place of exercise. Dobutamine, which has a less limited patient exclusion profile and a different mechanism of action, may provide a means of intervention for those patients excluded from other exercise or pharmacologic stress protocols.

Each of these agents has been studied extensively, and for the most part, exclusively, in any given study. The following is a comparison of these agents taken from the literature and our experience; it includes the mechanism of action, safety, and appropriate patient population and procedure for each agent.

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MECHANISMS OF ACTION

In the normal resting stage, high coronary circulatory resistance results in relatively low coronary blood flow with high oxygen extraction by the myocardium. Therefore, increased oxygen delivery depends primarily upon increased blood flow through the coronary arteries. The efficacy of any pharmacologic agent to be used in the assessment of coronary flow reserve and CAD depends upon that agent's ability to influence coronary blood flow. Intravenous administration of either dipyridamole or adenosine increases levels of circulating adenosine (*1*), thus increasing coronary blood flow in normal coronary arteries by as much as four to five times the resting flow rate (*2*).

Figure 1 is a simplified model of adenosine and dipyridamole action. Adenosine activates the adenosine A2 receptors, which reside on the cell membrane of the endothelium and smooth muscle of the coronary resistance vessels. This results in coronary vasodilation through smooth muscle relaxation and increases blood flow in normal coronary arteries (*2,3*). Intravenous adenosine is the mediator of vasodilator action, with a plasma half-life of <10 sec (*2,4*). Dipyridamole inhibits the clearance pathway of adenosine across the cell membrane, which increases endogenous adenosine levels. Dipyridamole has a plasma half-life of 15–30 min (*5,6*). This effect may be suppressed by methylxanthines, such as aminophylline and caffeine, which act as receptor site blockers (*4,7*).

Dobutamine is a positive inotropic agent (i.e., it increases muscular contraction), with a two-min plasma half-life, which increases myocardial contraction and left ventricular oxygen consumption by direct stimulation of the heart's beta-1 receptors (*8*). This effect is independent of and does not increase endogenous norepinephrine stores. It also augments conduction at the atrial ventricular (AV) node, so that at high doses (20 μg/kg/min or more), it has chronotropic effects on the heart (i.e., affects the heart's contraction rate) (*9*). Dobutamine, as a beta-1 stimulator, unlike dipyridamole or adenosine, stresses the myocardium by increasing contractile force and oxygen demand.

High doses of dobutamine, with an infusion range of up to

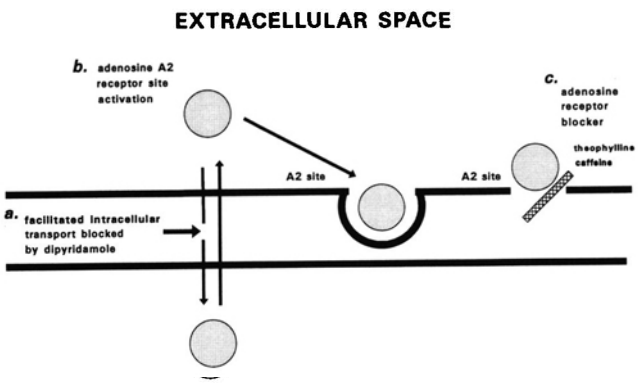

FIG. 1. (a) Facilitated intracellular transport of adenosine is blocked by dipyridamole, increasing extracellular adenosine. (b) Extracellular adenosine is taken up by adenosine A2 receptor sites. Coronary vasodilation follows. (c) Methylxanthines (aminophylline, caffeine) block adenosine uptake.

40 μg/kg/min, have produced dramatic increases in heart rate (from 70 ± 16 to 121 ± 23 bpm) and offer promising results for detecting CAD in patients unable to undergo exercise or pharmacologic vasodilation (*10*). Conversely, low doses, an infusion range of up to 15 μg/kg/min, demonstrated only small changes in hemodynamics and probably should not be substituted for exercise in patients with mild to moderate CAD (*11*).

By using pharmacologic vasodilation for the evaluation of CAD, the myocardial territory supplied by a significantly stenosed coronary artery will show relative hypoperfusion, compared to those myocardial territories supplied by normal or mildly stenosed coronary arteries (*12*). This disparity of blood flow during pharmacologic intervention can be evaluated by scintigraphic imaging techniques, using radioactive tracers that distribute in the myocardium proportionally to blood flow (*1*).

SAFETY

Adenosine, dipyridamole, and dobutamine can have serious side effects. Only persons qualified to administer medications with significant pharmacologic effects should be authorized to administer these agents or their inhibitors, such as aminophylline and esmolol. Further, the infusion and immediate post-infusion period should be monitored by an individual qualified to conduct stress testing.

When using intravenous adenosine or dipyridamole, the vasodilation caused by elevated adenosine levels can lead to several cardiac as well as noncardiac side effects (*13,14*). Tables 1 and 2 summarize reported side effects for adenosine and dipyridamole, respectively. The alteration of coronary blood flow may lead to ECG changes or angina; systemic hypotension may lead to dizziness and nausea; increase in cerebral blood flow may produce headache; shortness of breath may occur with bronchoconstriction (*13,15*); and with adenosine, transient second- and third-degree AV block may also occur in a small percentage of patients (*5,14,16*). Milder effects include flushing of the face or a general feeling of weakness.

TABLE 1. Adverse Events Reported by Patients Who Underwent IV Adenosine Thallium Imaging

Adverse Event*	(%)
Flushing	37.4
Chest pain	36.2
Dyspnea	35.1
Gastrointestinal discomfort	15.5
Headache	14.7
Throat/neck/jaw discomfort	12.3
Light-headedness	9.0
ST-T changes	6.0
Second-degree AV block	4.4
Arrhythmias	3.4
First-degree AV block	2.9
Upper extremity discomfort	2.6
Hypotension	2.0
Paresthesias	1.8
Dry mouth	1.6
Anxiety/nervousness	1.5

* At least 1% of total number of patients studied (5,552) reported these events.
Data provided by Medco Research, Inc.

TABLE 2. Adverse Events Reported by Patients Who Underwent IV Dipyridamole Thallium Imaging

Adverse Event*	Number of Patients	(%)
Chest pain	770	19.7
Headache	476	12.2
Dizziness	460	11.8
ST-T changes on ECG	292	7.5
Ventricular extrasystoles	204	5.2
Nausea	180	4.6
Hypotension	175	4.6
Flushing	132	3.4
Tachycardia	127	3.2
Pain (nonspecified)	102	2.6
Dyspnea	100	2.6
Blood pressure lability	61	1.6
Hypertension	58	1.5
Paresthesias	48	1.3
Fatigue	45	1.2
Dyspepsia	38	1.0

* At least 1% of total number of patients studied (3,911) reported these events.
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Direct administration of intravenous adenosine produces more acute, though more transient, side effects than intravenous dipyridamole. Due to adenosine's short half-life (<10 sec), administration of aminophylline is rarely required. The majority of side effects dissipate within two min of cessation of the adenosine infusion (*2,14,16*).

Aminophylline has been shown to rapidly reverse the cardiovascular effects of increased adenosine levels by blocking adenosine receptors (*1*). While many of the side effects produced by dipyridamole resolve spontaneously within 15–30 min, the user should not hesitate to administer IV aminophylline, if chest pain or ECG changes are severe enough to warrant intervention.

Hays et al. demonstrated that most patients (70%) experience transient side effects when undergoing high infusion rates (up to 40 μg/kg/min) of dobutamine. Chest pain, palpitations, tremulousness, headache, nausea, and ventricular tachycardia were the most predominant side effects. Ischemic electrocardiographic changes occurred in 44% of the patients studied (*10*). In another study, significant ST depression occurred with dobutamine, when compared with symptom-limited treadmill tests (88% concordance) (*17*). An intravenous beta blocker, such as esmolol, may be used to counteract the effects of dobutamine.

PATIENT POPULATION

Table 3 illustrates clinical indications for patients who will benefit from pharmacologic interventional stress testing. Any patient with these indications who cannot or will not achieve a maximal stress test is a potential candidate for one of these protocols.

While safety has been well documented for intravenous adenosine (*14*) and dipyridamole (*13,18*), contraindications for each agent must be carefully considered (Table 4). Users should remember that appropriate patient selection for pharmacologic stress testing is just as important as the evaluation conducted prior to a standard exercise stress test.

Recent studies have reported the use of interventional stress testing in patients with unstable angina or recent myocardial ischemic events, using adenosine (*14*) and dipyridamole (*19, 20*). However, it should be noted that the dipyridamole studies were done on patients who had been pain-free for at least 24 hr before the procedure. Table 4 summarizes contraindications for each of these agents.

TABLE 3. Clinical Indications for Pharmacologic Intervention

Pre-operative for peripheral vascular surgery
Pre-operative for aortic aneurysm repair
Evaluation of chest pain
Evaluation of known coronary artery disease
Evaluation of post-coronary bypass or percutaneous transluminal coronary angioplasty
Early myocardial infarction risk stratification

TABLE 4. Contraindications for Pharmacologic Intervention

Contraindications	Dipyridamole	Adenosine	Dobutamine
Unstable angina or resting ischemia	x	x	x
Poor LV function (EF <15%)	x	x	x
Hypertension (>200 mmHg systolic)		x	x
Hypotension (<90 mmHg systolic)	x	x	
Severe aortic stenosis			x
History of reactive airway disease (asthma)	x	x	
Active bronchospastic disease	x	x	
History of tachyarrhythmias			x
Second-degree AV block		x	
Oral dipyridamole		x	
Xanthine derivatives (theophylline; caffeine)	x	x	
Atrial fibrillation with rapid ventricular response			x

The "x" indicates the contraindications for the respective agent.

Most of the contraindications which apply to adenosine and dipyridamole also apply to dobutamine (see Table 4), with the notable exceptions of active bronchospastic disease and asthma. Theophylline, oral dipyridamole, or caffeine ingestion do not interfere with the action of dobutamine; however, oral beta blockers may inhibit the patient's hemodynamic response.

PROCEDURES

Each agent (adenosine, dipyridamole, and dobutamine) is delivered intravenously; however, the patient preparation, infusion parameters, and follow-up vary with each agent (Table 5).

Patient Preparation

Patients must have NPO for at least 3 hr prior to the test. When using the adenosine or dipyridamole protocols, the inhibitory effects of aminophylline on the adenosine receptors also necessitate the restriction of patient intake of xanthine derivatives prior to the test (*7*). Patients should be instructed not to consume coffee, decaffeinated coffee, tea, carbonated drinks, medications containing caffeine, or chocolate for at least 12 hr prior to testing. Additionally, all theophylline medications should be stopped 24–36 hr prior to dipyridamole or adenosine infusion. When using direct administration of intravenous adenosine, oral dipyridamole should be restricted to prevent an increase in the duration of vasodilation. If a patient qualifies for dobutamine administration, the patient should have NPO for at least 3 hr prior to the test and for best results, beta blockers should be withheld for 24-48 hr.

TABLE 5. Protocols for Administration of Dipyridamole, Adenosine, and Dobutamine

Patient Preparation	For 3 hr prior to test NPO except water. For at least 12 hr prior to test: If dipyridamole, withhold xanthine derivatives (caffeine, theophylline, etc.). If adenosine, withhold xanthine derivatives (caffeine, theophylline, etc.) and oral dipyridamole. If dobutamine, withhold beta blockers.
Imaging	Standard SPECT or planar myocardial perfusion imaging protocols.
Preparation	Dipyridamole: Patient weight in kg × .56 mg/kg drawn up in syringe from 5 mg/ml vials. Adenosine: Ten 2-ml vials (6 mg/ml) diluted in 30 ml normal saline for a concentration of 2.4 mg/ml *or* one 30-ml vial with a concentration of 3 mg/ml. Calculate dose relative to patient weight. Dobutamine: Dilute 120 mg/20 ml dobutamine with 30 ml saline. Calculate dose relative to patient weight.
Standard Procedure	1. Confirm physician's lab order; explain procedure; obtain consent. 2. Obtain resting 12-lead ECG and blood pressure. 3. Physician examines and questions the patient regarding relative contraindications. *If any of the exclusion criteria are present, discuss risk/benefit with the referral physician.*
Dipyridamole	1. Start normal saline or D5W IV drip. 2. Infuse dipyridamole over 4 min (infusion pump or manual administration). Inject radiopharmaceutical at 8 min. 3. Record ECG and blood pressure at rest and every min during infusion. 4. Keep aminophylline available: in the event of serious side effects, administer 1 to 2 min after myocardial perfusion agent is given. 5. Terminate monitoring at 15 min post-infusion if no adverse side effects, ECG changes, or hemodynamic changes have occurred. 6. Monitor until patient is stable, if aminophylline was given or changes were noted.
Adenosine	1. Start IV drip with normal saline, dual-port extension set and 3-way stopcock attached to an infusion pump. 2. Use the most appropriate of the following infusion sequences: Standard 6-min infusion: infuse adenosine at a rate of 140 μg/kg/min for 6 min, with slow radiopharmaceutical injection at the end of the 3 min; Alternate 7-min titrating infusion (typically used for high risk patients): infuse adenosine at a rate of 50 μg/kg/min for 1 min, followed by stepped increases to 75, 100, and 140 μg/kg/min for each consecutive min. Inject radiopharmaceutical at the end of 4 min. Continue infusion at the rate of 140 μg/kg/min for 3 min. 3. Record ECG and blood pressure at rest and every min during the infusion, and for the first 5 min after cessation of infusion. 4. Keep aminophylline available: in the event of serious side effects, administer at the discretion of the physician. 5. Terminate monitoring at 5 min post-infusion, if no adverse side effects, ECG changes, or hemodynamic changes have occurred. 6. Monitor until patient is stable, if aminophylline was given or changes were noted.
Dobutamine	1. Start IV drip with normal saline, dual-port extension set and 3-way stopcock attached to an infusion pump. 2. Infuse dobutamine at a rate of 5 μg/kg/min for 3 min followed by stepped increases to 10, 20, 30, and 40 μg/kg/min for each consecutive 3 min. Inject radiopharmaceutical at the initiation of the maximum dose (13 min or 1 min following initiation of the maximally tolerated dose). Continue infusion at the rate of 40 μg/kg/min for 2 min. 3. Record ECG and blood pressure at rest and every min during the infusion, and for the first 6 min after cessation. 4. Keep esmolol available: in the event of serious side effects, administer at the discretion of the physician. 5. Terminate monitoring at 5 min post-infusion, if no adverse side effects, ECG changes, or hemodynamic changes have occurred. 6. Monitor until patient is stable, if esmolol was given or changes were noted.

Drug preparation varies, of course, as each pharmaceutical has a distinct concentration and rate of administration, relative to patient weight. Users should refer to the drugs' protocols, timelines, and package inserts for appropriate preparation.

For adenosine and dobutamine, a dual-port extension set may be used, with a three-way stopcock, connected to the port closest to the IV site and the second port immediately distal to the first (Fig. 2). The extension set connected to the three-way stopcock is attached to an infusion pump (or syringe pump). The second port is used for slow (>30 sec) radiopharmaceutical injection during the pharmacologic agent's peak effect. A slow injection is essential, as the adenosine infusion continues for three min and the dobutamine infusion for two min post-injection of the myocardial perfusion agent. The infusion should not be interrupted. More important, the adenosine and dobutamine in the vein and venous catheter would be delivered as a bolus if the radiopharmaceutical was injected rapidly through the same IV line (*21*).

Due to these factors, dual IV sites have been previously recommended and may be used in the place of the single IV site described in this article. An automatic infusion system must be used to ensure a constant delivery rate of the adenosine and of each level of dobutamine.

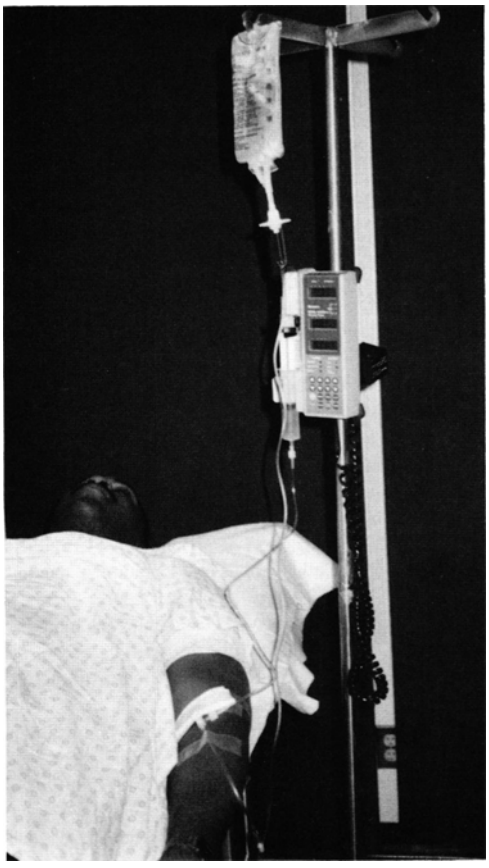

FIG. 2. When administering adenosine or dobutamine, one IV with a dual port may be used. The port proximal to venipuncture contains a three-way stopcock and extension set, connected to an infusion pump for the adenosine or dobutamine infusion; the distal port is used for administering the radiopharmaceutical.

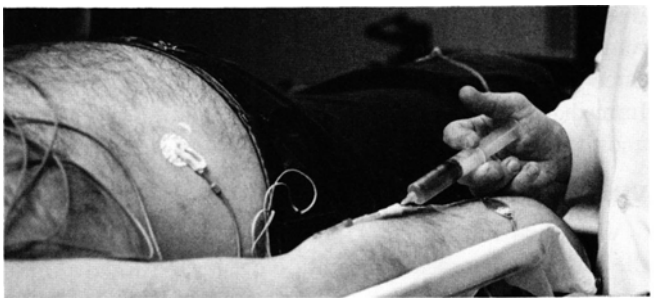

FIG. 3. When administering dipyridamole, one IV site may be used; infuse the dipyridamole first and the radiopharmaceutical 3–5 min after cessation of dipyridamole.

Figure 3 illustrates the IV preparation for a patient receiving dipyridamole. A single IV line is used for both the dipyridamole infusion and radiopharmaceutical administration. The dipyridamole may be delivered with an infusion pump, by IV drip, or, more simply and just as effectively, by manual IV push over the four-min time period.

Pharmacologic Infusion

The timelines for adenosine, dipyridamole, and dobutamine are represented in Figure 4. Little overall time difference is appreciated from one protocol to the next, at 11, 18, and 20 min for adensoine, dipyridamole, and dobutamine, respectively. However, the timing of the infusion, rate of infusion, and radiopharmaceutical injection is critical, and varies considerably with each agent.

Adenosine is infused for six min; the radiopharmaceutical is injected slowly during the third min of infusion. Dipyridamole is infused for four min; the radiopharmaceutical is

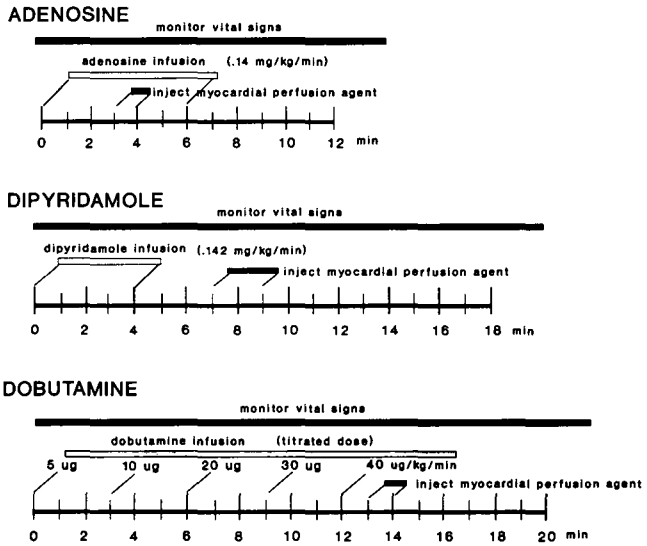

FIG. 4. Adenosine infusion timeline: radiopharmaceutical injection occurs at the 3-min point of the infusion. Dipyridamole infusion timeline: radiopharmaceutical injection occurs 3- to 5-min post-infusion. Dobutamine infusion timeline: radiopharmaceutical injection occurs 2 min prior to cessation of maximally tolerated dose.

injected between three and five min post-infusion. Dobutamine is infused with an increase in concentration levels every three min until the maximally tolerated dose is reached. Immediately thereafter the radiopharmaceutical is injected, and the infusion continues for two additional min.

Vital Signs

Vital signs must be monitored every minute throughout the infusions for each intervention agent, and for five min post-infusion for adenosine and dobutamine. Patients receiving dipyridamole should be monitored for 15 min post-infusion.

Aminophylline Administration

Aminophylline administration may be necessary following the infusion of dipyridamole, and more rarely, following the infusion of adenosine. The myocardial perfusion imaging agent of choice must be given at least 1 min before aminophylline administration to ensure uptake of the radiopharmaceutical in the myocardium during maximum coronary arterial dilatation. In addition, once aminophylline has been administered to a patient post-dipyridamole or post-adenosine infusion, careful observation of the patient should continue until all symptoms have resolved.

DISCUSSION

Each pharmacologic cardiac interventional agent discussed has its respective application and will benefit various members of the patient population. Adenosine, with its short half-life may be a desirable choice for certain patients in whom a rapid reversal of any side effects is important. Symptoms usually subside within 2 min of the cessation of the adenosine infusion (*14,21,22*). However, the necessity of a dual-port IV setup and an infusion pump may make the procedure appear cumbersome for routine use.

Dipyridamole is convenient, easy to administer through a single IV site, has a milder onset of symptoms, and can accommodate many patients who cannot exercise. However, dipyridamole's longer half life (15–30 min) may limit its use with critically ill patients and aminophylline may be required to treat side effects if they occur.

Dobutamine may be useful for studying those patients who have been excluded from the adenosine and dipyridamole protocols due to aminophylline or dipyridamole medication, reactive airway disease, or the consumption of caffeine prior to the test. In addition, since myocardial blood flow increases secondary to an increase in oxygen demand, the radiopharmaceutical uptake may remain linear under the influence of dobutamine (*23*). This is in contrast to the lower net tracer extraction seen at the high flow levels, evoked by pharmacologic coronary vasodilation (*12*).

With these new protocols, nuclear medicine is able to evaluate an estimated 25% of patients referred for cardiac workup who otherwise would not be able to undergo an adequate stress test. The value of these tests as a group is unquestionable, but the choice of the interventional agent used must be highly individualized. Each patient's clinical presentation must be studied and a careful evaluation should be made of the risk/benefit ratio. Some patients will still be excluded from any stress test, exercise or pharmacologic. A good rule of thumb to follow is this: If a patient is too sick to undergo submaximal exercise, he is too sick for pharmacologic stress.

Any state-of-the-art nuclear medicine department can and probably should offer pharmacologic cardiac stress testing. Currently, IV dipyridamole is the only agent approved for pharmacologic stress. Adenosine is approved for supraventricular tachycardia (SVT), and FDA approval is expected soon for its use in stress testing. Dobutamine may be used at the discretion of the physician.

It is our hope, that by presenting the options currently available, the choice of which pharmacologic cardiac stress protocol to use will be simplified.

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