Adenosine Cardiac Imaging

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This is the fourth article in a four-part series on nuclear medicine updates. Upon completion of this article, the reader should be able to: (1) explain the purpose for using adenosine, (2) list the types of patients who would benefit from an adenosine stress, and (3) describe the technique used in adenosine cardiac imaging.

Exercise cardiac perfusion scintigraphy with thallium-201 (^{201}Tl) is a well-established method for the noninvasive diagnosis of coronary artery disease (*1*). Frequently, however, patients referred for cardiac scintigraphy are unable to exercise to the desired maximal heart rate, due to drug therapy, peripheral vascular disease, or other physical limitations. Intravenous pharmacologic coronary vasodilation with dipyridamole or adenosine has been shown to be an effective, safe, and accurate substitute for exercise in determining the presence of coronary artery disease in this group of patients (*2,3*).

The purpose of this article is to provide the standard nuclear medicine laboratory with information necessary to perform intravenous adenosine coronary vasodilation in association with ^{201}Tl scintigraphy.

ADENOSINE MECHANISM OF ACTION

The ideal pharmacologic coronary vasodilatory agent would have an insignificant systemic effect and a maximal selective action on the coronary arteries. It would have a short-lived duration of action, lasting just long enough to permit extraction of the radiopharmaceutical from the systemic circulation, i.e., at least a few minutes. Yet the agent's action would be brief enough that effects and side effects would disappear shortly after drug administration was terminated. A number of agents have partially fulfilled these conditions, including: contrast material, papaverine, dipyridamole, and adenosine.

Adenosine is a potent vasodilator in most vascular territories (with the exception of the kidneys); it has a reported plasma half-life of less than 10 sec (*4,5*). Studies show that an adenosine dose of 140 μg/kg/min maximally increases coronary blood flow to an average of 4.4 times the resting blood flow in 84% of normal patients, and that adenosine induces a flow increase similar to that produced by intracoronary papaverine in 92% of patients (*6*). The maximal effect of adenosine occurred at 123 sec during intravenous infusion, with a return to baseline at 113 sec after cessation of the infusion (*7*).

It is not precisely known how adenosine regulates the coronary blood flow. However, several aspects of the mechanism that results in microvascular vasodilation are understood. Adenosine A_2 receptors reside on the cell membrane of the endothelium and smooth muscle of coronary resistance vessels. When adenosine interacts with the A_2 receptors, it causes an increase in adenylate cyclase activity, followed by an increase in intracellular cyclic AMP. Adenosine also reduces coronary vasoconstriction during neural sympathetic stimulation through presynaptic inhibition of norepinephrine release and reduction of cellular calcium uptake (*6*). Of note, methylxanthines (theophylline, caffeine, etc.) inhibit adenosine receptor activity through direct competition. Therefore, patients who receive methylxanthines prior to adenosine infusion may not develop maximal coronary hyperemia (*7,8*).

Researchers believe that dipyridamole's action is indirect, blocking the cellular adenosine uptake, which increases the adenosine concentration in both myocardium and arterial wall. This hypothesis views endogenous adenosine as the direct mediator of coronary dilation through smooth muscle relaxation (*9–13*).

RADIOPHARMACEUTICAL KINETICS DURING ADENOSINE ADMINISTRATION

Pharmacologic coronary vasodilation with adenosine increases blood flow through the normal coronary arteries by as much as four to five times the resting flow. However, blood flow through the stenosed arteries increases less or may not change (Figs. 1 and 2). This disparity in regional myocardial perfusion results in differential uptake of radiopharmaceuticals (*8*), such as ^{201}Tl.

The preferred myocardial perfusion radionuclide agent should be extracted by the myocardium proportionally to coronary flow both at rest and during coronary hyperemia.

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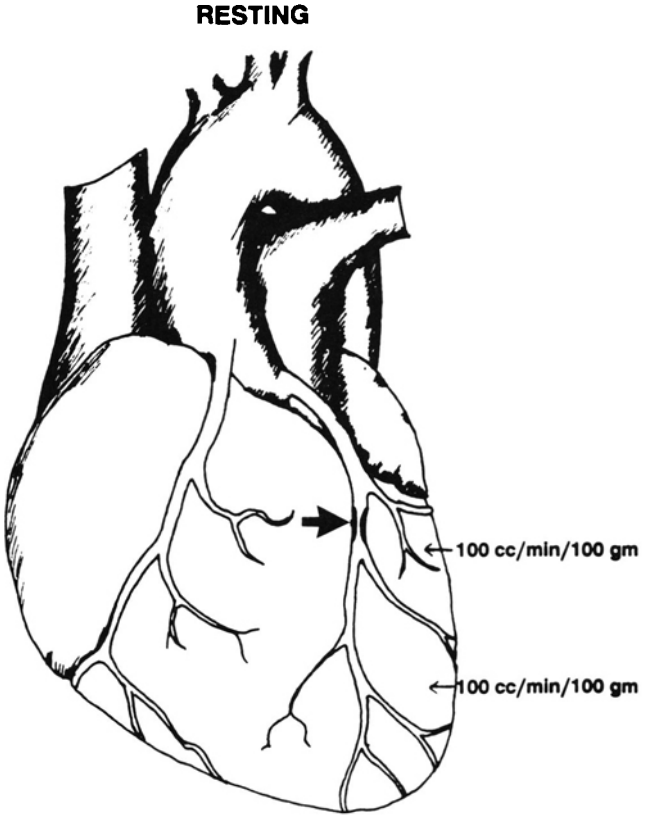

FIG. 1. Myocardial perfusion at rest. The myocardial zone distal to the coronary lesion (large arrow) has a flow rate equal to that of the normal zones.

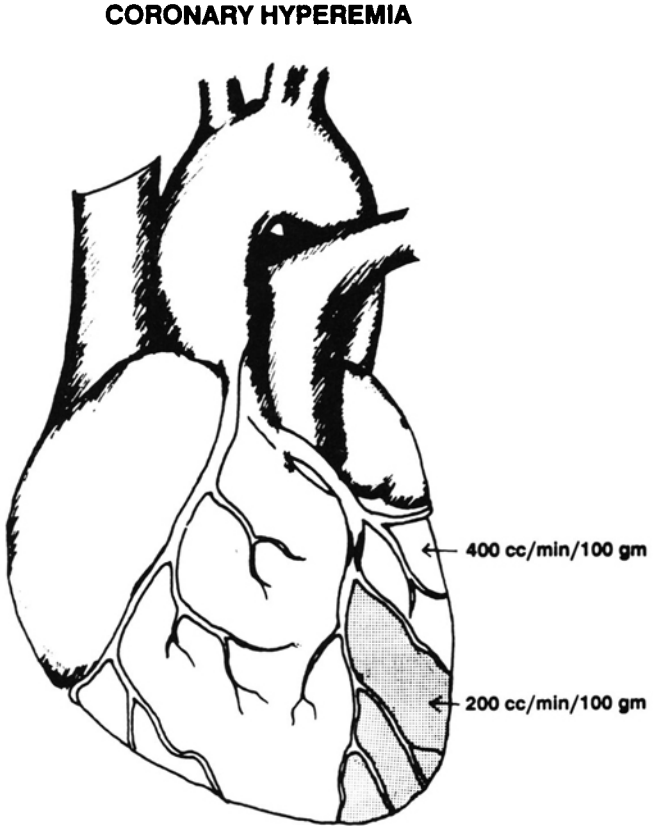

FIG. 2. Myocardial perfusion under the influence of coronary hyperemia. While the normal zone's flow increased to four times the resting flow, the flow in the zone perfused by the stenotic artery only increased two times. The latter zone will present with a relatively decreased ^{201}Tl uptake, ie., perfusion defect (illustrated by the stippled area).

The uptake of ^{201}Tl, as well as the new technetium-99m (Tc-99m) perfusion agents sestamibi and teboroxime, is proportional to flow at rest (*14–15*). During hyperemia, however, the myocardial extraction fractions of both ^{201}Tl and sestamibi fall considerably, so myocardial tracer uptake is lower than true flow. Fortunately, this well-known phenomenon has not had a major impact on the detection of coronary stenoses during pharmacologic imaging. Interestingly, teboroxime demonstrates a closer relationship to the increase in coronary flow, even at high flow rates (*15*).

PATIENT POPULATION

Patients who may benefit from adenosine cardiac imaging include those who cannot perform an adequate stress test due to a number of incapacitating factors such as debilitating diseases, strokes, advanced age, morbid obesity, or simply poor physical conditioning. Moreover, exercise stress may be contraindicated in patients with dissection of the aorta or large aortic aneurysms. Exercise stress is often suboptimal in patients on antianginal therapy (beta blockers, nitrates, or calcium antagonists). The clinical indications for adenosine perfusion imaging are shown in Table 1.

Not all patients are suitable candidates for the adenosine infusion protocol. Patients with severe hypertension, hypotension, presence of bronchospasm, second- or third-degree AV block, sick sinus syndrome, and those who received theophylline, caffeine, or dipyridamole within 12 hours prior to the test are excluded in our laboratory (Table 2). Furthermore, patients with unstable angina, very recent infarction (<2 days), or severe heart failure should be studied only after careful consideration of the risk/benefit ratio. Patients with severe chronic obstructive pulmonary disease requiring bronchodilators and those with asthma should undergo the protocol with great caution, if at all, due to the potential for increased bronchospasm with adenosine (or dipyridamole).

TABLE 1. Clinical Indications for Adenosine Perfusion Imaging

1. Assessment of chest pain syndrome.
2. Risk stratification after acute myocardial infarction.
3. Evaluation before and after coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty.
4. Risk evaluation prior to peripheral vascular or other major surgeries.
5. Assessment of the functional significance of known coronary artery stenoses.

ADENOSINE INFUSION PROTOCOL

Table 3 illustrates a typical nuclear medicine imaging protocol for adenosine perfusion scintigraphy. Patient preparation, infusion, and acquisition of the initial images will require approximately one hr; acquisition of the delayed images will require an additional 25 min of laboratory time. However, the adenosine infusion may be performed in a room adjacent to the imaging room, providing additional scheduling flexibility.

TABLE 2. Adenosine Scintigraphy: Contraindications at Baylor College of Medicine

1. Severe hypertension (>200 mmHg systolic and >120 mmHg diastolic).
2. Hypotension (<90 mmHg systolic).
3. Presence of bronchospasm (wheezing).
4. Second- or third-degree AV block.
5. Sick sinus syndrome.
6. Theophylline, caffeine, or dipyridamole within 12 hours prior to the test.

The adenosine consent form is explained to the patient, who then signs the consent form; the form is cosigned by a witness. This is an important step because adenosine is only approved for use as an antiarrhythmic (Adenocard™, Fujisawa Pharmaceutical Co., Deerfield, IL). Approval for use with perfusion imaging is under consideration by the Food and Drug Administration (FDA).

Preferably, two distinct venous sites are used (Fig. 3). The purpose of this is to avoid a bolus of the adenosine, which is stored in the infusion tubing; this might occur if thallium were injected in the same intravenous line that is being used for infusion.

The infusion rate is computed based on the patient's weight and the concentration of adenosine. Table 4 shows two examples of this computation: one utilizing the 2 cc vials currently available; the other utilizing the pre-mixed vials, which should be commercially available in the future.

The adenosine is administered intravenously by a volumetric infusion pump at a set rate, which may be increased, decreased, or stopped as desired. Another option is an automatic syringe pump (Fig. 3), which uses a 60 cc syringe and extension set.

TABLE 3. Adenosine Infusion Protocol

Purpose	To demonstrate the presence of coronary artery disease in patients unable to exercise
Study Time	1 hr initially; 25 min for delayed images
Patient Preparation	For 3 hr prior to test NPO except water For 12 hr prior to test withhold the following: caffeine, theophylline, dipyridamole
Imaging	Standard SPECT or planar ^{201}Tl imaging protocols
Radiopharmaceutical	3.0 mCi ^{201}Tl (^{99m}Tc perfusion agents may also be used)
Adenosine Preparation	Ten 2 ml vials (6 mg/ml) diluted in 30 ml normal saline for a concentration of 2.4 mg/ml **OR** one 150 mg, 30 ml vial with a concentration of 3 mg/ml (follow rate determination formula)
Procedure	1. Identify patient and confirm physician's lab order. 2. Explain adenosine consent form and test to patient; in presence of witness have patient sign the form. 3. Place standard 12-lead ECG, radioluscent wires and electrodes. 4. Physician examines and questions the patient regarding relative contraindications. *If any of the exclusion criteria are present, discuss risk/benefit with the referral physician.* 5. Start two normal saline IV drips, preferably one in each arm. A dual port intravenous set in a single vein may be used in lieu of two IVs. —Use one IV for ^{201}Tl injection at the specified time interval. —Use the other IV for adenosine administration with an infusion pump. Also place a 3-way stopcock at the infusion site. 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 the ^{201}Tl injection at the end of 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 ^{201}Tl at the end of 4 min. Continue infusion at the rate of 140 μg/kg/min for 3 min. 6. Record ECG and blood pressure at rest every min during the infusion and for the first 5 min after cessation of infusion. 7. Keep aminophylline available: in the event of serious side effects, administer at the discretion of the physician. 8. Begin initial imaging within 10 min and delayed imaging within 3 to 5 hr of infusion. In the event of a persistent defect, additional 24-hr delayed or reinjection images may be indicated.

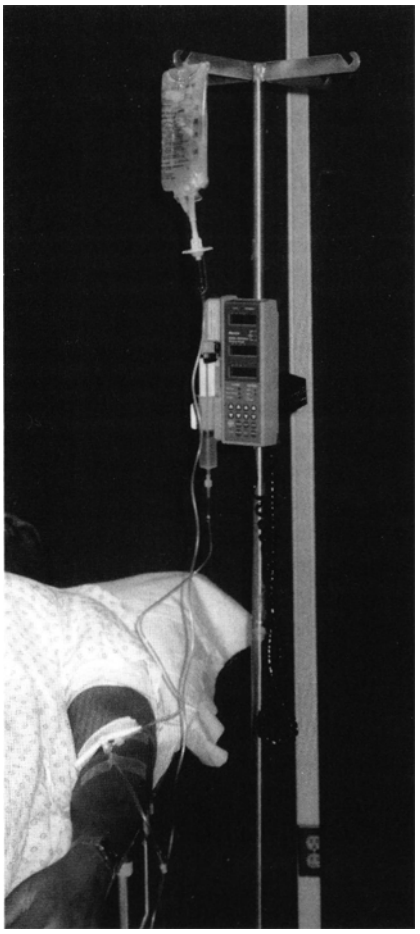

FIG. 3. The IV site with the infusion pump has a three-way stopcock and extension set.

Two infusion protocols are used. In the standard protocol, adenosine is infused for 6 min at a rate of 140 μg/kg/min, with the ^{201}Tl injection taking place at the end of 3 min of infusion (Fig. 4). An alternative protocol may be used in patients considered at high risk, such as those who have experienced a recent myocardial infarction, those with documented severe three-vessel coronary disease or left main stenosis, those with severe or unstable angina, or those with a questionable history of asthma or bronchospasm. In these patients, a 7-min titrating protocol may be preferable (Fig. 5).

TABLE 4. Computing the Infusion Rate

1. Determine the infusion rate/kg, based on the concentration of mixed or pre-mixed adenosine, for the desired μg/kg/min:
   FORMULA
   (desired μg × 60 min)/concentration in μg/cc = μg/kg/hr
   EXAMPLES (at a rate of 140 μg/kg/min)
   Mixed from 2 cc vials (2.4 mg/cc)
   (140 μg × 60 min)/2,400 μg/cc = 3.5 cc/kg/hr
   - or -
   Pre-Mixed (3.0 mg/cc)
   (140 μg × 60 min)/3,000 μg/cc = 2.8 cc/kg/hr
2. To determine the correct setting for the infusion pump, multiply the rate by the patient's weight in kg:
   EXAMPLE (a 70 kg patient)
   70 kg × 3.5 cc/kg/hr = 245 cc/hr
   70 kg × 2.8 cc/kg/hr = 196 cc/hr

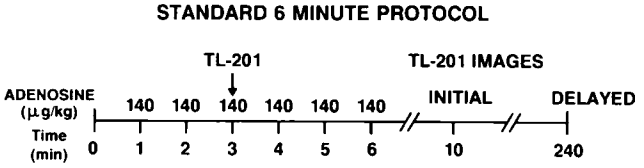

FIG. 4. Standard six-min adenosine infusion protocol. Thallium-201 is injected at the end of the third min of adenosine infusion.

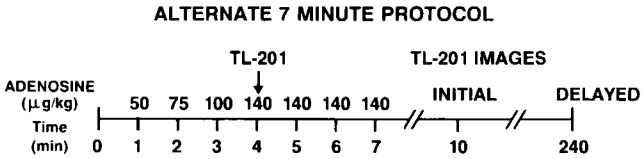

FIG. 5. Alternative seven-min infusion protocol. Thallium-201 is injected at the end of the fourth min of the adenosine infusion.

OUR CLINICAL EXPERIENCE

In the Nuclear Cardiology Laboratory of The Methodist Hospital/Baylor College of Medicine, we have performed over 1,500 intravenous adenosine thallium studies since 1988. All studies were performed in accordance with the guidelines set forth in this paper. Most studies were done in patients with documented or suspected coronary artery disease. A subset of 120 patients were studied within 2 to 7 days after an acute myocardial infarction to develop a pre-discharge risk stratification.

Our group has previously reported on a subset of 89 patients who received a titrating adenosine infusion (*2*): 55 with stable angina, remote myocardial infarction, or both; 12 status post coronary artery bypass surgery; and 34 with atypical chest pain or for risk assessment. At the maximum rate of 140 μg/kg/min, the systolic pressure decreased by 8.7 ± 19.3 mmHg and the diastolic pressure by 6.7 ± 9.4 mmHg, whereas the heart rate increased by 14.5 ± 11.0 beats/min (bpm). The most frequent side effects included chest, throat, and jaw pain (57% of patients). All side effects subsided within 1 or 2 min after termination of the infusion. All symptoms were well-tolerated and short-lived. Twelve percent of the patients studied experienced ischemic electrocardiographic ST segment changes. A statistically significant increase in the electrocardiographic PR interval (from 172 ± 27 to 179 ± 30 msec) occurred at the maximal infusion rate. Second-degree atrioventricular (AV) block developed in one patient and resolved after decreasing the infusion rate (from 100 to 75 μg/kg/min).

The overall sensitivity for coronary disease detection was 83% utilizing quantitative tomography; sensitivity was 73% in patients with one-vessel, 90% in those with two-vessel, and 100% in patients with three-vessel coronary artery disease. Only 1 of 16 patients who had normal coronary angiography had an abnormal tomography (94% specificity).

Safety and Quantification

Tolerance and safety were analyzed by our group in a large cohort of 607 patients (351 males, 256 females, mean age 63 ± 11 yr) referred for adenosine cardiac imaging to rule out coronary artery disease (n = 492) or for risk stratification after myocardial infarction (n = 125). Heart rate increased from 74.5 ± 14.0 to 91.8 ± 15.9 bpm and systolic blood pressure decreased from 137.8 ± 26.8 to 120.7 ± 26.1 mmHg (*16*). Both groups experienced frequent and similar side effects to those we have previously described (*2*). First-degree AV block occurred in 9.6%, second-degree AV block in 3.6%, and ischemic electrocardiographic changes in 12.5%. Severe side effects were experienced by only 1.6% of all patients but no serious complications occurred. In particular, myocardial infarction or death did not occur in any of our patients. Hemodynamics, electrocardiographic changes, and side effects returned to baseline within two min of cessation of the adenosine infusion in most patients (*16*).

In yet another subset of 101 patients, our group studied the diagnostic value of adenosine cardiac imaging when compared to coronary arteriography (*17*). Seventy patients had >50% luminal diameter stenosis. Quantitative analysis demonstrated sensitivity of 87% for the total group; 82% for those patients without myocardial infarction and 96% for those with previous myocardial infarction. The overall specificity was 90%.

Case Studies

Patient One (Fig. 6). This 63-yr-old female was referred for ^{201}Tl adenosine scintigraphy for evaluation of atypical chest pain and shortness of breath. Adenosine was preferred over exercise due to the low exercise tolerance of the patient. She had no previous history of coronary artery disease but had a history of hyperlipidemia, hypertension, and a positive family history for heart disease.

The six min adenosine infusion protocol was used. Mild chest and throat pain occurred four min into infusion, followed by a slight headache during the fifth min. No ECG changes were noted. All symptoms resolved within two min of cessation of infusion.

Tomographic images were obtained using a standard SPECT system. The images were acquired immediately after the adenosine infusion and four hr later. SPECT reconstruction utilizing a 0.5 Butterworth filter (order 5) followed by reorientation in the short, horizontal long, and vertical long axes demonstrated normal perfusion in the initial and delayed images.

Patient Two (Fig. 7). This 80-yr-old male was referred for ^{201}Tl adenosine scintigraphy for evaluation prior to surgery to repair an aortic aneurysm. He presented with a history of ischemic heart disease and atrial fibrillation and had a permanent transvenous pacemaker, but was asymptomatic at the time of the study.

The six min adenosine infusion protocol was used. The patient experienced no symptoms during the infusion. Nonspecific ECG changes present at baseline did not change during adenosine infusion.

The initial SPECT images revealed mildly diminished inferoposterior, inferoapical, septal, anteroseptal, and posterior septal uptake, which normalized four hr later during redistribution imaging.

CONCLUSION

Adenosine is presently approved for use only as an antiarrhythmic. Thus, its use for perfusion imaging is considered investigational at the present time and requires signed informed consent.

Given its reported safety and accuracy, the potential of adenosine scintigraphy appears substantial. Adenosine is a

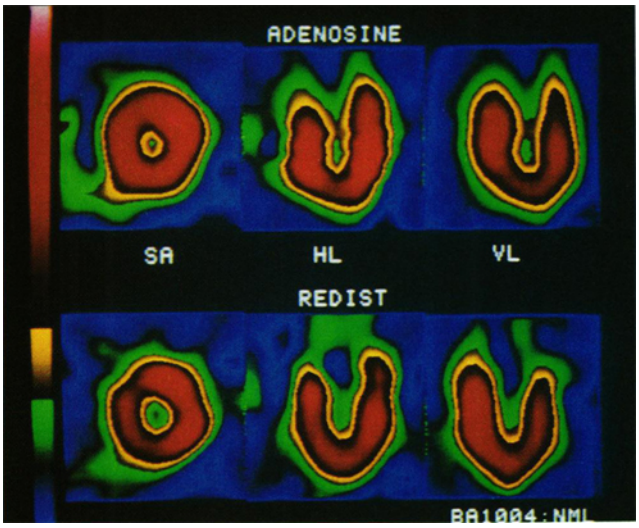

FIG. 6. Selected midcavity slices during adenosine infusion (top row) and during redistribution (bottom row). Note the homogeneous distribution after adenosine infusion and four hr later. Abbreviations: SA = short axis, HL = horizontal long axis, VL = vertical long axis.

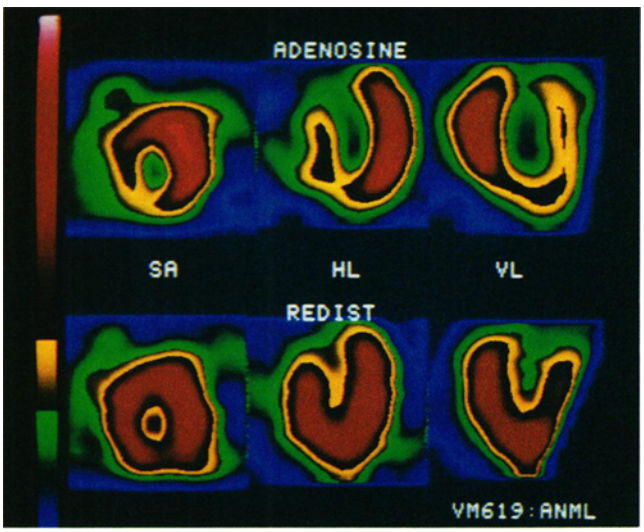

FIG. 7. Mildly diminished inferoposterior, inferoapical, septal anteroseptal, and posterior septal uptake in another patient, which normalized four hr later. SA = short axis, HL = horizontal long axis, VL = vertical long axis.

rapidly metabolized (<10 sec plasma half-life), practical agent that safely produces maximal coronary hyperemia (*2,6,8*) while rarely requiring administration of aminophylline (an adenosine antagonist) to relieve untoward effects. Dipyridamole, in comparison, is an indirect coronary dilator with a prolonged duration of action (>30 min), which frequently requires aminophylline administration and monitoring of vital signs for up to 30 min post infusion (*3*).

The sensitivity, predictive accuracy, and positive and negative predictive values of adenosine scintigraphy have been shown to be slightly higher than with exercise, albeit in a small group of patients (*8*).

Myocardial extraction of the recently approved ^{99m}Tc perfusion agents (sestamibi and teboroxime) has been shown to be proportional to coronary flow at rest and disparities in regional flow result in differential uptake during increased coronary flow. Thus, it is reasonable to assume that suitable imaging may also be achieved with adenosine in association with these new ^{99m}Tc perfusion agents.

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REFERENCES

1. Kotler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. *Annals of Internal Medicine* 1990;113:684–702.
2. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–87.
3. Iskandrian AS, Heo J, Askenase A, Segal BL, Auerbach N. Dipyridamole cardiac imaging. *Am Heart J* 1988;115:432–443.
4. Klabunde RE. Dipyridamole inhibition of adenosine metabolism in human blood. *Eur J Pharmacol* 1983;93:21–26.
5. Moser GH, Schrader J, Deussen A. Turnover of adenosine in plasma of human and dog blood. *Am J Physiol* 1989;256:C799–C806.
6. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;82:1595–1606.
7. Wilson RF, Christensen B, Zimmer S, Laxson D, White CW. Effects of adenosine on the coronary circulation in humans. (Abstract.) *J Am Coll Cardiol* 1989;13:132A.
8. Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia: correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. *J Am Coll Cardiol* 1990;16:1375–1383.
9. Pounds BK, Moore WH, Ladwig EJ, Blust JS, Viguet MG, Blust MJ, Dhekne RD. Dipyridamole thallium imaging. *J Nucl Med Technol* 1990;18:165–173.
10. Rubio R, Berne RM. Release of adenosine by the normal myocardium in dogs and its relationship to the regulation of coronary resistance. *Circ Res* 1969;25:407–415.
11. Berne RM. The role of adenosine in the regulation of coronary blood flow. *Circ Res* 1980;47:807–813.
12. Knabb RM, Gidday JM, Ely SW, Rubio R, Berne RM. Effects of dipyridamole on myocardial adenosine and active hyperemia. *Am J Physiol* 1984;247:H804–H810.
13. Melin JA, Becker LC. Quantitative relationship between global left ventricular thallium uptake and blood flow: effects of propranolol, quabain, dipyridamole, and coronary artery occlusion. *J Nucl Med* 1986;27:641–652.
14. Leppo JA, Meerdink DJ. Comparison of the myocardial uptake of a technetium-labeled isonitrile analogue and thallium. *Circ Res* 1989;65:632–639.
15. Seldin DW, Johnson LL, Blood DK, et al. Myocardial perfusion imaging with technetium-99m SQ30217: comparison with thallium-201 and coronary anatomy. *J Nucl Med* 1989;30:312–319.
16. Abreu AA, Mahmarian JJ, Nishimura S, Boyce TM, Verani MS. Tolerance and safety of pharmacologic coronary vasodilation with adenosine in association with thallium-201 scintigraphy in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1991: in press.
17. Nishimura S, Mahmarian JJ, Verani MS. Adenosine thallium-201 tomography: diagnostic accuracy in coronary artery disease. (Abstract.) *Circulation* 1990;82(suppl III):731.