Clinical Decision Making: Dipyridamole Thallium Imaging

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The purpose of this article is to provide an exposition of a clinical problem facing nuclear medicine physicians today and provide a discussion of the specific role of the radionuclide procedure in answering the clinical question. Since clinical decisions require careful integration of the history, physical examination, and the results of appropriate laboratory investigations, the case will be presented from the perspective of the clinician caring for the patient.

CASE HISTORY

A 71-yr-old white female was referred with a 3-yr history of throat tightness occuring while walking or lifting heavy objects. This discomfort was relieved after 5 to 10 min of inactivity or 5 to 10 min after taking nitroglycerine. She did not complain of chest, arm, or jaw pain. At the onset of her symptoms she had an exercise test which was positive for the reproduction of her symptoms but without electrocardiographic evidence of ischemia. Recently, her discomfort began to occur at rest, particularly after she ate. This throat tightness was often prolonged and was not relieved by nitroglycerine. Ingestion of fatty foods caused bloating, nausea, and throat tightness. She said, at times the throat tightness could be reproduced by bending over. Antacids provided variable relief. The addition of a calcium channel blocker and propranolol to her nitrates did not appear to affect her symptoms. She was particularly upset, since she had led a very active and healthy life until the onset of these symptoms and now felt significantly limited.

Her past history was unremarkable. Both her mother and father had died of heart disease in their seventies. She had no other risk factors for coronary artery disease.

Physical examination revealed an obese female who was normotensive with normal peripheral pulses and no bruits. Her neck veins were not elevated and of normal contour. Her cardiac apex was palpated in the fifth intercostal space and mid-clavicular line. First and second heart sounds were normal. She did have an S4 heart sound at the apex and a grade 2/6 systolic ejection murmur along the left sternal border radiating to the neck. The carotid upstroke was normal. The murmur was felt to be compatible with atherosclerosis. Her chest was clear and her abdomen unremarkable.

Her electrocardiogram and chest x-ray were within normal limits. An exercise thallium scan was performed. The test was terminated at 3 min because of reproduction of her symptom of throat tightness accompanied by severe anxiety. Her heart rate increased from a rest value of 72 to 115 bpm at the time of injection. Her blood pressure rose from a rest value of 132/90 to 180/110 mmHg at peak exercise. The electrocardiogram and scan were interpreted as normal [Fig. 1 (rest and exercise) and Fig. 2]. An abdominal ultrasound did not reveal gallstones. She was scheduled for a Bernstein test and esophageal manometry.

FORMULATION

This patient presented a diagnostic and management dilemma to her physicians. Initially, she was felt to have symptoms consistent with angina pectoris. The inability to demonstrate ischemia on her exercise thallium study led to alternate diagnoses and investigations. However, the persistence of atypical symptoms, and the lack of gallstones on her ultrasound increased the concern of her physicians that they were missing the diagnosis of coronary artery disease in a patient with escalating symptoms and an inadequate, though negative, exercise thallium scan.

The pretest likelihood of significant coronary artery disease in a woman of this age with atypical symptoms is ~50% (*1*). With this intermediate likelihood of disease the negative thallium study reduces this probability to ~15%. However, although the thallium scan was negative, the heart rate achieved at the time of injection is inadequate to exclude significant coronary narrowing as a cause of the patients symptoms. In this patient, the injection of thallium at the time of inadequate exercise

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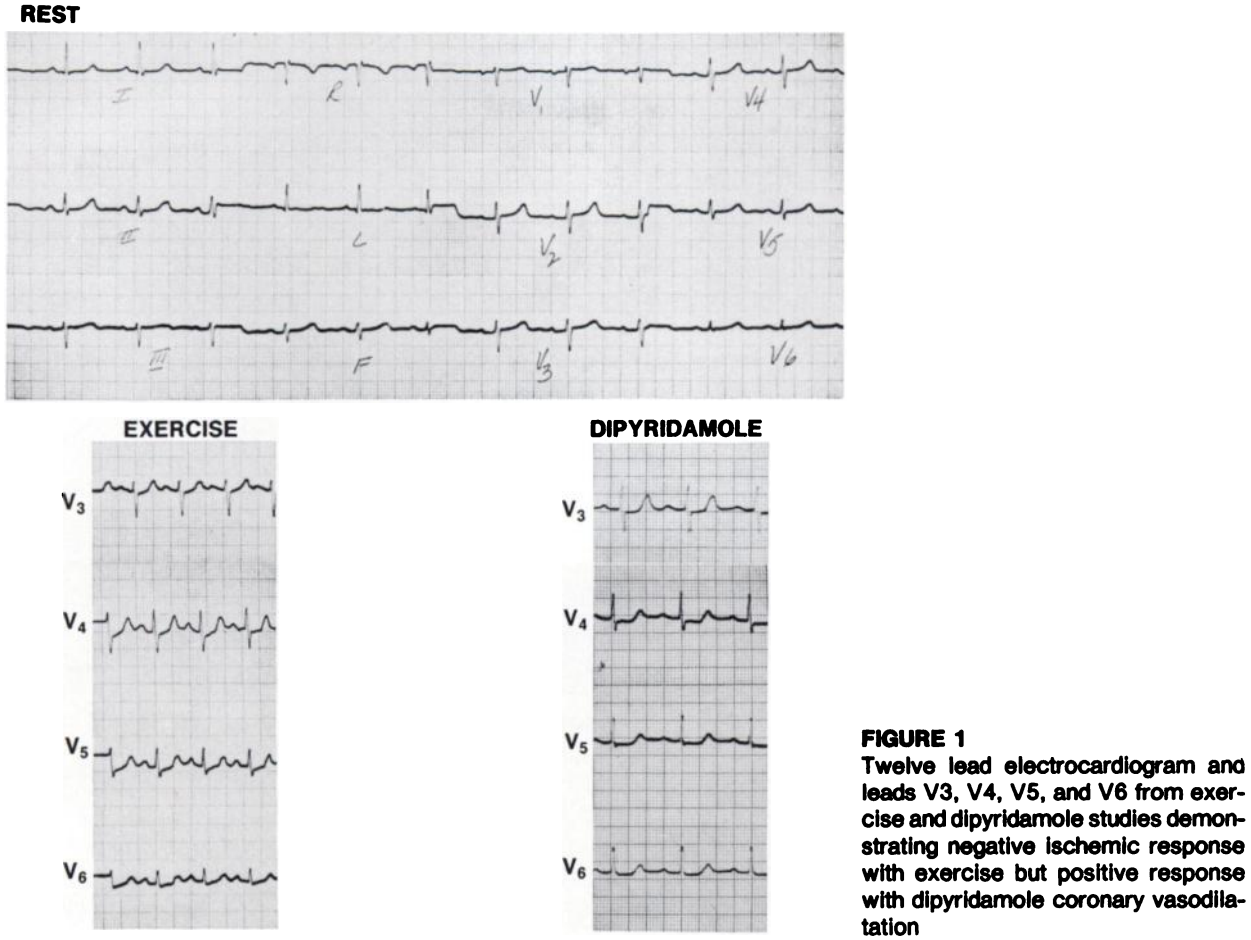

FIGURE 1
Twelve lead electrocardiogram and leads V3, V4, V5, and V6 from exercise and dipyridamole studies demonstrating negative ischemic response with exercise but positive response with dipyridamole coronary vasodilatation

stress, reproduction of the patients symptoms, and a negative thallium scan presents a major challenge to the nuclear cardiologist. In our experience, although the reproduction of symptoms is important, it is the combination of heart rate-blood pressure product and duration of time on the treadmill that is most important in defining the adequacy of the stress test to test the coronary reserve of the patient. To minimize the likelihood that the thallium scan result was a false-negative due to inadequate exercise, a dipyridamole thallium study was performed.

DIPYRIDAMOLE THALLIUM IMAGING

Dipyridamole was administered according to the i.v. protocol detailed in Table 1. Two minutes following the completion of the i.v. infusion of dipyridamole the patient experienced her typical throat discomfort. At this time her electrocardiogram demonstrated 1 mm of ST depression in leads V3, V4, and V5 (Fig. 1 dipyridamole). Seventy-four MBq of thallium-201 (^{201}Tl) were injected intravenously and imaging commenced. In parallel with commencement of imaging, 75 mg of aminophylline was administered to reverse the effects of dipyridamole. Her symptoms and electrocardiographic changes resolved. Initial and delayed thallium images revealed anterolateral, septal, and inferoapical ischemia (Fig. 3).

FOLLOW-UP

This dypyridamole study was surprisingly useful since it reproduced the patients symptoms, was accompanied by electrocardiographic changes and provided scintigraphic evidence of extensive myocardial ischemia. This conclusive evidence of significant coronary artery disease led to cancellation of her esophageal studies and an increase in her anti-anginal medication. Despite this, she continued to be limited by her symptoms. Three months later, she underwent coronary angiography which revealed severe three-vessel coronary artery disease (Fig. 4). She subsequently had surgical coronary revascularization and is presently enjoying an improved lifestyle.

DISCUSSION

Exercise ^{201}Tl scintigraphy is an often used technique in the noninvasive assessment of coronary artery disease. However, not all patients with suspected coro-

TABLE 1
Regimen for Administration of Dipyridamole in Both its Intravenous and Oral Form As Well As Corresponding Imaging Protocol*

Intravenous administration

Administer	Administer
Dipyridamole 0.142 mg/kg/min	74 MBq ^{201}Tl
	Imaging commenced
i.v.	
t = 0′ t = 4′	t = 7′

(ECG, HR, BP monitored every minute for 10 min and longer if necessary).

Oral administration

Administer	Administer
dipyridamole 300 mg p.o.	74 MBq thallium-201
	Imaging commenced
t = 0′	t = 45′

(ECG, HR, BP monitored every 5 min for 45 min and longer if necessary).

* Note that thallium is administered earlier if the patient experiences angina. (t = time in min).

nary artery disease are capable of a maximal exercise test. This problem is seen most often in patients with peripheral vascular disease, lung disease, poor physical conditioning, and those patients taking beta blockers. A submaximal exercise test may be less sensitive in the detection of myocardial ischemia (*2*). Myocardial ^{201}Tl imaging with pharmacologic coronary vasodilation using dipyridamole is an alternative approach which is particularly useful in this group of patients. There are substantial differences between exercise induced increased coronary blood flow and that due to pharmacological vasodilatation. Exercise stress has been reported

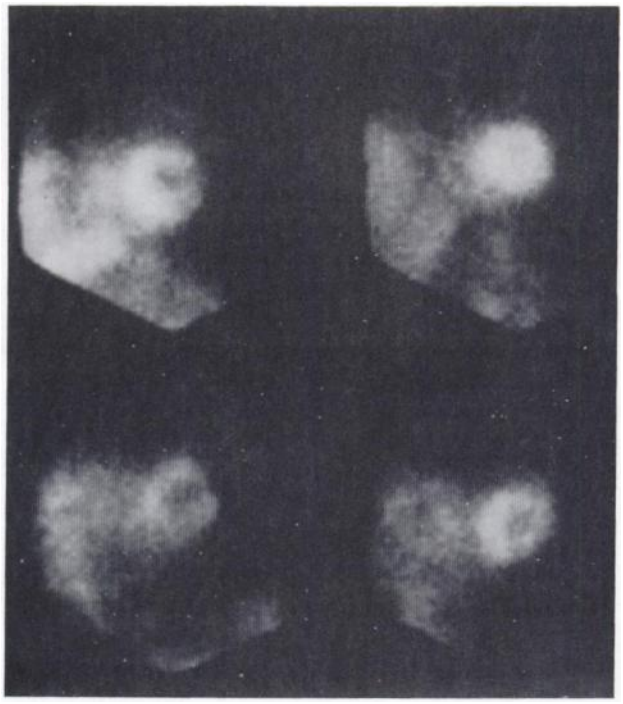

FIGURE 3
Anterior and LAO projections from initial and delayed dipyridamole study showing extensive anterolateral, apical, septal, and inferoapical ischemia

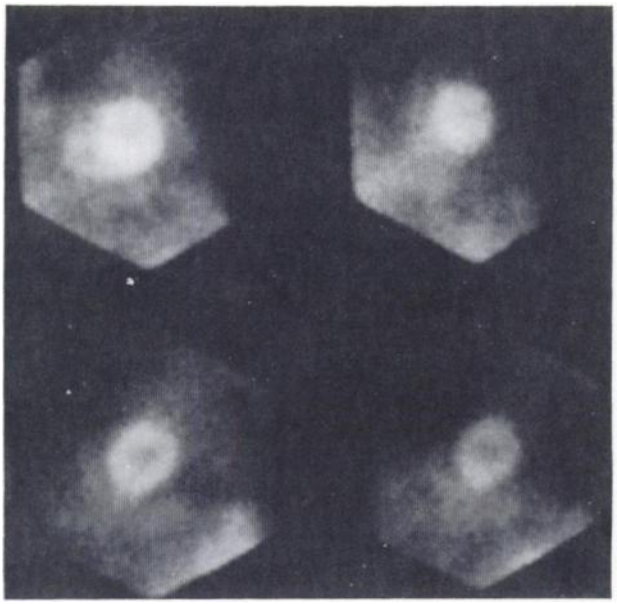

FIGURE 2
Anterior and LAO projections from initial and delayed exercise thallium study showing no evidence of myocardial ischemia

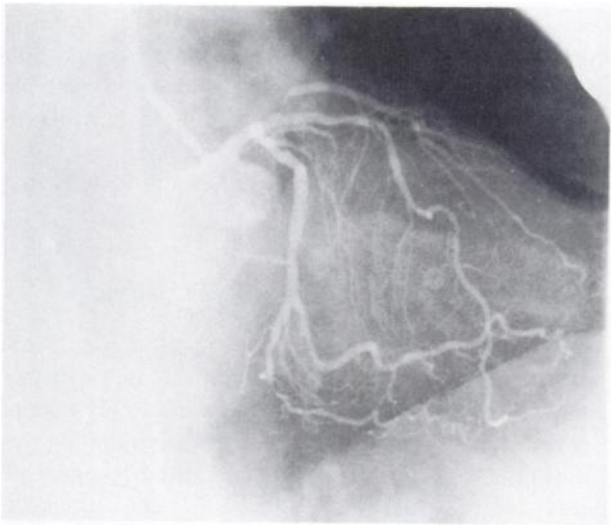

FIGURE 4
Injection of left coronary artery in RAO projection revealing significant disease of the LAD, first diagonal branch LAD and circumflex coronary arteries. Right coronary artery was occluded at origin

to increase coronary flow one to three times in man (*3*, *4*). The effectiveness of exercise as a stimulus for coronary flow is dependent on the level of work achieved. This is determined by the patients motivation, pulmonary and periperal vascular status, physical training and drugs such as propranolol. Dipyridamole, an effective coronary vasodilator in man, has been reported to increase coronary blood flow up to five times normal (*5*).

To assess the regional distribution coronary flow, the myocardial uptake of the imaging agent must be proportional to flow. The uptake of ^{201}Tl is linearly proportional to flow at resting levels and at decreased flows to zero but at higher flow rates, particularly when the increased flow is secondary to coronary vasodilatation, the uptake is not linearly related to flow. Strauss has reported that the percent change in myocardial uptake of ^{201}Tl by tissue counting was 40 to 50% of the increase in coronary flow over resting values using microspheres (*6*) under circumstances of pronounced coronary vasodilatation. Similarly, Gould found that the maximal thallium uptake by tissue counting during peak coronary vasodilatation after dipyridamole was only 50 to 60% higher than control levels (*7*). Thus, while thallium uptake is increased as coronary blood flow increases, this relationship is not linear and cannot be used as an absolute quantitative index of flow changes. Studies in dogs have shown that a flow differential between a normal and stenotic coronary artery of ~2 to 1 is required before a definite defect is noted in the thallium image (*7*). Thus, the diagnostic technique that utilizes the maximal stimulus for coronary blood flow and a myocardial imaging agent that is linearly related to flow should be the most sensitive indicator of a significant coronary artery stenosis. This has important implications when exercise is the stimulus for increasing coronary blood flow. The development of angina pectoris during exercise may limit exercise at a sufficiently low level that coronary blood flow to normal myocardium does not increase enough to produce a regional perfusion defect by thallium imaging.

DOES DIPYRIDAMOLE CAUSE MYOCARDIAL ISCHEMIA?

Myocardial ischemia results when there is an imbalance between myocardial oxygen supply and demand. Under these circumstances, the difference in perfusion between normal and ischemic zones is probably sufficient to provide the 2:1 signal required for lesion detection on a thallium scan. The mechanism for the production of a perfusion defect with dipyridamole vasodilatation is less clear. Angina and electrocardiographic evidence of myocardial ischemia occur less frequently with dipyridamole coronary vasodilatation than with exercise stress. The explanation for angina during coronary vasodilatation is that coronary vasodilatation in the presence of a coronary stenosis results in an increase in the pressure gradient across the stenosis and a decrease in the distal coronary perfusion pressure. With decreasing distal pressure, the already maximally dilated resistant vessels cannot further dilate to increase local perfusion. Despite an increase in epicardial flow the subendocardium becomes under perfused. This has been referred to as a "subendocardial steal" phenomena where blood is shunted away from the subendocardium by dilated epicardial vessels. Whether a thallium defect after the administration of dipyridamole without chest pain or electrocardiographic changes represents a relative perfusion defect without overt ischemia remains unclear, but seems likely. This can be inferred considering that the majority of patients with perfusion defects do not develop clinical or electrocardiographic evidence of ischemia. In this case a perfusion defect is not necessarily equivalent with myocardial ischemia which now begs for a functional definition such as a wall motion abnormality.

IMAGING CHARACTERISTICS

Myocardial uptake of ^{201}Tl is greater with dipyridamole than exercise stress in cardiac regions in normal volunteers (unpublished results). There is no significant difference in lung uptake. Clearance rates from myocardial segments and lung do not differ. There is significantly greater initial uptake of thallium by the liver, spleen, and splanchnic regions with dipyridamole as compared with exercise. There is clearance of this activity with time with dipyridamole but an increase in activity with time with exercise.

DIPYRIDAMOLE ADMINISTRATION

The standard regimen for the administration of the oral and intravenous forms of dipyridamole are shown in Table 1. Injection in the upright or standing position or with isometric handgrip may increase myocardial uptake (*9*). There is a mildly reduced systemic blood pressure, increased heart rate and cardiac output and an increase in coronary blood flow up to five times resting values. Thallium should be injected at peak increase of coronary blood flow. Peak coronary blood flow was reported by Brown to occur 1 to 2 min after the 4-min drug infusion and then disappears exponentially with a half-life of 33 min (*9*). It has been noted that the difference in regional coronary flow and resistance responses may persist for 15 min after an i.v. bolus dose and that the coronary hemodynamic changes were not apparent after 20 min (*10*). Using a small Doppler catheter Wilson found the time and dose response characteristics to dipyridamole infusion heterogeneous but the mean time from onset of infusion to peak flow

TABLE 2
Adverse Effects for Both Intravenous and Oral Forms are Similar and Occur in 30 to 40% of Patients, and are Usually Mild and Short-Lived (*11*)*

Adverse effects	
Noncardiac	
Nausea	20%
Headache	13%
Dizziness	10%
Facial flush	8%
Vomiting	6%
Cardiac	
Angina	25%
ST depression	14%
Ventricular arrhythmia	2%

* Symptoms of angina pectoris can be alleviated by the intravenous injection of aminophylline.

velocity was a 6.5 min (2.5 min after a 4-min infusion) (*5*). They also found that the conventional dose of dipyridamole did not produce maximal vasodilatation in all patients. Dipyridamole may also be given orally with similar effects as the intravenous form (*11*, *12*). Thallium-201 is administered intravenously 45 min following ingestion or with the occurence of angina if it should occur before this time.

Adverse effects are listed in Table 2. Symptoms of angina pectoris can be alleviated by the intravenous injection of aminophylline, a direct antagonist to the effects of dipyridamole on the coronary vasculature (*13*). If a large dose of aminophylline (~200 mg) does not relieve the patients symptoms within several minutes, nitroglycerine can be administered, relieving angina by its direct effect on coronary stenoses and through its reduction of preload. We routinely administer 75 mg of aminophylline following initial imaging because of the frequency of perfusion defects even in the absence of symptoms of myocardial ischemia. Even if these defects simply signify "regional perfusion inequalities" myocardial ischemia may result with increased activity and thus an increase in myocardial oxygen demand following the test.

CLINICAL STUDIES

The sensitivity and specificity of serial ^{201}Tl imaging after dipyridamole infusion is comparable with those reported for thallium exercise stress testing. The major advantages are that dipyridamole imaging can be performed in patients who are unable to undergo maximal exercise testing. The major disadvantage is the lack of additional information provided by the electrocardiographic response to exercise.

The clinical utility of this test is illustrated by two recent studies. The first evaluated the safety and usefulness of dipyridamole thallium scintigraphy in patients recovering from acute myocardial infarction (*14*). The presence of redistribution on the dipyridamole-thallium scan was the only significant predictor of death, reinfarction or readmission for unstable angina. The second involved the determination of cardiac risk by dipyridamole-thallium in patients prior to peripheral vascular surgery (*15*). In this study a postoperative ischemic event was predicted by the presence of thallium redistribution. These events could not have been predicted by any clinical factor. Also patients with a normal dipyridamole-thallium study or a persistent defect only, are at low risk for an ischemic event postoperatively. In this issue of the *Journal* (*16*) Gould et al. used high dose oral dipyridamole and found it comparable to maximum exercise stress in at least 75% of cases. Finally, the ability of dipyridamole-thallium imaging in patients with a negative submaximal exercise thallium test to uncover coronary artery disease is currently being investigated.

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