Teaching Editorial

Dipyridamole Thallium-201 Myocardial Scintigraphy

Thallium-201 (^{201}Tl) myocardial scintigraphy is a sensitive technique for detecting coronary artery disease. Standardized exercise testing is the most common method for inducing myocardial stress for ^{201}Tl imaging. Unfortunately, a significant number of patients are unable to undergo adequate treadmill or bicycle exercise. In these patients, pharmacologic *stress* with dipyridamole provides a safe, efficacious, and reliable alternative (*1-9*).

PHYSIOLOGIC BASIS OF THALLIUM-201 MYOCARDIAL PERFUSION IMAGING

Concentration of ionic ^{201}Tl into the myocardium is directly proportional to myocardial blood flow (*10-12*). Active transport of thallium into the cell is by the sodium potassium ATPase system. Eighty-eight percent of ^{201}Tl is extracted from the intravascular space in a single-pass through the coronary circulation. The resting myocardium receives ~ 4% of the cardiac output; therefore, 3.5% of the ^{201}Tl dose localizes in the myocardium. Following maximal exercise, a slight increase in coronary flow results in ~ 4.4% dose localization of ^{201}Tl (*10*).

Clearance of ^{201}Tl from the myocardium is complex. A state of equilibrium exists between the influx of ^{201}Tl from the systemic circulation into the myocardium and the influx or washout from the myocardium. The difference or net ^{201}Tl washout rate has a half-life of four hours (*12*). In general, the rate of thallium clearance or washout is relatively constant. Ischemic zones initially contain relatively low concentrations of thallium; thus, the gradient between intra- and extracellular environments is lower and the rate of thallium loss is accordingly slower. Exceptions to this rule occur when there is abnormal metabolism of glucose and insulin resulting in accelerated loss of thallium from both normal and ischemic zones (*10*).

Areas of decreased or absent thallium activity on stress images can "fill-in" with activity on delayed images. This is called redistribution. Redistribution is the basis by which ischemic coronary artery disease is detected.

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PHARMACOLOGY OF DIPYRIDAMOLE

Dipyridamole (2,6-bis-[diethanolamino]-4,8-diperidinopyrimido-[5,4,-d]-pyrimidine), commonly known as Persantine*, is available in both oral and intravenous forms. Use of the intravenous form currently requires an IND from the FDA. Hopefully, by 1989, the intravenous form will be commercially available.

Studies have shown equivalent serum concentrations of dipyridamole following a 300-mg oral dose or a standard 0.56-mg/kg intravenous infusion (*8*). The oral preprartion is usually supplied as tablets; however, wide variations of peak serum levels occur with the tablet form (*8*). An oral suspension should be prepared by pulverizing 300 mg of dipyridamole tablets and mixing them with 30 ml of corn extract and carbonated drink (*13*). This mixture provides a higher, earlier, and more uniform peak serum dipyridamole concentration than does the tablet form. Peak serum concentration time for oral dipyridamole in fasting patients range from 20-60 min (*5,8,14*). The peak absorption time in patients with late absorption, such as diabetics, may not be reached until after 120 min (*14*).

Dipyridamole is widely distributed throughout body tissues, with small amounts crossing the placenta. It is metabolized by the liver and excreted into the bile, principally as a monoglucuronide.

Coronary blood flow may increase up to five times the resting level following dipyridamole administration (*15*). This results in 8%-10% of the ^{201}Tl dose reaching the myocardial tissues, a significant increase over rest and maximal exercise thallium studies (*1,10*).

The adverse effects of dipyridamole may be classified as cardiac or noncardiac (*8*). By far, the most common cardiac side effect is angina, occuring in up to 25% of patients. ST segment depression due to myocardial ischemia and ventricular dysrhythmias occur in 15% and 2% of patients, respectively. Nausea and/or vomiting occur in 20%-30% of patients, while headaches and dizziness occur less frequently. Except for headache and nausea, adverse effects appear to be less severe with the oral form (*9*).

The induction of myocardial ischemia by dipyridamole is caused by the inhibition of adenosine deaminase in the blood, allowing the accumulation of adenosine, a potent vasodilator.

Adenosine acts predominantly on the small resistance vessels with little effect on vascular resistance in ischemic coronary zones where small vessels are already maximally dilated. This may cause ischemia by two mechanisms: an increase in myocardial oxygen consumption or the "coronary steal" phenomenon (*1,5,11,14*).

Increased myocardial oxygen consumption results from the small increase in heart rate of approximately seven beats per minute following dipyridamole administration (*8*). Because myocardial oxygen consumption is increased only slightly with dipyridamole, a more favorable explanation for dipyridamole-induced myocardial ischemia relates to the coronary steal phenomenon.

Increased flow through an arterial narrowing produces an increased pressure gradient across a stenosis with a drop in pressure distally. Reduction of arterial pressure distal to the stenosis also may occur due to lowered systemic arterial pressure induced by dipyridamole. The result is subendocardial hypoperfusion, even though epicardial coronary flow is actually increased. When pressure in the coronary artery falls below 30 mm Hg, endocardial flow approaches zero and frank ischemia occurs (*11*). In addition, dilation of vessels supplying zones of normal perfusion may steal flow from regions dependent on collateral circulation (*14*).

ORAL DIPYRIDAMOLE PROTOCOL

Patients should fast after midnight and avoid coffee, tea, carbonated soft drinks, and chocolate for 24 hr prior to the study. These compounds contain theophylline, a dipyridamole antagonist. In addition, patients requiring theophylline should discontinue their medication 24–36 hr prior to this study (*8*).

With the patient in the supine position, a 20-gauge cannula is placed in an upper extremity vein. Heart rate, blood pressure, and EKG are recorded every 10 min for 45–60 min following ingestion of a 300-mg dipyridamole suspension according to Taillefer's protocol (Fig. 1) (*9*). Forty-five to 60 min after dipyridamole administration, the patient is injected, in the upright position, with a 2–3-mCi bolus of ^{201}Tl followed by a 10-ml flush of normal saline. The patient should then ambulate several minutes in order to reduce the incidence of postural hypotension. A 10–15-min period between ^{201}Tl injection and initiation of imaging allows peak myocardial thallium uptake and maximum blood-pool clearance (*13*). Myocardial imaging is performed in the same manner as in exercise myocardial imaging, including four-hour delayed imaging. In the event of clinical signs or symptoms suggesting myocardial ischemia, aminophylline (50–200 mg) should be injected intravenously at a rate not exceeding 25 mg/min (*7-9,16*). This should be done after injecting ^{201}Tl. Some authors have advocated routine administration of aminophylline following initial imaging because of the unpredictable absorption of oral dipyridamole and frequency of perfusion defects even in the absence of symptoms of myocardial ischemia (*9,16*).

DIPYRIDAMOLE INFUSION PROTOCOL

Instructions to the patient, attentive medical supervision, and baseline monitoring should be identical to those described for oral dipyridamole. Lead II of the EKG should be monitored continuously. A 20-gauge cannula is placed in an upper extremity vein. Dipyridamole is intravenously infused at a rate of 0.142 mg/kg per min for 4 min, with vital signs and EKG recorded every minute, according to Taillefer's protocol (Fig. 2) (*9*). Following dipyridamole infusion, ^{201}Tl injection and image acquisition are performed in the same manner as with oral dipyridamole and exercise thallium scintigraphy.

CLINICAL APPLICATION

Numerous studies have shown dipyridamole ^{201}Tl images (oral and intravenous) have the same sensitivity and specificity for coronary disease as exercise thallium scans (*3,5,9*). A review of the literature reveals a broad range in sensitivity and specificity from 67% to 100% for standard planar dipyridamole studies (*3,4,14*). Applying single-photon emission computed tomography (SPECT) imaging increases the sensitivity and diagnostic accuracy (*17*).

Dipyridamole thallium scintigraphy's primary use is in those patients with pulmonary, musculoskeletal, vascular, neurological, or motivational limitations that prevent standard exercise thallium scans (*5,6*). Patients with significant dysrhythmias may tolerate dipyridamole stress testing better than exercise treadmill testing (*5*).

Another group of patients who can benefit from dipyridamole are those on beta-blockers. These patients often fail to achieve maximal stress with standard exercise treadmill

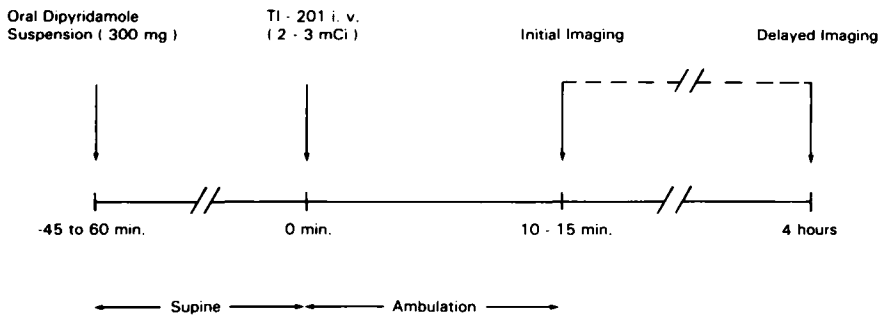

FIG. 1. Oral dipyridamole protocol,* adapted from Taillefer and Gill (*9, 16*). EKG, HR, and BP is monitored every 10 min for 45–60 min, and longer if necessary.
[*Thallium-201 is administered earlier if patient experiences signs or symptoms of ischemia.]

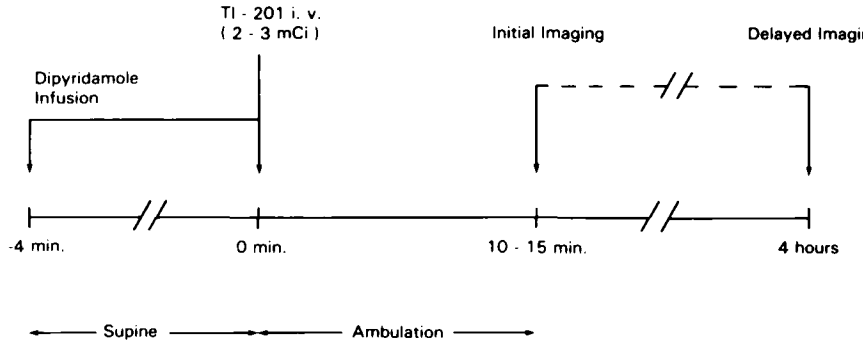

FIG. 2. Dipyridamole infusion protocol,* adapted from Taillefer and Gill (*9, 16*). EKG, HR, and BP monitored every minute (or longer if necessary) until initial imaging starts. [*Thallium-201 is admininstered earlier if the patient experiences signs or symptoms of ischemia.]

testing. Since dipyridamole produces myocardial stress relatively independent of changes in heart rate, the ability to achieve maximum stress with dipyridamole is unaffected by the chronotropic effects of beta-blockade.

Dipyridamole is the method of choice in patients who have undergone a submaximal exercise thallium test because the sensitivity of detecting myocardial ischemia is significantly reduced when patients fail to reach a maximum stress level (*10*). At our institution, a maximal exercise stress study is defined as achievement of 85% of the age-predicted maximal heart rate for the patient [maximal heart rate (100%) = 220 − age]. Occurrence of angina, EKG changes, or hemodynamic instability such as a 10% decrease in systolic blood pressure are also criteria for a maximal stress study. A significant number of our patients, approximately a third of those who undergo exercise thallium imaging, fail to achieve adequate stress.

Leppo et al. (*18*) found dipyridamole thallium imaging to be the most sensitive predictor of a future serious cardiac event (myocardial infarction, death) in pre-operative vascular surgery patients. Table 1 lists the pre-operative factors for myocardial infarction or death after vascular surgery in the 89 patients studied. In the entire group, the presence of thallium redistribution was the best predictor for a significant cardiac event. Only the presence of ST segment depression during dipyridamole infusion and a history of diabetes had prognostic value in addition to thallium redistribution. The relative risk predicted for a subsequent post-operative cardiac event in the patients with thallium redistribution was 23 times greater than in patients without redistribution. The presence of diabetes or ST segment depression with dipyridamole redistribution increased the risk about thirty-fold. Leppo's results indicate dipyridamole thallium scintigraphy is superior to standardized exercise treadmill testing in the cardiac risk assessment of pre-operative vascular surgery patients who may not be able to achieve maximal exercise. In another study comparing submaximal exercise treadmill testing to dipyridamole thallium scintigraphy in patients who recently suffered a myocardial infarction, Leppo again demonstrated dipyridamole thallium scintigraphy to be a more sensitive predictor of a serious future cardiac event (*7*).

TABLE 1. Clinical Characteristics of Preoperative Peripheral Vascular Surgery Patients by Leppo*

Mean age	Diabetes
Sex	Hypertension
History of CAD	History of COPD
Angina	Abdominal surgery
History of MI	Digoxin
EKG Q wave	Diuretics
History of CHF	Beta-blocker
History of CABG	Calcium channel blocker
Claudication	Antiarrhythmic agent
	Nitroglycerin

*See Ref. *18*.
CABG = coronary artery bypass surgery.
CAD = coronary artery disease.
CHF = congestive heart failure.
COPD = chronic obstructive pulmonary disease.
EKG = electrocardiogram.

The quality of ^{201}Tl images is a reflection of the myocardial-to-background activity ratio. Improved myocardial-to-background ratios are achieved both with exercise and dipyridamole, although through different mechanisms (*3*). Following exercise, the decrease in background activity is disproportionately larger than the decrease in myocardial activity, thereby increasing the myocardial-to-background ratio. Following dipyridamole administration, background activity remains constant while myocardial activity increases due to a dramatic increase in coronary flow. The result is a myocardial-to-background ratio significantly higher than that seen in exercise thallium images (*3*). The following case illustrates the clinical utility of improved image quality with dipyridamole compared to exercise thallium images following submaximal stress.

A 31-yr-old white male, recently status-post cadaveric renal transplant, developed dyspnea on exertion. Stress radionuclide ventriculography demonstrated a dilated cardiomyopathy with a left ventricular ejection fraction of 28% at rest and 32% at peak submaximal exercise stress. Exercise stress ^{201}Tl myocardial scintigraphy was performed. Failure to achieve an adequate heart rate because of exertional dyspnea resulted in a submaximal stress study. Visual interpretation was complicated by decreased thallium myocardial activity on stress images, causing apparent redistribution in the anteroapical region on delayed images (Fig. 3).

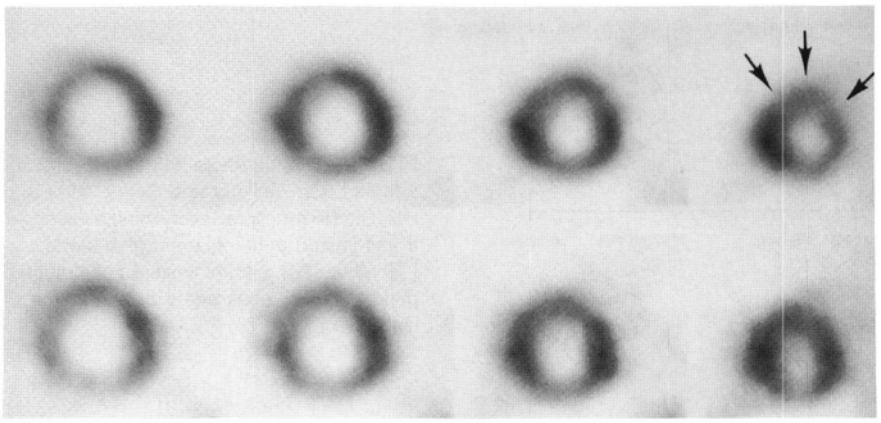

FIG. 3. Short-axis slices of the heart following SPECT exercise ^{201}Tl imaging. Immediate (top row) and 4-hr delayed (bottom row) images are reconstructed transaxial slices from the base of the heart to the apex (left to right). Arrows depict region of decreased thallium myocardial activity on stress image with apparent redistribution in the anteroapical region on delayed image.

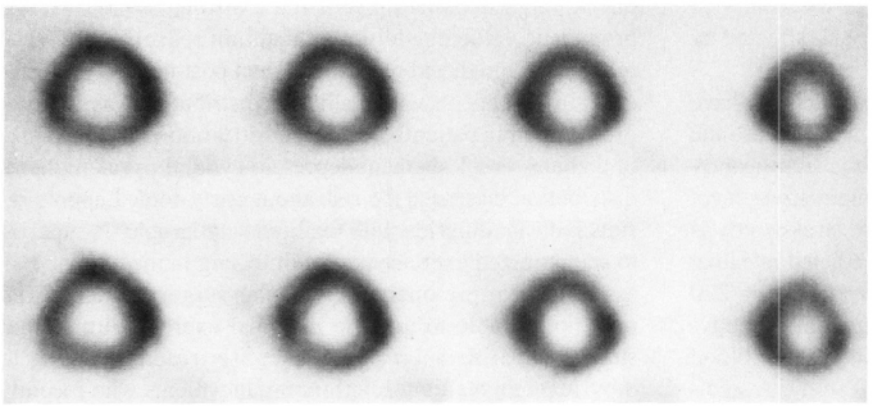

FIG. 4. Short-axis slices of the heart following SPECT dipyridamole ^{201}Tl imaging. Immediate (top row) and 4-hr delayed images (bottom row), demonstrating normal distribution of thallium.

A dipyridamole thallium scan was subsequently performed because of low confidence in the submaximal exercise thallium study (Fig. 4). The area of suspicion showed normal uptake of thallium, and the patient was diagnosed as having a nonischemic cardiomyopathy; this was confirmed by coronary arteriography.

Quantitative analysis of the above case example reveals a doubling of the myocardial counts with dipyridamole in both stress (immediate) and redistribution (delayed) images, in comparison to exercise images. On the stress images, the myocardial-to-background activity ratios (mean myocardial pixel counts/background activity) for exercise and dipyridamole are 7.2 and 16.4, respectively. The myocardial-to-background count ratios in the delayed images for exercise and dipyridamole are 3.4 and 8.6, respectively. Decreased activity of the anteroapical myocardium noted on exercise thallium images appears to be an artifact caused by low counting statistics.

DISADVANTAGES

There are several disadvantages with dipyridamole thallium imaging. First, the oral dipyridamole study requires longer medical supervision. This should not be a problem when intravenous dipyridamole becomes commercially available. Second, dipyridamole thallium imaging cannot be performed on theophylline-dependent patients. The most significant disadvantage of dipyridamole is the decreased sensitivity of EKG information obtained without exercise. The usefulness, however, of EKG information is related to the pre-test probability or prevalence of coronary artery disease in the patient population. Furthermore, any increased sensitivity gained by additional EKG information may be offset by a decrease in specificity. This is due to the large number of false-positive stress EKGs (*3*).

SUMMARY

Dipyridamole is a powerful coronary vasodilator that offers a safe, effective, and reliable alternative in those patients who are unable to achieve maximal stress with standard exercise thallium testing. It significantly increases thallium myocardial uptake in comparison to exercise resulting in improved image quality and visual interpretation. Close medical supervision and adherence to established protocols for dipyridamole administration are important.

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NOTE

*Boehringer-Ingelheim, Ltd, Ridgefield, Connecticut.

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