

Dipyridamole Myocardial Perfusion Imaging

Jeffrey A. Leppo

Myocardial Isotope Research Lab, Departments of Nuclear Medicine and Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts

Dipyridamole is a pharmacologic stressor used in place of exercise for myocardial perfusion imaging in patients who cannot exercise due to various physical limitations. Perfusion studies with dipyridamole can identify coronary artery disease (CAD) as accurately as maximal exercise stress testing. In addition, dipyridamole myocardial perfusion studies are useful to stratify patients according to risk of subsequent cardiac events. As dipyridamole is infused, it blocks the reabsorption and metabolism of adenosine normally produced in the body, producing the desired effect on the heart, coronary hyperemia. Dipyridamole can be used with ^{201}Tl and $^{99\text{m}}\text{Tc}$ myocardial perfusion tracers, for either planar or SPECT imaging, in patients who cannot exercise or who can only exercise at submaximal levels.

Key Words: dipyridamole; myocardial perfusion imaging

J Nucl Med 1994; 35:730-733

The principle underlying myocardial perfusion imaging is to effect maximum exertion on the heart to attain maximum coronary blood flow. The purpose of stressing the heart is to create a disparity in blood flow between normal and stenosed arteries. This stress can result from increased oxygen demand in response to exercise, or by vasodilatory effects of a pharmacologic stress agent, such as dipyridamole. Pharmacologic stressors are useful for patients who cannot exercise for various reasons, including physical limitations, medications, lung disease, peripheral vascular disease, motivational conditioning and aortic aneurysms.

Pharmacologic or physiologic stress is needed to detect coronary artery disease (CAD) when using myocardial perfusion imaging because, even in the presence of high-grade stenoses, resting blood flow is typically normal since distal arterial resistance is reduced to allow for a normal perfusion pattern. With dipyridamole infusion, myocardial regions supplied by normal or near-normal arteries will experience increasing blood flow due to decreased coronary vascular resistance. In contrast, myocardium sup-

plied by stenosed vessels may have only a minimum reserve capacity to dilate and will therefore be unable to increase blood flow at the same rate seen in more normal territories. An actual coronary steal can occur if the area distal to a severe stenosis is dependent on collateral flow for normal resting blood flow supply. With a pharmacologic stressor, the collateral flow may be significantly reduced, resulting in an absolute decrease in nutrient blood flow and subsequent production of acute myocardial ischemia. However, the production of true ischemia is not necessary in order to produce a disparity in regional blood flow that can be detected by myocardial perfusion imaging.

PROTOCOL

Dipyridamole is administered in a bolus infusion with an optimal total dose of 0.56 mg/kg over a period of 4 min. During the 3 to 5 min between cessation of dipyridamole infusion and the resultant stress on the heart, interventions can be requested of the patient, such as low-level hand-grip exercises, and walking or sitting in place. These interventions stimulate catecholamines, which reduces some splanchnic blood flow. This is important to consider when using $^{99\text{m}}\text{Tc}$ -labeled compounds because they have more uptake in the splanchnic bed than ^{201}Tl . Ancillary exercise also produces a higher quality image, but does not result in higher sensitivity to detect CAD. The radiotracer is injected 7 to 9 min after dipyridamole infusion. The time from injection to image acquisition is the same with dipyridamole as with exercise myocardial perfusion studies.

Aminophylline is recommended to counteract any adverse reaction to dipyridamole infusion. Routine use of this agent is still somewhat controversial, but may be appropriate in situations where the physician is not continuously available to monitor the occurrence of side effects for 10 to 20 min after the infusion has been terminated. The patient should be supine and all vital signs should be monitored during dipyridamole infusion. All methylxanthine medications and caffeine consumption should be discontinued before a dipyridamole perfusion study.

MECHANISM

As dipyridamole is infused, it blocks the reabsorption and metabolism of adenosine normally produced in the body. At basal conditions, normal adenosine levels are relatively low. The biologic half-life of natural adenosine, normally 15 to 30 sec in the bloodstream, increases with dipyridamole infusion, tripling or quadrupling the level of circulating adenosine. The increased level of natural adenosine actually produces the desired effect on the heart, i.e.,

Received Dec. 9, 1993; revision accepted Dec. 24, 1993.

This paper was presented in part at the Annual Meeting of the Society of Nuclear Medicine on June 9, 1993, as part of a Continuing Medical Education Seminar organized by the Cardiovascular Council.

For correspondence or reprints contact: Jeffrey A. Leppo, MD, Department of Nuclear Medicine, UMass Medical Center, 55 Lake Avenue North, Worcester, MA 01655.

TABLE 1
Reported Results of Exercise and Dipyridamole-Thallium Scans for Detection of CAD*

Year	Patients (no.)	Exercise- ²⁰¹ Tl			Dipyridamole- ²⁰¹ Tl			Investigators (Location)
		Sensitivity	Specificity	Angina	Sensitivity	Specificity	Angina	
1978	62	34/51 (67%)	10/11 (91%)	41/62 (66%)	34/51 (67%)	10/11 (91%)	25/62 (40%)	Albro et al. (14) (Seattle, WA)
1980	20	18/20 (90%)	N/A	N/A	17/20 (85%)	N/A	4/20 (20%)	Timmis et al. (15) (Brighton, U.K.)
1981	50	25/35 (71%)	15/15 (100%)	29/50 (58%)	24/35 (69%)	15/15 (100%)	13/50 (26%)	Narita et al. (16) (Osaka, Japan)
1981	68	54/60 (90%)	8/10 (80%)	42/68 (62%)	52/58 (90%)	9/10 (90%)	20/68 (29%)	Machecourt et al. (17) (Grenoble, France)
1982	15	10/12 (83%)	3/3 (100%)	10/15 (67%)	12/12 (100%)	3/3 (100%)	5/15 (33%)	Wilde et al. (18) (Bristol, U.K.)
Totals	215	141/178 (79%)	36/39 (92%)	122/195 (63%)	139/176 (79%)	37/39 (95%)	67/215 (31%)	

*CAD = 50% stenosis, except for Machecourt et al. study (1981), in which CAD = 70% stenosis.
N/A = not available.

coronary hyperemia (1). Overall, heart rate increases 20% to 40%, depending on whether the patient walks or performs other ancillary exercises. Blood pressure and diastolic blood pressure drop slightly (2,3).

Clinical Considerations

Myocardial and splanchnic radiotracer uptake is greater with dipyridamole than with exercise, and blood clearance is slower. The splanchnic uptake re-enters the circulation and reduces the washout rate from normal myocardium.

Patients on effective antianginal therapy, such as beta-blockers and calcium-channel blockers, will still have a positive myocardial perfusion image with dipyridamole, despite adequate therapy. Although the scan will be positive, prognosis may be better in these patients compared with patients not treated with antianginal medication.

SAFETY AND ADVERSE EFFECTS

The database for dipyridamole perfusion studies now totals 46,000 patients; the death rate is approximately the same as for exercise stress testing, even when patients are administered a 50% increase in the recommended dose of dipyridamole (4).

Although the risk of dipyridamole is comparable to that of exercise, there are precautions to consider during dipyridamole infusion in patients with unstable angina or recent myocardial infarction (MI). Elevated adenosine levels, triggered by dipyridamole infusion, can provoke bronchospasm. Patients with recent respiratory failure, severe chronic obstructive pulmonary disease (COPD) or acute asthma should not undergo a dipyridamole stress test. If an outpatient with a history of lung disease, COPD or asthma is not using a bronchodilator and is not wheezing before the perfusion study, it is safe to use dipyridamole. However, if this patient complains of shortness of breath or begins to wheeze, the dipyridamole infusion must be halted immedi-

ately and intravenous aminophylline should be administered quickly.

Caffeine consumption prior to the perfusion study can blunt the hemodynamic response to dipyridamole. For patients who forget to discontinue coffee before their tests, the dose of dipyridamole may be increased, or dobutamine may be used in place of dipyridamole. A note of caution: a minimal hemodynamic response does not necessarily indicate absence of hyperemia. Some patients, particularly those with diabetes or vascular disease who have autonomic dysfunction, do not exhibit hemodynamic responses to stress testing.

The major contraindication is allergy to dipyridamole or aminophylline, which is not very common (1 in 10,000) (3).

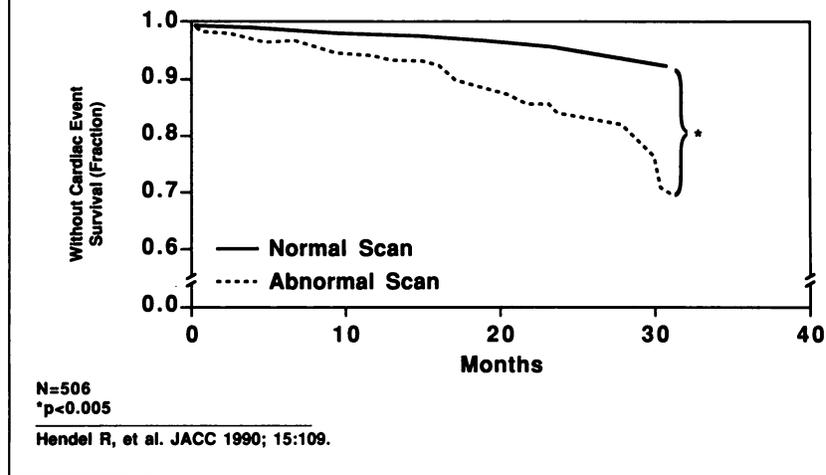
EFFICACY

In one of the early dipyridamole perfusion imaging studies, patients who had undergone negative ²⁰¹Tl studies after submaximal exercise stress testing returned for a repeat study with dipyridamole substituted for exercise (5). Submaximal was defined as <70% of predicted heart rate. The dipyridamole perfusion studies demonstrated ischemia not detected by submaximal exercise studies in about 25% of patients.

In the clinical setting, when a patient is referred to rule out CAD, it is not cost-effective to perform a submaximal exercise stress test for 3 min, which typically results in low heart rate, no symptoms, a normal electrocardiogram (ECG) and a homogenous myocardial perfusion scan, because such a patient will often be referred again for another myocardial perfusion study with a pharmacologic stress agent. Even when patients seem as if they might achieve an adequate level of exercise, dipyridamole infusion can prevent false-negative results and help ensure a diagnostic test.

Life Table Analysis of I.V. Dipyridamole Thallium-201 Imaging

FIGURE 1. Life table analysis comparing the event-free survival of 172 patients with normal dipyridamole-thallium scans (solid line) with that of 332 patients with abnormal scans (dashed line). Cardiac death or MI occurred more frequently in patients with abnormal dipyridamole-thallium scintigrams ($p < 0.005$). Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1990; 15:109).



A review of the literature (Table 1) offers results from hundreds of patients who underwent exercise ^{201}Tl perfusion imaging, dipyridamole-thallium imaging and coronary angiography (3). These data show that myocardial perfusion studies were predictive of catheterization findings, independent of whether exercise or dipyridamole studies were performed. The significant difference was the increased presence of angina in patients who exercised. Does this conclusion indicate that every patient had the same result on both the exercise and dipyridamole studies? No. The concordance is about 80%. The concordance rate, however, for repeat exercise stress testing in the same patient is about 80% to 85%, without changing technique.

For the majority of patients who can exercise, perfusion studies with dipyridamole will provide the same results. For patients who cannot exercise, perfusion studies with a pharmacologic stressor will provide better results than submaximal exercise. Pharmacologic coronary vasodilation with dipyridamole is also used in conjunction with PET tracers for detection and evaluation of CAD, as discussed elsewhere in this section by Schwaiger (see pages 693–698).

When dipyridamole was first used for myocardial perfusion imaging, nuclear cardiologists questioned whether it would provide the same prognostic value as exercise stress testing. Of the first 500 patients studied at the University of Massachusetts, a normal dipyridamole perfusion scan was predictive of a 95% survival rate over a mean 2-yr follow-up, compared with 85% for an abnormal scan (Fig. 1). When risk of subsequent cardiac events is assessed by the number and severity of perfusion defects, patients can be stratified into low-, moderate-, and high-risk categories (6).

The patient population studied most extensively with dipyridamole perfusion imaging is the group at risk for perioperative cardiac events (7–12). All patients referred to our institution for surgery are screened for vascular disease. The presence of redistribution or transient defects on myocardial perfusion images is the most powerful predictor of these events. Other factors that influence this risk assessment include diabetes, prior MI, angina and Q-waves on ECG. Patients with no clinical or ECG risk factors are at low risk; patients with one or two risk factors can be risk-stratified on the basis of dipyridamole myocardial perfusion images.

A clinical trial in Japan evaluated the use of dipyridamole-thallium imaging in patients with idiopathic cardiomyopathy (13). Transient perfusion defects are more common in CAD patients than in patients with idiopathic dilated cardiomyopathy; however, multiple small defects are more common in idiopathic cardiomyopathy than in patients with an ischemic cause of disease. Because CAD patients can benefit from antianginal therapy or revascularization, this differential diagnosis is of value.

CONCLUSION

Dipyridamole myocardial perfusion imaging can identify CAD as accurately as maximal exercise stress testing. In addition, dipyridamole perfusion studies are useful to stratify patients according to risk of subsequent cardiac events. Dipyridamole can be used with ^{201}Tl and $^{99\text{m}}\text{Tc}$ myocardial perfusion tracers, for either planar or SPECT imaging, in patients who cannot exercise or who can only exercise at submaximal levels.

ACKNOWLEDGMENTS

Supported in part by U.S. Public Health Service grant HL34199 of the National Heart, Lung and Blood Institute, Bethesda, MD.

REFERENCES

1. Sollevi A, Ostergren J, Fagrell B, Hjemdahl P. Theophylline antagonizes cardiovascular responses to dipyridamole in man without affecting increases in plasma adenosine. *Acta Physiol Scand* 1984;121:165-171.
2. Iskandrian AS, Heo J, Askenase A, Segal BL. Dipyridamole cardiac imaging. *Am Heart J* 1988;115:432-443.
3. Leppo JA. Dipyridamole-thallium imaging: the lazy man's stress test. *J Nucl Med* 1989;30:281-287.
4. Lette J. Safety of dipyridamole testing: preliminary results in 43,000 patients [Abstract]. *J Am Coll Cardiol* 1993;21:207A.
5. Young DZ, Guiney TE, McKusick KA, et al. Unmasking potential myocardial ischemia with dipyridamole thallium imaging in patients with normal submaximal exercise thallium tests. *Am J Noninvas Cardiol* 1987;1:11-14.
6. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. *J Am Coll Cardiol* 1990;15:109-116.
7. Lane SE, Lewis SM, Pippin JJ, et al. Predictive value of quantitative dipyridamole-thallium scintigraphy in assessing cardiovascular risk after vascular surgery in diabetes mellitus. *Am J Cardiol* 1989;67:1275-1279.
8. Eagle KA, Singer DE, Brewster DC, et al. Dipyridamole-thallium scanning in patients undergoing vascular surgery: optimizing preoperative evaluation of cardiac risk. *JAMA* 1987;257:2185-2189.
9. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989;110:859-866.
10. Boucher CA, Brewster DC, Darling C, et al. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985;312:389-394.
11. Cutler BS. Interpretation and results of intravenous dipyridamole thallium scintigraphy. *Semin Vasc Surg* 1991;4:83-89.
12. Lette J, Waters D, Lassonde J, et al. Multivariate clinical models and quantitative dipyridamole-thallium imaging to predict cardiac morbidity and death after vascular reconstruction. *J Vasc Surg* 1991;14:160-169.
13. Chikamori T, Doi YL, Yonezawa Y, et al. Value of dipyridamole thallium-201 imaging in noninvasive differentiation of idiopathic dilated cardiomyopathy from coronary artery disease with left ventricular dysfunction. *Am J Cardiol* 1992;69:650-653.
14. Albro PC, Gould KL, Westcott RJ, et al. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. III. Clinical trial. *Am J Cardiol* 1978;42:751-760.
15. Timmis AD, Lutkin JE, Fenney LF, et al. Comparison of dipyridamole and treadmill exercise for enhancing thallium-201 perfusion defects in patients with coronary artery disease. *Eur Heart J* 1980;1:275-280.
16. Narita M, Kurihara T, Usami M. Noninvasive detection of coronary artery disease by myocardial imaging with thallium-201: the significance of pharmacologic interventions. *Jpn Circ J* 1981;45:127-140.
17. Machecourt J, Denis B, Wolf JE, et al. Sensibilite et specificite respective de la scintigraphie myocardique realisee apres injection de thallium-201 au cours de l'effort, apres injection de dipyridamole et au repos: comparaison chez 70 sujets coronarographies. *Arch Mal Coeur* 1981;74:147-156.
18. Wilde P, Walter P, Watt I, Rees JR, Davies ER. Thallium myocardial imaging: recent experience using a coronary vasodilator. *Clin Radiol* 1982;33:43-50.