

Editorial Comment

Dipyridamole Thallium-201 Scintigraphy: An Excellent Alternative to Exercise Scintigraphy*

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Intravenous infusion of dipyridamole is an acceptable alternative to physical exercise for myocardial imaging with thallium-201. The coronary dilating effect of dipyridamole results in a substantial increase in regional blood flow to areas perfused by normal coronary vessels, but abnormal flow reserve is observed in areas supplied by stenotic vessels (1). This inhomogeneity of flow is detected by abnormal thallium uptake when the radionuclide is injected during the peak vasodilative effect of the drug. Redistribution occurs in areas of viable, but hypoperfused, myocardial regions, comparable to what is observed with exercise scintigraphy. Reported studies (2-6) have demonstrated that the sensitivity and specificity of dipyridamole thallium imaging for detecting coronary artery disease are in the range of 80% to 90%. In studies (3,7) in which the results of dipyridamole and exercise scintigraphy were compared in the same patients, sensitivity and specificity values were not significantly different. As with exercise imaging, computer-assisted quantitative approaches to assessment of thallium uptake and subsequent washout have been shown to improve sensitivity and specificity (5). Oral administration of 300 to 400 mg of dipyridamole has been shown to yield scintigraphic results comparable to those of intravenous dipyridamole infusion (8), although side effects are greater.

Detection of coronary artery disease. Because sensitivity and specificity values for detecting coronary artery disease with dipyridamole thallium scintigraphy are comparable to values obtained with exercise scintigraphy, the pharmacologic "stress test" should be strongly considered in patients who are deemed unable to exercise because of such noncardiac abnormalities as peripheral vascular disease, arthritis,

previous stroke and orthopedic problems. Similarly, dipyridamole scintigraphy should be considered in individuals who are strongly suspected to have underlying coronary artery disease despite a normal exercise myocardial perfusion scan at suboptimal heart rate responses. Some patients have poor motivation to exercise or are significantly deconditioned and, thus, may not reach a double (rate-pressure) product sufficient to yield a diagnostic test.

Casale et al. (9) have recommended combining a low level treadmill exercise with intravenous dipyridamole thallium-201 imaging whenever possible in order to achieve fewer noncardiac side effects, a higher heart to background ratio and a higher incidence of clinical electrocardiographic ischemia than with dipyridamole alone.

Prognostic value. Dipyridamole thallium-201 scintigraphy has been shown to provide useful prognostic information in patients with coronary artery disease, particularly those who are undergoing risk assessment prior to peripheral vascular or aortic surgery (10-13). Leppo et al. (10) reported that the presence of thallium redistribution on dipyridamole thallium scintigrams performed before hospital discharge in survivors of myocardial infarction was the most significant predictor of subsequent death, reinfarction or unstable angina. In that study the standard submaximal exercise test was a less sensitive predictor of cardiac events than was dipyridamole thallium imaging. Boucher et al. (11) first reported the application of dipyridamole thallium imaging for preoperative risk stratification in patients with peripheral vascular disease undergoing vascular surgery. They found that in patients with a prior history of angina or myocardial infarction, the presence of thallium redistribution on dipyridamole scintigrams preoperatively was superior to any other clinical variable in predicting perioperative cardiac death, infarction, unstable angina or ischemic pulmonary edema. In that study, 50% of patients with redistribution on preoperative dipyridamole thallium scintigrams had a perioperative cardiac event. The Massachusetts General Hospital group (12,13) subsequently confirmed these earlier results. However, they showed that because patients scheduled for vascular surgery who had no clinical variables of prior myocardial infarction, congestive heart failure, angina pectoris or diabetes mellitus had a low likelihood of a perioperative cardiac event, dipyridamole thallium imaging was not of great value in risk stratification in this group. These patients could already be considered as having a low risk on clinical criteria alone. In contrast, in patients who had one or more of these clinical markers, the presence of redistribution on preoperative dipyridamole thallium scans predicted an increased likelihood of a perioperative event. It has been estimated that dipyridamole thallium imaging will not provide added prognostic value in 50% of patients scheduled for vascular

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surgery because a very high or low cardiac event rate postoperatively can be predicted by knowledge of clinical information alone (13).

The present study. In the present issue of the Journal, Younis et al. (14) report on their evaluation of the prognostic utility of dipyridamole thallium-201 imaging in 107 asymptomatic patients, including 33 with a previous myocardial infarction and 47 with prior bypass surgery or angioplasty. In nearly one half of the patients, the indications for the dipyridamole thallium test were symptomatic peripheral vascular disease ($n = 28$) and preoperative clearance for major noncardiac surgery ($n = 26$). Fifty-one patients had poor exercise tolerance. Despite the heterogeneity of this patient cohort, the authors found that by stepwise logistic regression analysis, a reversible thallium defect was the only significant predictor of subsequent cardiac events in the 14 months of follow-up. Of the 13 asymptomatic patients who subsequently died or had a nonfatal infarction, 12 had a reversible dipyridamole thallium defect at the index imaging study. None of the 36 patients with a normal dipyridamole thallium scan died or had a nonfatal infarction. The majority of patients who died or had a subsequent nonfatal infarction had underlying multivessel coronary artery disease. These findings are remarkably similar to the findings of reported prognostic studies (15-18) utilizing exercise thallium-201 scintigraphy, as pointed out by the authors. These observations are also similar to those made in a previous study by Younis et al. (19) assessing the prognostic value of dipyridamole thallium scintigraphy in patients after either unstable angina or acute myocardial infarction. In that study, logistic regression analysis revealed that a reversible thallium defect and the extent of angiographic coronary artery disease were the only independent predictors of a cardiac event.

Side effects. Intravenous infusion of dipyridamole can induce severe asthma in patients with lung disease and a history of bronchospasm. A history of asthma is a relative contraindication to dipyridamole thallium imaging. Patients receiving methylxanthines (such as theophylline) will not be able to undergo the test because these drugs inhibit the vasodilatory effect of dipyridamole secondary to adenosine receptor antagonism (20). Minor side effects include headache, dizziness and nausea. Approximately 30% of patients will experience a fall in systolic pressure of 20 mm Hg or greater. Chest pain will be provoked in approximately 25% to 30% of patients, whereas ischemic ST segment depression is seen only in approximately 15% to 20% of individuals undergoing testing. There have been rare reports of myocardial infarction and even mortality in the 24 h following intravenous dipyridamole infusion. These catastrophic complications were observed chiefly in patients undergoing testing while still in the acute phase of unstable angina. The anginal chest pain and ischemic ST depression consequent to infusion of the vasodilator are most likely due to transmural coronary "steal" in the distribution of the stenotic vessel

(21). Intravenous aminophylline will promptly reverse all side effects resulting from dipyridamole administration.

Exercise or dipyridamole thallium scintigraphy for prognostication? The data reported by Younis et al. (14) and other investigators have clearly demonstrated that high- and low-risk subsets can be identified by dipyridamole thallium-201 imaging and yield comparable prognostic information, as reported for exercise thallium scintigraphy. Therefore, which test should one employ once dipyridamole thallium imaging is granted approval for clinical use by the Food and Drug Administration (FDA)? Exercise stress is probably the preferred choice in patients who are judged able to exercise without apparent physical limitations. This is because non-imaging variables contribute independent prognostic information for predicting subsequent cardiac events. In a study of Kaul et al. (17), these other independent variables included the change in heart rate from rest to peak exercise, occurrence of ST segment depression and occurrence of ventricular arrhythmias on exercise. Although the number of segments demonstrating thallium redistribution was the best noninvasive predictor of future cardiac events, these other variables provided independent predictive information. Similarly, the workload achieved and the blood pressure response to exercise have been reported to be important prognostic variables. Thus, one might expect to be able to identify more high-risk patients employing exercise as a stress compared with dipyridamole infusion in which only scintigraphic prognostic variables are identified.

Conclusions. There is no doubt that dipyridamole thallium-201 scintigraphy will play a clinically useful role in the noninvasive detection of coronary artery disease, determining its functional severity (extent and degree of hypoperfusion) and aid in identifying high- and low-risk subgroups. The precise clinical indications for the test as a substitute for exercise stress have not been definitively ascertained, although patients with symptomatic peripheral vascular disease with diabetes or clinical risk factors for cardiac disease should be prime candidates for dipyridamole thallium imaging for preoperative risk stratification. The test is relatively safe when cognizant of the contraindications, and side effects can be reversed promptly with aminophylline administration. At this writing, the FDA still has not approved dipyridamole thallium scintigraphy for clinical practice, although approval is anticipated in the very near future.

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