Editorial Comment

Dipyridamole Thallium 201 Imaging
How Safe Is It?

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Dipyridamole thallium 201 scintigraphy is increasingly being used as an alternative to exercise scintigraphy for detection of coronary artery disease and risk stratification. Intravenous infusion of 0.56 mg/kg dipyridamole, the average dose used in clinical studies, causes a significant increase in myocardial blood flow in zones perfused by normal coronary arteries but only a slight increase in zones perfused by stenotic vessels. Furthermore, experimental studies have shown that the regional flow alterations distal to a coronary stenosis after intravenous or intracoronary dipyridamole infusion are similar to those produced by intracoronary infusion of adenosine. Blood is redistributed from the endocardial to the epicardial layers; this redistribution is referred to as intramural or transmural coronary "steal" and is characteristically associated with a fall in distal coronary perfusion pressure. These flow responses are not surprising, because dipyridamole acts by blocking the uptake of adenosine in red blood cells and endothelium, thereby increasing plasma levels and potentiating the activity of the endogenous vasodilator. Systemic hemodynamic effects of intravenously administered dipyridamole include a fall in arterial blood pressure associated with a reflex increase in heart rate.

The inhomogeneity of regional myocardial blood flow produced when dipyridamole is administered in the setting of coronary obstructive disease can be imaged after intravenous injection of $^{201}$TI during peak vasodilation. As with exercise $^{201}$TI imaging, initial defects with delayed redistribution are detected in myocardial zones exhibiting abnormal coronary flow reserve. Persistent defects are noted in areas of irreversible myocardial cellular injury. Previous studies indicate that the sensitivity, specificity, and predictive accuracy of coronary artery disease detection with dipyridamole are comparable to values obtained with exercise stress testing. In a recent study from our laboratory, exercise stress testing and dipyridamole quantitative planar $^{201}$TI imaging performed several weeks apart in the same patients yielded a 97% concordance rate in detecting and localizing scan segments with normal or abnormal perfusion. Similarly, the prognostic information derived from dipyridamole $^{201}$TI scintigraphy in asymptomatic patients with suspected or known coronary artery disease and in patients experiencing a recent myocardial infarction is comparable to that derived from studies with exercise stress testing. Younis et al recently reported that by stepwise logistic regression analysis, $^{201}$TI redistribution was the only significant predictor of subsequent cardiac events in 107 asymptomatic patients undergoing dipyridamole $^{201}$TI scintigraphy. Based on the clinical investigations to date, dipyridamole infusion should be used as a substitute for exercise stress testing for myocardial perfusion imaging in patients who are unable to exercise adequately because of peripheral vascular disease, arthritis, neurologic deficits, and orthopedic abnormalities. Dipyridamole perfusion imaging will undoubtedly be used in patients with an intermediate or high-pretest likelihood of underlying coronary artery disease despite a normal exercise scintigram at suboptimal heart rate responses. This can occur because of poor motivation, deconditioning, or noncardiac-limiting factors to exercise or $\beta$-blocker drug usage that blunts the exercise heart rate response.

The question may be posed as to why, after more than 12 years of clinical experience with thousands of imaging studies in patients, has intravenous dipyridamole imaging not been formally approved for general application by the Food and Drug Administration (FDA). One might speculate that lack of approval by this regulatory agency has been a concern for the safety of the procedure. In this issue of Circulation, Ranhosky and Kemphorne-Rawson, from Boehringer Ingelheim Pharmaceuticals, report the safety data from 3,911 patients collected from 64 investigators, who underwent dipyridamole $^{201}$TI imaging from 1978 to 1985. All adverse events occurring within 24 hours after the administration of dipyridamole were recorded. As cited by the investigators, 10 patients (0.26%) had major adverse events.

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and 1,820 (46.5%) had minor side effects. Two patients (0.05%) died as a consequence of myocardial infarctions, and two (0.05%) had nonfatal infarctions. Six patients (0.15%) developed acute bronchospasm, which was reversed in all instances with intravenous aminophylline. Lesser side effects included chest pain (19.7%), headache (12.2%), dizziness (11.8%), electrocardiographic ST segment changes (7.5%), nausea (4.6%), and hypotension (4.6%). Of the 454 patients receiving aminophylline (an adenosine receptor antagonist) to treat side effects, 97% experienced complete relief of symptoms.

Interestingly, sublingual nitroglycerin, a vasodilator of large resistance vessels that does not produce a coronary steal effect, when used alone in 59 patients, reversed the side effects in 88%.11 The mechanism for relief of chest pain or ST segment depression with nitroglycerin may be an enhancement of collateral blood flow to the relatively underperfused endocardium produced by the endocardial-to-epicardial flow redistribution after dipyridamole infusion.

The four “hard events” described by Ranhosky and Kempthorne-Rowson from their registry deserve further comment. One of the two patients who had a fatal infarction and both patients who had a nonfatal infarction had unstable angina before dipyridamole 201TI imaging. We do not know whether these three patients had “stabilized” with remission or reduction of episodes of ischemic pain before dipyridamole infusion. Some possible mechanisms for infarction due to intravenous infusion of the vasodilator in a patient with unstable angina might be 1) a sudden fall in coronary perfusion pressure secondary to systemic hypotension in the setting of a critically stenotic lesion; 2) prolonged coronary steal with subendocardial hyperperfusion without adequate collateral flow; or 3) an enhanced tendency for thrombus formation due to further intimal injury that may result from increased turbulent flow across the stenotic lesion secondary to hyperemia. Unstable angina and myocardial infarction can also occur as a consequence of exercise stress testing. Ciampicotti and Gamali12 reported seven patients who developed unstable angina (n=2), acute myocardial infarction (n=4), or ventricular fibrillation (n=1) after an exercise stress test. Coronary angiography revealed eccentric stenoses or thrombosis in six. Data from earlier studies before the advent of exercise stress testing in patients with a higher risk of postinfarction or postunstable angina indicated a mortality rate of 0.5/10,000 and a nonfatal infarction rate of 3.58/10,000.13 It is quite possible that in the present era the complication rate of exercise stress testing and dipyridamole stress testing in patients with active unstable angina would be comparable.

Recent reports have indicated that in patients with stable chest pain syndromes, chronic ischemic heart disease, or recent infarction intravenous dipyridamole 201TI imaging is, indeed, quite safe. Homma et al14 reported no deaths or infarctions in 293 consecutive patients undergoing dipyridamole imaging. Of interest in that study, appearance of chest pain or ST segment depression after dipyridamole infusion was unrelated to the number of stenotic coronary vessels. Dipyridamole imaging also appears to be safe in more elderly patients. Lam et al15 found the side-effect profile comparable between 101 patients 70 years of age or more and 236 patients less than 70 years of age. Among the total group of 337 patients tested, there were no deaths or myocardial infarction. Similarly, Gerson et al16 reported a comparable side-effect rate between patients 65 years of age or more (33%) and patients less than 65 years of age (36%). Twenty-five patients older than 75 years of age underwent testing in that study. Again, even in these quite elderly patients, there were no deaths or infarctions.

Importantly, patients with a recent myocardial infarction can undergo intravenous dipyridamole imaging for prognostication without an increased risk. Pirelli et al,17 Gimple et al,18 and Bolognese et al19 reported a total of 164 patients undergoing intravenous dipyridamole stress testing within several weeks of the onset of an acute infarction. No major adverse cardiac events occurred as a result of the procedure. Bolognese et al19 actually administered a high dose of dipyridamole (0.84 mg/kg).

As described in the present study by Ranhosky and Kempthorne-Rowson, the incidence of chest pain is significantly higher than the incidence of ST segment depression after dipyridamole infusion. This is an interesting observation also made by others, and it suggests that some instances of chest pain after dipyridamole infusion is not secondary to ischemia from epicardial coronary artery disease. Laaman et al20 found a 47% incidence of chest pain but only a 12% incidence of ischemic ST segment depression in their cohort of 101 patients undergoing dipyridamole imaging. When low-level exercise was combined with dipyridamole infusion in another 200 patients in that study, the incidence of chest pain was similar to that in the patients undergoing only the dipyridamole protocol, but the incidence of ST segment depression was twice as high at 25%. Anginalike chest pain can be provoked by intravenous adenosine administration and subsequently reversed by aminophylline in normal healthy volunteers.21 Pearlman and Boucher22 found that 9% of patients with no demonstrable coronary artery disease developed chest pain during dipyridamole administration. The etiology of this chest pain in the presence of normal coronary arteries remains unclear.

Ischemic ST segment depression developing during or soon after dipyridamole administration is far less frequently observed than is a myocardial perfusion abnormality (10–15% vs. 80–90%). Chambers and Brown23 found that only the presence of “good” coronary collateral vessels (p<0.02) and increases in rate-pressure product (p<0.02) after dipyridamole infusion were significant predictors of dipyridamole-induced ST segment depression. These investigators
speculated that presence of “good collateral vessels” may act by facilitating coronary steal.

Noncardiac side effects of intravenous dipyridamole infusion are usually well tolerated and promptly reversed by aminophylline. The registry data reported in this issue of *Circulation* reveal only an average 4.7% decrease in systolic pressure and 7.8% decrease in diastolic pressure during infusion of the vasodilator. When low-level exercise stress is combined with dipyridamole infusion, there are fewer noncardiac side effects,24 and arterial blood pressure increases rather than decreases.11

In summary, the cumulative clinical experience in the United States and abroad with intravenous dipyridamole infusion as an alternative to exercise stress testing suggests that the test is relatively safe and clinically useful for detecting coronary artery disease and assessing prognosis. As with exercise stress testing, patients with active unstable angina should not undergo pharmacologic stress with this potent vasodilator until symptoms have stabilized for at least 2–3 days. Caution is advised in the use of dipyridamole imaging patients with a history of active bronchospasm. However, should wheezing be precipitated by dipyridamole, it can be promptly relieved by aminophylline. Patients expected to benefit greatly from dipyridamole myocardial perfusion imaging with either 201Tl, one of the new technetium 99m isonitriles, or with rubidium 82 and positron scintigraphy are those judged to be unable to perform adequate exercise. It is hoped that the drug will soon become available for general use.

References


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