# Dipyridamole-Thallium Imaging: The Lazy Man's Stress Test

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Dipyridamole-thallium imaging is a relatively safe and accurate method to evaluate myocardial perfusion and "stress." It is independent of patient motivation, exercise capacity and antianginal medications. Overall it detects coronary artery disease as well as exercise thallium and has already shown utility in prognostic determinations. The continued use of this test on a wide scale appears warranted and additional large scale experience needs to be critically evaluated.

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The evaluation of coronary artery disease (CAD) utilizing thallium scintigraphic studies has been clinically performed since 1977 and is currently the most common noninvasive technique for the assessment of myocardial perfusion. This clinical assessment depends upon the production of a physiologic stimulus to provoke coronary hyperemia as part of a "stress" study and comparison to a resting perfusion pattern. The necessity for stress and rest evaluations of coronary perfusion have been well documented in earlier reports utilizing intracoronary xenon (*1*) administration. The observation that resting cardiac perfusion remains homogeneous until arterial diameter narrowing exceeds 85–90% has been previously described (*2*) and further emphasizes the effect of coronary autoregulation on perfusion imaging. Basically, coronary stenoses that may be clinically insignificant at rest may be revealed by maneuvers that increase coronary blood flow.

Exercise is a physiologic stress that requires increased cardiac perfusion to match the increase in myocardial oxygen demand. However, the level of exercise achieved has a direct relationship to oxygen demand and consequently coronary blood flow (*3*). Therefore, maximal exertion is needed to stimulate maximal coronary blood flow. When this cannot be achieved, potential disparities in regional myocardial perfusion may not be apparent. Previous experimental and clinical reports have noted that at peak hyperemia, flow through a 50% coronary stenosis is diminished enough to cause a defect on an initial thallium scan (*4,5*).

If patients are unable to exercise to a maximal exertion, then nonreproducible thallium scans have been noted (*6*) and CAD can be missed. The main reasons for submaximal stress tests are listed in Table 1. When such limitations occur, dipyridamole administration can be used as an alternative to physical exercise (*4,5,7,8*). The original protocol, described by Gould (*7*) and co-workers has had many modifications, but the basic dipyridamole dose (0.57 mg/kg infused intravenously over 4 min) has remained unchanged. Although there are several reports of oral dipyridamole protocols (*7,9,10*), this review will only deal with the parenteral route.

### Dipyridamole: Mechanism of Action

Dipyridamole is a complex pyridimine derivative. It has a molecular weight of 504, is basic (pKa of 6.1) and lipophilic. It is also practically water insoluble unless the solution is acidic. The presence of hydroxyl groups on the diethanolamino portion of the molecule results in metabolism by hepatic biotransformation to the monoglucuronide and primarily biliary and fecal excretion with some enterohepatic circulation. Only minute amounts are excreted in the urine, (*11,12*) so caution should be used in dipyridamole administration to patients with severe hepatic dysfunction. The initial description of coronary vasodilation with intravenous dipyridamole was reported in animal studies by Kadatz (*13*) and Elliot (*14*). The actual mechanism of selective coronary hyperemia appears to be due to an elevation of endogenous plasma adenosine levels (*15*). Some investigators suggested that dipyridamole increases

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adenosine blood levels by inhibiting the uptake of adenosine across red cell membranes and endothelial cells in the lung and elsewhere (*16,17*). In another series of canine experiments, Afonso showed that intravenous aminophylline inhibited the coronary vasodilation produced by either dipyridamole or adenosine infusions (*18*).

In a human study, 13 healthy male volunteers received dipyridamole (0.4 mg/kg over 8 min) and plasma adenosine values were noted to double. The adenosine levels remained elevated for 30–45 min despite a relatively rapid fall in dipyridamole plasma levels. When theophylline (6 mg/kg) was given to five of the subjects prior to dipyridamole infusion, adenosine levels increased significantly, but no hemodynamic changes associated with dipyridamole were noted (*19*). This suggests that theophylline does not directly affect the rise in adenosine levels produced by dipyridamole but, rather reverses the cardiovascular effects of the enhanced plasma adenosine levels by blocking specific adenosine receptors. Other experimental (*20*) and clinical (*21*) studies have also suggested a similar adenosine receptor blocking action by theophylline.

It appears safe to conclude from both clinical and experimental studies that intravenous dipyridamole produces a vasodilating effect on coronary arterial vessels by enhancing endogenous adenosine levels. It is also apparent that theophylline (aminophylline) is a direct antagonist to the systemic and local actions of this increased adenosine level.

**Imaging Protocols**

The first description of dipyridamole-thallium imaging was made by Gould who with his co-investigators established the feasibility and clinical protocol for this technique (*4,5,7*). Other investigators would subsequently confirm that coronary flow increases after intravenous dipyridamole in cardiac catheterization studies (*22–24*). These studies suggest that dipyridamole increases coronary blood flow or velocity by three- to five-fold compared to baseline measurements. This increase in flow is greater than exercise induced hyperemia (*3*) and myocardial oxygen demand is obviously much lower during dipyridamole.

The original protocols for dipyridamole-thallium imaging utilized both intravenous and oral dipyridamole over a variable dose schedule. Table 2, Figure 1 is an update of the intravenous protocols and shows the variations of different interventions (*7,8,23,25–28*) that can be employed just prior to and after thallium administration. In a recent study, low level treadmill combined with dipyridamole resulted in a significant increase in heart rate, blood pressure, ST segment depression, and target (heart) to background (liver) ratio (*29*). However, there is as yet no statistical proof that any specific intervention results in superior imaging results (higher sensitivity), or is any better than no intervention (patient supine).

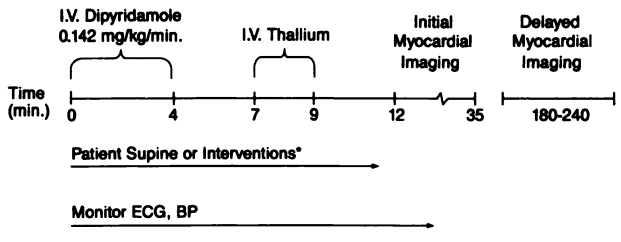
There are some practical points that should be noted. Most patients should be studied in a fasting state or NPO for 4–6 hr because nausea and emesis may occur. Patients should not be on any xanthine medications (theophylline) for 36 hr prior to the test and caffeine containing beverages should also be avoided for 2–4 hr. It is important to check for over-the-counter drugs that contain caffeine (headache pills) and xanthines (asthma pills). The intravenous route should be an antecubital vein because smaller hand veins are more sensitive (painful) to the acidic pH of dipyridamole. The infusion can be given by a mechanical pump or by a piggyback-type infusion in which the total dose of dipyridamole is diluted in 40–50 cc of normal saline (or any parenteral solution). Thallium is given 3–4 min after stopping the

**TABLE 1**
Limitations to Maximal Exercise Testing

| |
|---|
| Peripheral vascular disease |
| Cerebral vascular disease |
| Chronic respiratory disease |
| Orthopedic problems |
| Arthritis (back or legs) |
| Medications (Beta-Blocker, Ca-Channel Blocker) |
| Poor motivation |
| Nondiagnostic but severely limiting symptoms (fatigue, chest pain syndrome) |

**TABLE 2**
Protocol for Intravenous Dipyridamole Thallium Imaging

| Time (min) | Procedures |
|---|---|
| 0–4 | i.v. Dipyridamole, 0.142 mg/kg/min |
| 0–12 | Patient supine, or intervention with hand-grip, low-level exercise, stand, walk, sit up, tilt table |
| 0–15 | Monitor electrocardiogram and blood pressure |
| 7–9 | i.v. Thallium-201 chloride |
| 12–35 | Initial myocardial imaging |
| 180–240 | Delayed myocardial imaging |




*Interventions: Hand grip, exercise (low level), stand, walk, sit up, tilt table.

**FIGURE 1**
Protocol: I.V. Dipyridamole thallium imaging.

dipyridamole infusion, but can be given earlier if adverse reactions need to be reversed with aminophylline.

**Diagnostic Efficacy**

Using this type of protocol, several investigators have compared the results of dipyridamole and exercise thallium imaging in a group of patients who also had cardiac catheterization. A summary of five reports (*7,25–28*) are shown in Table 3. A total of 215 patients had both imaging procedures and the sensitivity was 79% for both dipyridamole and exercise. There was not any significant differences in the specificity of 95% for dipyridamole and 92% for exercise. As expected, patients were twice as likely to experience angina during exercise (63%) compared to dipyridamole (31%). These results suggest that dipyridamole-thallium myocardial perfusion imaging yields the equivalent diagnostic information of a symptom limited exercise thallium scan. Therefore, dipyridamole appears to be an excellent alternative to exercise in those patients who cannot perform an adequate level of exertion.

Table 4 shows a summary of eight reports (*8,30–36*) which includes 960 patients, of which 764 had cardiac catheterization. In this group sensitivity was 90% and specificity was 70%. This decrease in specificity compared to Table 2 may be a result of a much larger (fivefold) population of "normal" catheterization patients as well as observers reading at a higher sensitivity. There may also be a difference in patient type since no exercise testing was done in patients from Table 4.

Overall, (Tables 3 and 4) 979 patients had cardiac catheterization and sensitivity was 87% (647/742) and specificity was 74% (175/237). As experience increases with dipyridamole thallium imaging, one would expect results that are similar to the larger patient studies reported for exercise thallium. However, the two populations are different and specificity for dipyridamole studies may decrease due to obese (nonexercising) patients. In addition, there are recent reports of abnormal coronary flow responses (*37*) and thallium imaging (*38*) with dipyridamole in patients with "normal" coronary arteries. Clearly dipyridamole thallium imaging is an accurate test for the evaluation of myocardial perfusion, but there will not be complete correlation of scans to coronary anatomy as determined in the catheterization laboratory.

**Symptomatic and Hemodynamic Response to Dipyridamole**

Table 4 shows that 51% of all patients studied with dipyridamole had some adverse reaction. A review of specific side effects and hemodynamic changes demonstrate the summary presented in Table 5. This summary suggests that angina is the most common side effect and in many cases ST depression occurs as well. However, cardiac arrhythmia is relatively rare in these

**TABLE 3**
Reported Results of Exercise and Dipyridamole - Thallium Scans in the Detection of CAD

| Year | Investigators (Location) | Patients (n) | CAD (% Stenosis) | Dipyridamole-$^{201}$ T1 | | | Exercise-$^{201}$T1 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Sens | Spec | Angina | Sens | Spec | Angina |
| 1978 | Albro et al. (Seattle, WA, USA) | 62 | 50 | 34/51 (67%) | 10/11 (91%) | 25/62 (40%) | 34/51 (67%) | 10/11 (91%) | 41/62 (26%) |
| 1980 | Timmis, et al. (Brighton, UK) | 20 | 50 | 17/20 (85%) | N/A | 4/20 (20%) | 18/20 (90%) | N/A | N/A |
| 1981 | Narita et al. (Osaka, Jpn) | 50 | 50 | 24/35 (69%) | 15/15 (100%) | 13/50 (26%) | 25/35 (71%) | 15/15 (100%) | 29/50 (58%) |
| 1981 | Machencourt, et al. (Grenoble, Fr) | 68 | 70 | 52/58 (90%) | 9/10 (90%) | 20/68 (29%) | 54/60 (90%) | 8/10 (80%) | 42/68 (62%) |
| 1982 | Wilde et al. (Bristol, UK) | 15 | 50 | 12/12 (100%) | 3/3 (100%) | 5/15 (33%) | 10/12 (83%) | 3/3 (100%) | 10/15 (67%) |
| | Totals | 215 | | 139/176 79% | 37/39 95% | 67/215 31% | 141/178 79% | 36/39 92% | 122/195 63% |

Sens = sensitivity; Spec = specificity; N/A = not available.

**TABLE 4**
Dipyridamole - Thallium Scans to Detect CAD

| Year | Investigators (location) | Patients (n) | CAD (% stenosis) | Sens | Spec | Angina | Any side effects |
|---|---|---|---|---|---|---|---|
| 1982 | Ando et al. (Sapporo, Jpn) | 42 | 50 | 18/22 (81%) | 17/20 (85%) | 4/22 (18%) | 4/22 (18%) |
| 1982 | Francisco et al. (Iowa City, IA, USA) | 75 | 70 | 41/51 (80%) | 16/24 (67%) | 0/75 (0%) | 25/75 (33%) |
| 1982 | Harris et al. (Southampton, UK) | 38 | 50 | 19/21 (90%) | 11/17 (65%) | 26/38 (68%) | 26/38 (68%) |
| 1983 | Leppo et al. (Boston, MA, USA) | 60 | 50 | 37/40 (93%) | 16/20 (80%) | 11/60 (18%) | 26/60 (43%) |
| 1984 | Sochor et al. (Vienna, Aust) | 194 | 70 | 137/149 (92%) | 36/45 (80%) | 60/194 (31%) | 107/194 (55%) |
| 1985 | Demangeat et al. (Strasbourg, Fr) | 184 | 50 | 147/155 (95%) | 12/29 (41%) | N/A | N/A |
| 1986 | Laarman et al. (Nieuwegan, Netherlands) | 30 | 50 | 16/18 (89%) | 8/12 (67%) | 14/30 (47%) | 14/30 (47%) |
| 1988 | Lam et al. (St. Louis, MO, USA) | 337 | 70 | 93/110 (85%) | 22/31 (71%) | 83/337 (25%) | 184/337 (55%) |
| | Totals | 960 | | 508/566 90% | 138/198 70% | 198/756 26% | 386/756 51% |

Sens = sensitivity; Spec = specificity; N/A = not available.

patients. The range in the hemodynamic changes is due to different types of interventions after intravenous dipyridamole. Specifically, small changes are noted in patients who remain supine, while larger shifts in pulse rate and pressure are associated with exercise, hand grip, and tilt table. Myocardial oxygen demand, as assessed by the pressure-rate product, is minimally increased compared to exercise.

In addition to these reported adverse reactions, there is a report of severe chest pain and emergency coronary angioplasty after dipyridamole (*39*), and I have seen three similar prolonged chest pain reactions in over 1,000 cases performed in our laboratory. It is possible that patients could have a fatal infarction, despite being closely monitored and treated after these severe reactions. Therefore, it would appear prudent for most investigators to avoid dipyridamole infusions in patients with acutely unstable angina or fresh infarction. Coronary steal is a possible mechanism in this type of adverse reaction but this topic remains controversial (*22,38,40,41*). Overall, it seems unlikely that an absolute reduction in coronary flow (steal) is needed to produce positive test results. However, in the presence of high grade stenoses, dipyridamole can cause subendocardial ischemia (*42,43*).

The presence of chest pain during a dipyridamole infusion study does not predict angiographically significant CAD (*8,38,44,45*). The mechanism for chest pain is unclear and even when ST segment depression occurs, the severity or extent of CAD cannot reliably be predicted (*45*). However, it is likely that dipyridamole induced chest pain and significant ST depression are more likely to occur in patients with angiographic evidence of CAD compared to those patients without CAD (*8,45*). In addition, increased lung uptake on thallium images after dipyridamole also does not predict the

**TABLE 5**
Dipyridamole: Adverse Effects and Hemodynamics

| | | Adverse Effects |
|---|---|---|
| Cardiac | | |
| Angina | | 18–42% |
| ST Depression | | 6–21% |
| Arrhythmia | | <2% |
| Noncardiac | | |
| Headache | | 5–23% |
| Dizziness | | 5–21% |
| Nausea | | 8–12% |
| Flushing/Mild Headache | | 15–38% |
| Hemodynamics | | |
| Heart rate | Increase | 12–38% |
| Mean aortic pressure | Decrease | 6–10% |
| Pressure-rate product | Increase | 9–27% |

severity or extent of CAD. However, increased thallium lung uptake does correlate with the presence of CAD as compared to normal patients (*46*).

There are also reports of dipyridamole producing some enhancement of adenosine induced bronchoconstriction (*47*) in asthma patients and theophylline provided some protection from this adenosine effect on airways (*48*). We have observed two episodes of acute bronchoconstriction (severe and mild) secondary to dipyridamole, which required prompt aminophylline administration. These respiratory problems suggest that caution should be exercised when dipyridamole is given to patients in respiratory distress or those who have recently recovered from respiratory failure. Patients who are dependent on theophylline may be ill-advised to stop this therapy before undergoing dipyridamole-thallium imaging. Careful clinical judgment must be employed in these type of patients, but for the most part, reactions are rare in outpatient studies.

**Prognostic Utility**

Dipyridamole-thallium imaging does not provide hemodynamic or aerobic capacity information that are easily derived from an exercise test. It was also initially possible that pharmacologically induced perfusion defects would have relatively little, if any, clinical impact on patient care.

Although there is not as much experience with dipyridamole compared to exercise thallium scans, there is evidence that prognostic information can be obtained. In stable postinfarction patients (n = 51), Leppo et al. showed that the presence of thallium redistribution just prior to discharge was the most significant predictor of subsequent cardiac events (reinfarction, death or unstable angina). It is important to note that standard modified exercise testing was a significantly less sensitive predictor of cardiac events than dipyridamole-thallium imaging in this initial report (*49*).

The evaluation of cardiac risk in patients having noncardiac vascular surgery is another clinical area that has benefitted from dipyridamole-thallium imaging. In an initial (*50*) and subsequent report (*51*), a total of 154 patients undergoing elective vascular surgery were evaluated. The presence of thallium redistribution was again the most significant predictor of perioperative cardiac events (death, infarction, or unstable angina). Patients who also had diabetes or ST depression during dipyridamole as well as thallium redistribution were at even higher risk (*51*), while only one of 78 patients without redistribution experienced a cardiac event (*50,51*). It is equally important to note that an additional 36 patients showed thallium redistribution, but did not have any cardiac events. Therefore, dipyridamole-thallium imaging cannot be used as an absolute yes or no screening test for vascular surgery, and clinical judgment is still an important consideration. In fact, further studies suggest that only certain clinical profiles (history of angina, infarction, heart failure, diabetes, or ECG Q waves) need routine preoperative imaging (*52*). The clinical necessity of routine dipyridamole-thallium scans on all vascular surgery patients continues to be evaluated.

**Clinical Limitations and Indications**

As with exercise thallium imaging, there are clear technical limitations that are also seen with dipyridamole. Specific problems involving soft-tissue attenuation, anatomic variants, cardiac rotation, and cardiomyopathic infiltrative disease can yield nondiagnostic dipyridamole imaging studies. The need to stop all xanthine derivatives prior to testing is typically not a problem for most outpatients, but the referring physician must be consulted before this type of medication is summarily discontinued. There appears to be no need to alter oral dipyridamole dosages prior to this test. Since there is also no evidence that coronary artery spasm can be reproduced with dipyridamole, it is not likely that this test would be diagnostic in patients who are suspected to have normal coronary vessels and acute symptomatic spasm. Finally, patient selection should be limited to those who are relatively stable and angina free. A good rule-of-thumb is to perform dipyridamole-thallium testing only on those patients who would otherwise be referred for exercise testing except for their physical limitation (Table 1). As with exercise testing, a physician with advanced life support training should be immediately available to manage any complications.

The indications for dipyridamole-thallium imaging include the diagnostic evaluation of patients suspected of having CAD who are unable to do a maximal exercise stress test. We have also noted that dipyridamole testing is a useful technique in evaluating the presence of an ischemic component in patients with congestive heart failure and no firm cardiac diagnosis. This test can also be used to evaluate the effect of therapeutic interventions such as coronary reperfusion (bypass surgery or

angioplasty) but would not be expected to assess the effect of medical therapy (*8,53*). Because dipyridamole thallium imaging has shown significant prognostic utility, it can also be used to assess the severity of known cardiac stenoses for clinical or surgical management as well as helping to establish cardiac risk and prognosis in selected patient groups.

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