Robert J. Boudreau, MD, PhD • John T. Strony, MD • Rene P. duCret, MD • Christopher C. Kuni, MD • Yang Wang, MD • Robert F. Wilson, MD • Jeffrey S. Schwartz, MD • Wilfrido R. Castaneda-Zuniga, MD

# Perfusion Thallium Imaging of Type I Diabetes Patients with End Stage Renal Disease: Comparison of Oral and Intravenous Dipyridamole Administration[1]

**Eighty patients with type I diabetes and end stage renal disease were prospectively evaluated for coronary artery disease with dipyridamole-thallium-201 scintigraphy and quantitative coronary angiography. Forty patients received dipyridamole orally, and 40 received it intravenously. The prevalence of coronary artery disease was 53%. There were no significant differences in the accuracy of the two dipyridamole tests (sensitivity = 85%, specificity = 85%, accuracy = 85% for the oral group; sensitivity = 86%, specificity = 72%, accuracy = 79% for the intravenous group). Combining the 80 patients into a single group gave a sensitivity of 86%, a specificity of 79%, and an accuracy of 83% for the detection of coronary disease. Although the accuracy of this test in this patient population was similar to that previously reported for other groups, the prevalence of disease was high and resulted in a low predictive value of a negative test (83%).**

**Index terms:** Coronary vessels, diseases, 54.76 • Coronary vessels, radionuclide studies, 54.1299 • Diabetes mellitus, complications, 96.724 • Dipyridamole • Heart, effects of drugs on • Kidney, failure, 81.79 • Thallium, radioactive

**Radiology 1990;** 175:103-105

[1] From the Department of Radiology, Division of Nuclear Medicine (R.J.B., R.P.d., C.C.K, W.R.C.), and the Department of Medicine, Section of Cardiology (J.T.S., Y.W., R.F.W., J.S.S.), Box 382, University of Minnesota Hospital and Clinics, 420 Delaware St SE, Minneapolis, MN 55455. From the 1989 RSNA annual meeting. Received July 24, 1989; revision requested September 29; revision received November 7; accepted December 18. **Address reprint requests to** R.J.B.

© RSNA, 1990

CORONARY artery disease leading to myocardial infarction and death is a serious problem in type I diabetes patients with end stage renal disease. These patients often have silent myocardial ischemia due to associated neuropathies. It is important to identify patients with coronary artery disease before kidney transplantation, since not only will the quality of the patient's life be potentially adversely affected but a donor organ may be wasted. Since these organs are in short supply, they must be used in the most appropriate patients. Once potential recipients are identified as having coronary artery disease, they can undergo bypass grafting or coronary angioplasty, be treated medically before the transplant procedure, or have the operation canceled.

We previously investigated the role of thallium-201 treadmill stress testing in this group of patients (1). The results obtained were unsatisfactory because of the low levels of stress achieved. In fact, only six of 86 patients reached 85% of their predicted maximum heart rate. Similar results were reported by Philipson et al (2). In that study, only 12 of 60 patients achieved adequate heart rates. These results motivated us to prospectively evaluate the efficacy of dipyridamole-thallium scintigraphy in screening for ischemia in this patient population.

Dipyridamole-thallium imaging has been shown to be a relatively safe and effective method of evaluating myocardial perfusion (3). Both the oral and intravenous routes of dipyridamole administration have been used with similar results (4–7). Since intravenous dipyridamole has not yet been approved in the United States, many institutions can use only the oral formulation. There is concern that the variable absorption associated with oral administration of the drug may affect the blood levels obtained and therefore the clinical results. This potential problem would be even more likely in diabetes patients, since they often have gastroparesis. As part of a comprehensive prospective study to determine the appropriate treatment for uremic type I diabetes patients before and after renal transplantation, we determined the accuracy of dipyridamole-thallium scintigraphy in the detection of coronary artery disease, using both the oral and intravenous routes of dipyridamole administration.

## MATERIALS AND METHODS

This study is a prospective evaluation of the accuracy of dipyridamole-Tl-201 scintigraphy in screening for myocardial ischemia in type I diabetics referred for organ transplantation. Quantitative coronary angiography was used as the standard for presence or absence of disease. To be admitted into the study the patients had to give informed consent to undergo both coronary angiography and dipyridamole–Tl-201 scanning. The most common reasons for excluding patients were logistic problems in scheduling both tests during a short admission and concern with regard to radiographic contrast agents affecting severely compromised renal function in patients not yet on dialysis. Eighty patients were evaluated between December 1985 and March 1988 (40 receiving oral and 40 receiving intravenous dipyridamole). The majority of the patients receiving oral dipyridamole were studied first. There was no known or expected change in the patient referral profile over the course of the study.

Methylxanthines were withheld before the test and coffee and tea prohibited. Oral dipyridamole was prepared by pulverizing 300 mg of dipyridamole tablets (Boehringer Ingelheim, Ridgefield, Conn) with a mortar and pestle and then suspending them in 6 mL of orange-flavored methylcellulose. Tl-201 (3 mCi [111 MBq]) was administered intravenously 45 minutes after the oral administration of the dipyridamole. Intravenous dipyridamole was infused at a rate of 0.14 mg/kg/

**Table 1**
**Data for Patients Who Underwent Dipyridamole-Tl-201 Imaging**

| Category | Oral Group | Intravenous Group |
|---|---|---|
| Patient age (y) | 25–69; mean, 37 | 22–60; mean, 38 |
| Duration of diabetes (y) | 5–36; mean, 22 | 13–40; mean, 23 |
| No. of men | 22 | 29 |
| No. of women | 18 | 11 |
| No. with history of myocardial infarction | 4 | 6 |
| No. with positive angiogram | 20 | 22 |

min for 4 minutes. Three minutes after the end of the infusion the Tl-201 was injected. Imaging was begun within 10 minutes with a gamma camera equipped with a ¼-inch (0.6-cm) detector and a high-resolution collimator. A 10-minute computer acquisition (GE STAR [GE Medical Systems, Milwaukee]) and a 500,000-count analog image were obtained with both emissions of Tl-201. Three views were obtained (anteroposterior, 45° left anterior oblique, and 70° left anterior oblique). Patients were imaged again 2–3 hours later with the same protocol.

The scans were interpreted by consensus of three experienced radiologists who were unaware of the angiography results or patient history. Each view was subdivided into five segments, and the stress views (first set of images) were examined for areas of reduced activity. No indeterminate category was allowed. If a stress segment was classified as abnormal, the redistribution image was examined for definite, possible, or absent redistribution. The former two categories constituted our positive results for redistribution, and the latter category was classified as a fixed defect. If there were areas of partial redistribution in a fixed defect or fixed defects in association with reversible defects, the study was classified as having mixed defects. Quantitative analysis, including count profiles and washout rates, was performed. However, only qualitative results were used to reach the final diagnosis, since no normal quantitative values are available for this test in this patient population. Washout rates were noted to be variable and of no diagnostic value.

Coronary angiograms were analyzed by a blinded observer who was unaware of the results of the Tl-201 scan or the patient's history. This necessitated that the reader not be the person who performed the angiography. Quantitative analysis of the coronary angiograms was performed to determine the percentage of cross-sectional narrowing and absolute cross-sectional diameter (8). Coronary lesions were traced from two perpendicular views and transmitted in digitized form to a computer, with compensation for magnification and distortion. The catheter (usually 8 F external diameter) was used as the calibration reference. The artery in question was reconstructed spatially, assuming an elliptical cross section. Arterial diameters were then computed at intervals along the center line for calculation of absolute maximum and minimum diameters and percentage stenosis. The method is not without errors, but the correlation with histologic findings is good, as is the reproducibility (standard deviation, <5%). The criterion for positive test results was a 70% or greater reduction in cross-sectional area. A $\chi^2$ test was used to determine if there were significant differences between the sensitivities, specificities, and accuracies of the two routes of administration of dipyridamole.

## RESULTS

The characteristics of the patients in each group are listed in Table 1. There was no significant difference between the two groups with respect to any of the variables listed. No serious side effects were noted in either group. Minor side effects such as nausea, vomiting, headache, dizziness, and shortness of breath occurred in 18 patients receiving oral dipyridamole and in 17 receiving intravenous dipyridamole. There were three episodes of chest pain in the oral group and four in the intravenous group. The accuracy of the tests is given in Table 2. There was no significant difference between the two tests ($P > .2$ for all comparisons). Combining the results of both the intravenous and oral routes of administration gave an overall sensitivity of 86%, a specificity of 79%, and an accuracy of 83% for detection of coronary artery disease. There were no fixed defects in any of the studies with positive results; all defects were present in association with some reversible areas of ischemia. The intravenous group had five defects classified as mixed, and the oral group had three mixed defects.

In the patient group with negative thallium scans and positive angiograms, two patients had one-vessel disease, three patients had two-vessel disease, and one patient had balanced three-vessel disease. All of these patients had additional angiographically insignificant lesions. Eight patients had positive thallium scans and negative arteriograms. Six of these arteriograms were completely normal, and two showed insignificant disease. Only one of these lesions approached being significant (60% narrowing). Ten patients had a history of myocardial infarction. Six of these patients had thallium scans with reversible defects, two had scans with mixed fixed and reversible defects, and two had normal scans.

## DISCUSSION

Our results for both the intravenous and oral routes of dipyridamole administration compare favorably with previously published reports. In a recent review the mean sensitivity of dipyridamole-thallium imaging was 90% and the specificity was 70% (3). Our sensitivity of 86% is comparable with this value, and our overall specificity of 79% is actually somewhat higher than those in some of these previous reports. In view of the potential problems with thallium imaging in the diabetic patient population—which include hypertension, neuropathy, gastroparesis, possible small vessel disease, uremia, and insulin administration—it is interesting that such good results were obtained. We also showed that the oral route of dipyridamole administration produced results that are as accurate as those obtained with the intravenous route in this patient population. These results are in accordance with several previous published reports documenting the accuracy of oral dipyridamole scintigraphy (4–7).

Taillefer et al (4) studied 50 patients by means of both the oral and intravenous routes of dipyridamole administration. These patients were selected from those referred for coronary angiography, so a strong referral bias was present. However, the sensitivity for the two routes of administration was equivalent, with a value of 84% for the oral route and 79% for the intravenous route. Homma et al (5) showed that an oral dipyridamole suspension (300 mg) resulted in a similar blood level at 45 minutes after ingestion as an intravenous dose of 0.56 mg/kg at 5 minutes after injection. Borges-Neto et al (6) and Jain et al (7) found that oral dipyridamole with tomographic Tl-201 imaging was a useful clinical procedure.

In our experience, dipyridamole-thallium scintigraphy has been superior to treadmill-exercise studies. In our previous study, only six of 85 patients reached 85% of the target heart rate (1). Philipson et al also had an extremely low rate of diagnostic Tl-

201 treadmill studies (12 of 60) and found that a positive thallium scan was not predictive of coronary artery disease (2). In the latter study the results of the thallium scan were used by the clinicians to determine whether the patient would be referred for angiography, so one cannot address the issues of sensitivity or specificity. However, those patients with negative stress thallium tests who achieved 85% of the target heart rate did not have cardiovascular events after transplantation. Since only seven of 60 patients fit this category, the test was rarely helpful.

Our patient population had a coronary artery disease prevalence of 53%, which was within the range reported in the literature (34%–54%) (9–11). We did not exclude patients with previous myocardial infarction because it is often necessary to determine if they have residual ischemia or evidence of disease outside the area of infarction. Our pooled sensitivity for dipyridamole–Tl-201 imaging was 86%. Although this sensitivity is in accordance with the literature, one must question its adequacy for screening a group of patients with a high prevalence of coronary artery disease. If the thallium test had been used to screen for coronary artery disease, the 36 patients who had negative studies would not have had to undergo coronary angiography. However, six of these patients (17%) actually had significant coronary artery disease, resulting in a predictive value of a negative test of 83%. This value is probably too low to allow one to confidently exclude the presence of disease after a negative thallium scan, given the serious consequences of missing disease in these patients. The overall mortality rate during a mean follow-up period of 15.6 months in type I diabetic kidney transplant recipients with coronary artery disease varied between 20% and 62%, depending on whether the disease was moderate or severe (2). Patients with normal coronary arteries had a mortality rate of 5.4%. One must remember that an inappropriate transplantation affects both the recipient and another person who did not get the organ.

It is possible that the sensitivity could be improved by using single photon emission computed tomographic (SPECT) techniques. However, in our patient population the sensitivity of the test would have to be 96.4% to result in a predictive value of a negative test of 95%. Such a high sensitivity would probably result in an unsatisfactory specificity. Preliminary results with tomographic Tl-201 imaging in a similar group of uremic but not necessarily diabetic patients showed a sensitivity of 100% but a specificity of only 30% for the diagnosis of coronary artery disease (12). Thus, to our knowledge, the existing literature does not support the superiority of SPECT in a similar patient population. The safety of the test must also be a source of concern. Dipyridamole-thallium scintigraphy is not a classical "noninvasive" test. Although no serious problems occurred in this study, the combination of high disease prevalence and potential risk has led us to recommend coronary angiography as the imaging method of choice for all type I diabetes patients before renal transplantation at our institution. Perhaps positron emission tomography will be accurate enough to be useful in this patient population and help eliminate the need for angiography.

Our patients are being followed up long term to assess the risk factors (including the thallium scan) for cardiac events after renal transplantation. It is possible that prognostic information might be present in negative Tl-201 results that can only be uncovered with such long-term studies. However, since four of the six patients with negative studies had multivessel disease, we doubt that this will be the case. The effects of randomized medical and surgical interventions in patients with identified disease are also being evaluated and will be the subject of future reports. These data will, we hope, help us to more effectively treat these challenging patients in the future. ■

**Table 2**
**Results of Tl-201 Imaging in Oral and Intravenous Dipyridamole Groups**

| | Oral* | | Intravenous† | |
|---|---|---|---|---|
| Angiography Result | No. Positive | No. Negative | No. Positive | No. Negative |
| Positive | 17 | 3 | 19 | 3 |
| Negative | 3 | 17 | 5 | 13 |

* Sensitivity, specificity, accuracy = 85%.
† Sensitivity = 86%, specificity = 72%, accuracy = 79%.

**Acknowledgments:** We thank James Tennison, CNMT, for his help in scheduling and performing these tests, Mary Conway, RN, for her help in collecting the data, and Charla Zaccardi, for preparing the manuscript. The Du Pont Company kindly supplied the Tl-201 used in the study.

**References**

1. Morrow CE, Schwartz JS, Sutherland DER, et al. Predictive value of thallium stress testing for coronary and cardiovascular events in uremic diabetic patients before renal transplantation. Am J Surg 1983; 146:331–335.
2. Philipson JD, Carpenter BJ, Itzkoff J, et al. Evaluation of cardiovascular risk for renal transplantation in diabetic patients. Am J Med 1986; 81:630–634.
3. Leppo JA. Dipyridamole-thallium imaging: the lazy man's stress test. J Nucl Med 1989; 30:281–287.
4. Taillefer R, Lette J, Phaneuf DC, et al. Thallium-201 myocardial imaging during pharmacologic coronary vasodilation: comparison of oral and intravenous administration of dipyridamole. J Am Coll Cardiol 1986; 8:76–83.
5. Homma S, Callahan RJ, Ameer B, et al. Usefulness of oral dipyridamole suspension for stress thallium imaging without exercise in the detection of coronary artery disease. Am J Cardiol 1986; 57:503–508.
6. Borges-Neto S, Mahmarian JJ, Jain A, et al. Quantitative thallium-201 single photon emission computed tomography after oral dipyridamole for assessing the presence, anatomic location and severity of coronary artery disease. J Am Coll Cardiol 1988; 11:962–969.
7. Jain A, Mahmarian JJ, Borges-Neto S, et al. Clinical significance of perfusion defects by thallium-201 single photon emission tomography following oral dipyridamole early after coronary angioplasty. J Am Coll Cardiol 1988; 11:970–976.
8. Brown BG, Bolson E, Frimer M, Dodge HT. Quantitative coronary angiography. Circulation 1977; 55:329–337.
9. Weinrauch LA, D'Elia JA, Healy RW, et al. Asymptomatic coronary artery disease: angiography in diabetic patients before renal transplantation. Ann Intern Med 1978; 88:346–348.
10. Bennett WM, Kloster F, Rosch J, et al. Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. Am J Med 1978; 65:779–784.
11. Braun WE, Phillips D, Vidt AC, et al. Coronary arteriography and coronary artery disease in 99 diabetic and nondiabetic patients on chronic hemodialysis or renal transplantation programs. Transplant Proc 1981; 13:128–135.
12. Krawczynska EG, DePuey EG, Whelchel JD. Tl-201 cardiac SPECT to evaluate prerenal transplant patients (abstr). J Nucl Med 1988; 29:950.