Thallium-201 Myocardial Imaging During Coronary Vasodilation Induced by Oral Dipyridamole

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Myocardial perfusion imaging of ^{201}Tl injected during maximum exercise has been an important diagnostic tool for coronary artery disease. Pharmacologic coronary vasodilation by i.v. infusion of dipyridamole may be used in lieu of exercise stress for purposes of diagnostic perfusion imaging. However, i.v. dipyridamole is not currently available from commercial sources for widespread routine use. Accordingly, this study was carried out in order to determine whether high dose, oral dipyridamole would be useful as a coronary vasodilator for purposes of diagnostic perfusion imaging. Fifty-eight patients undergoing diagnostic coronary arteriography also had myocardial perfusion imaging with ^{201}Tl under conditions of rest, maximum exercise stress, and high dose oral dipyridamole. Of those patients who had a defect on exercise thallium images, 75% also had a perfusion defect on thallium images after high dose oral dipyridamole. These results indicate that oral dipyridamole causes sufficient coronary arteriolar vasodilation and increase of coronary flow in nonstenotic arteries to identify perfusion defects comparable to those seen on maximum exercise stress in at least 75% of cases. In 25% of patients with exercise defects, no perfusion defect was seen after oral dipyridamole. Thus, oral dipyridamole is a potent coronary vasodilator, comparable to exercise stress in most cases, but in a minority of patients may not be comparable to exercise stress.

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Myocardial perfusion scintigraphy using thallium-201 (^{201}Tl) in conjunction with symptom-limited exercise is a useful technique for detecting and assessing clinical severity of coronary artery disease (CAD). In lieu of exercise stress, i.v. infusion of dipyridamole during thallium myocardial perfusion scintigraphy has been shown to be a reasonable alternative to exercise thallium imaging *(1–4)*. Intravenous dipyridamole is a potent coronary arteriolar vasodilator which greatly increases myocardial blood flow with lesser changes in heart rate, blood pressure, myocardial work, and cardiac output compared to exercise stress. Although the usefulness of dipyridamole thallium imaging has been suggested primarily for patients who are physically unable to perform exercise, there are several potential advantages to pharmacologic perfusion scintigraphy for routine use. First, i.v. dipyridamole causes a greater increase in myocardial thallium uptake than exercise, thereby theoretically suggesting that it is a better stimulus than exercise for increasing coronary flow *(5)*. Second, ischemia is not an endpoint with pharmacologic perfusion imaging, and disparate flow in normal compared with narrowed coronary arteries may be achieved with diagnostic perfusion defects without significant ischemia. When ischemia does occur with dipyridamole infusion, it may be immediately reversed by the administration of aminophylline, thereby providing very rapid control of the ischemia, perhaps more than exercise requiring cessation of stress and fall of heart rate and blood pressure. Third, the drug may be used in conjunction with other pharmacologic agents or in conjunction with other forms of stress in order to achieve

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maximum coronary flow, thereby maximizing diagnostic sensitivity and specificity *(6)*. The magnitude of the resulting difference in coronary blood flow between stenosed and normal arteries may then permit more accurate assessment of the physiologic severity of disease or improve overall sensitivity/specificity.

Although i.v. dipyridamole thallium imaging has been shown to be equivalent to exercise thallium imaging for the detection of CAD, the i.v. form of dipyridamole is currently investigational and not widely available. Accordingly, we undertook the current study in order to determine whether thallium myocardial perfusion imaging during coronary artery vasodilation induced by oral dipyridamole was comparable to that provided by exercise thallium scintigraphy. Demonstration of perfusion defects after oral dipyridamole in patients with CAD would also indicate that it caused significant coronary arteriolar vasodilation.

MATERIALS AND METHODS

Patient Selection

Consecutive patients undergoing diagnostic coronary arteriography for chest pain syndromes were entered into the study if clinical status permitted the performance of separate rest, exercise, and oral dipyridamole thallium imaging. Exclusion criteria were myocardial infarction within 3 mo, unstable angina pectoris, concomitant significant valvular disease, uncontrolled ventricular arrhythmia, left main artery disease, need for prompt coronary artery revascularization, or essential use of xanthines for obstructive pulmonary disease. Informed consent was obtained in all patients, and the investigation was approved by the local human rights committee. Twenty-four patients were studied in Seattle and 34 were studied in San Antonio.

Coronary Arteriography

Selective coronary arteriography and contrast of ventriculography was performed in all patients by the transfemoral approach. Interpretation of coronary arteriograms was performed by two experienced observers blinded to the results of perfusion imaging.

Thallium Imaging

Thallium imaging was performed on three separate occasions following the administration of 1.5–2.0 mCi of [^{201}Tl]hydrochloride. In order to obtain consistent statistical count data in images, 300,000 count myocardial images were acquired in the sequence: anterior, 30, 45, 60° left anterior oblique, and left lateral projections using a gamma scintillation camera equipped with a high resolution collimator for optimum visualization of defects. Images were recorded on Polaroid film using a tri-lens camera and were also collected on magnetic disk using a dedicated computer system. Rest, exercise, and oral dipyridamole images were acquired with at least 7 days separating studies. The resting perfusion studies were acquired in the fasting state. Thallium was injected i.v. with the patient standing and walking in place for 90 sec. Imaging commenced 10 min following thallium injection. For exercise studies thallium was injected 45–60 sec prior to discontinuance of exercise following the Bruce protocol for symptom-limited maximal exercise.

Oral dipyridamole imaging was performed in the fasting state with all xanthines withheld (theophylline preparations and caffeinated beverages). A dose of 200 mg was initially given to five patients in order to test gastrointestinal tolerance to the drug. Subsequently, 300 mg was given to 53 patients. Oral dipyridamole was administered as crushed tablets mixed with corn syrup extract, and diluted with carbonated orange drink. Residual dipyridamole in the cup was resuspended and ingested to ensure that the entire dose of dipyridamole was administered. Supine and standing blood pressure, heart rate, and electrocardiogram were recorded before and 45 min after the ingestion of dipyridamole. Forty-five minutes after dipyridamole ingestion, the patient stood, walked slowly in place for 90 sec, and was injected with 1.5–2.0 mCi of ^{201}Tl. In order to allow maximum blood-pool clearance as is standard practice, 10 to 15 min after thallium injection, 300,000 count myocardial images were obtained as described above. In five patients given 300 mg dipyridamole p.o., assay for free and total dipyridamole levels were carried out on blood samples collected 45 min following the ingestion of oral dipyridamole. The serum dipyridamole levels were determined fluorometrically as previously described *(7,8)*.

Thallium Image Analysis

Visual Interpretation. The original Polaroid photographs of the myocardial perfusion images for rest, exercise, and dipyridamole studies were interpreted in blinded fashion by three experienced observers. Where disagreement existed, the consensus reading of two observers is reported. Due to the uncertain duration of effects of oral dipyridamole and the unknown effects of the drug upon redistribution, separate resting images were performed.

Computer Analysis. Studies in the 24 patients from Seattle were analyzed by one of the authors (J.H.C.) for quantitation distribution on rest, exercise, and oral dipyridamole images utilizing a computer program as previously described *(2)*. Software for this analysis was not available in San Antonio and quantitative analysis was therefore not carried out for the 34 patients studied in San Antonio. Briefly, myocardial and background areas were selected on the 45° LAO rest image. These

regions of interest (ROIs) were superimposed on the exercise and oral dipyridamole images by a computer program. The activity in each area of interest was normalized for the injected thallium dose in mCi, duration of imaging in sec, and number of computer elements (pixels) in each ROI. Myocardial counts and myocardial background ratios for exercise or oral dipyridamole images were compared to resting values. For statistical analysis, values from exercise and dipyridamole images were compared to rest values for each patient who then served as his own control using paired t-testing.

RESULTS

Fifty-eight patients undergoing coronary arteriography completed all three thallium imaging sessions (rest, exercise, oral dipyridamole). The duration between coronary arteriography and completion of image studies was within 3 mo for all patients. No changes in medications occurred between separate imaging periods. Of the 58 patients studied, ten patients had normal coronary arteries or minimal coronary artery irregularities. Forty-eight patients were considered to have significant CAD of at least one major coronary artery defined as at least 50% reduction in luminal diameter by visual estimation. Distribution of coronary anatomy within the group was: single-vessel disease, 19 patients; two-vessel disease, 17 patients; three-vessel disease, 12 patients.

Symptoms After Oral Dipyridamole

Angina pectoris developed in ten of 48 patients (21%) who had documented CAD. ST segment depression of 1.0 mV developing in comparison with the resting study occurred in five of these patients. Significant ST depression did not occur in the other patients, who had evidence of a previous myocardial infarction or nonspecific ST-T wave changes. Angina spontaneously disappeared except in two patients who required the administration of i.v. aminophylline for relief of symptoms. Mild headache or a flushing sensation was reported in 30 of 58 (52%) patients. Dizziness developed in eight of 58 (13%) patients. Nausea was reported in six of 58 (10%) patients but none had vomiting. None of these constitutional symptoms required therapy. No patient developed unstable angina, arrhythmia or required hospitalization due to prolonged chest pain. There were no apparent differences in side effects or perfusion defects between the 53 patients with 300 mg and the five patients with 200 mg doses and therefore all were analyzed together.

Hemodynamics After Oral Dipyridamole

Figure 1 demonstrates rest and oral dipyridamole images for an ANT projection image. A mild reduction

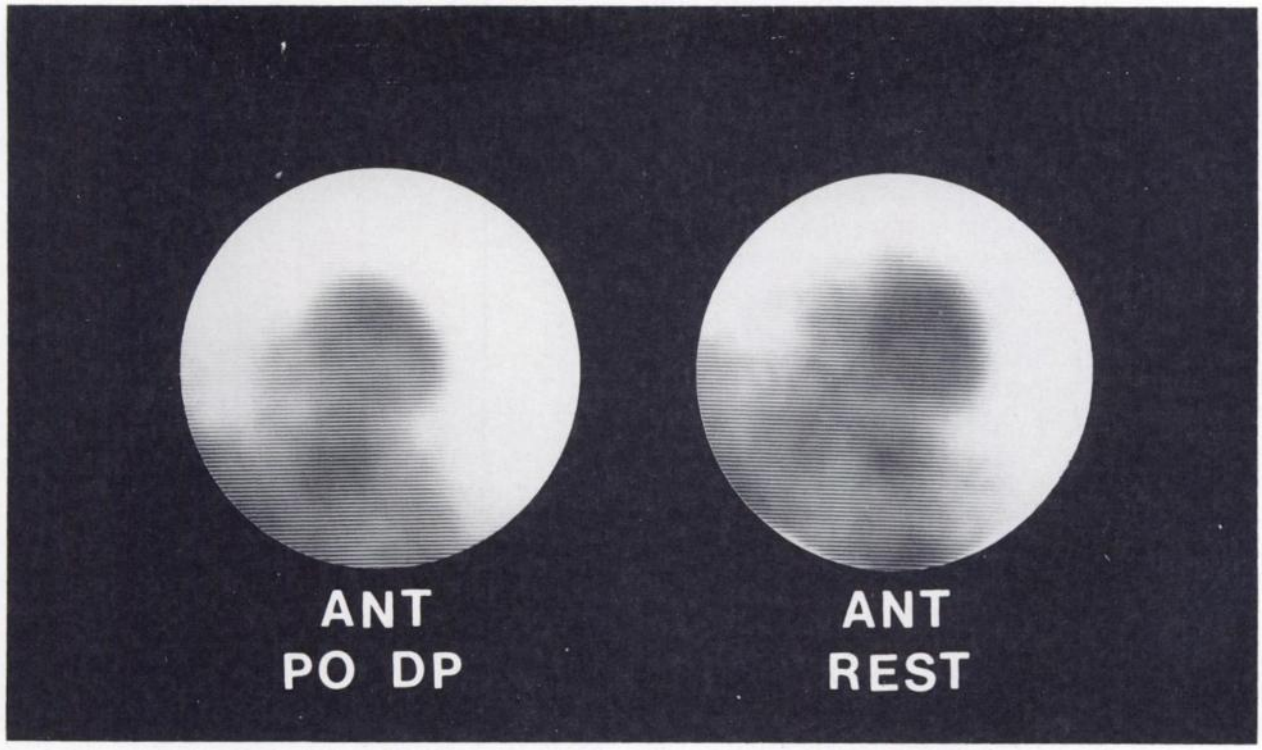

FIGURE 1
Unprocessed Polaroid thallium images are shown for ANT projection at rest and after oral dipyridamole

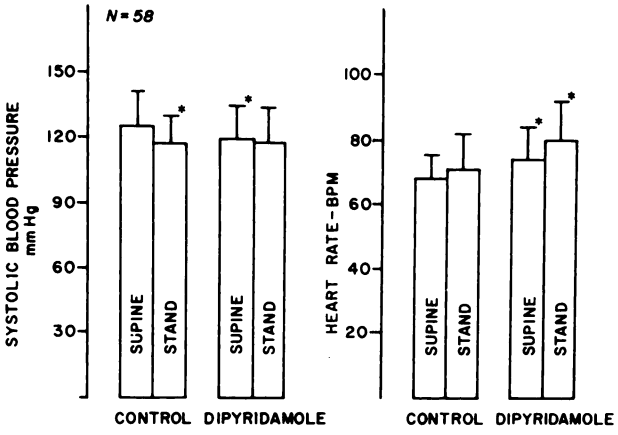

FIGURE 2
Hemodynamic responses to orthostatic position and dipyridamole are shown for 58 patients studied

in count activity in the inferoposterior area is evident on the oral dipyridamole studies indicating coronary artery disease.

Figure 2 illustrates systolic blood pressure and heart rate for supine and standing positions in the control state and 45 min following dipyridamole. A significant orthostatic decline in systolic blood pressure occurred in the control state in the absence of dipyridamole with blood pressure falling from 125 ± 15 (s.e.m.) to 117 ± 14. There was no significant difference between control supine heart rate of 68 ± 9 and standing heart rate of 71 ± 11 before dipyridamole. Supine systolic blood pressure following the administration of dipyridamole was significantly reduced compared to the resting supine level. However, a significant decline in systolic blood pressure was not evident on standing following the administration of dipyridamole. Supine heart rate after dipyridamole increased significantly from 68 ± 9 to 74 ± 10. Standing heart rate after dipyridamole was significantly elevated compared to the supine control and supine dipyridamole levels.

Visual Interpretation of Thallium Images

Interpretations were made visually from Polaroid images. Of the 48 patients with CAD, 29 patients demonstrated new or enlarged thallium defects on exercise compared with rest images for a diagnostic sensitivity of 60%. Of these 29 patients with evidence of ischemia by exercise thallium imaging, 22 demonstrated new or enlarged thallium defects after oral dipyridamole. One additional patient demonstrated a new defect after dipyridamole which was not demonstrated by exercise thallium imaging. By comparison to new or enlarged defects in 29 of 48 patients by exercise thallium imaging, oral dipyridamole imaging demonstrated new or enlarged defects in 23 of 48 patients with coronary artery disease. Therefore, of the patients with demonstrable reversible ischemia by exercise thallium imaging, 76% were detected by oral dipyridamole imaging. Of the ten patients who did not have significant CAD, one patient was falsely interpreted as being abnormal by both exercise and oral dipyridamole imaging for a specificity of 90%. Of the five patients receiving 200 mg oral dipyridamole, one was normal by arteriography and had normal images; three had CAD by arteriography and had thallium defects; one had coronary disease by arteriography but had no thallium defect. The percent of false negatives in the small group of patients receiving 200 mg of oral dipyridamole was comparable to the larger group receiving the 300 mg dose. Accordingly, the entire group was analyzed together for the sensitivity and specificity figures reported above.

Serum Dipyridamole Levels

Dipyridamole levels in five patients receiving the 300 mg dose demonstrated a range for free dipyridamole of 0.5 to 1.4 mcg/ml. Total serum dipyridamole ranged between 0.9 to 1.5 mcg/ml. These values are comparable with reported dipyridamole levels achieved follow-

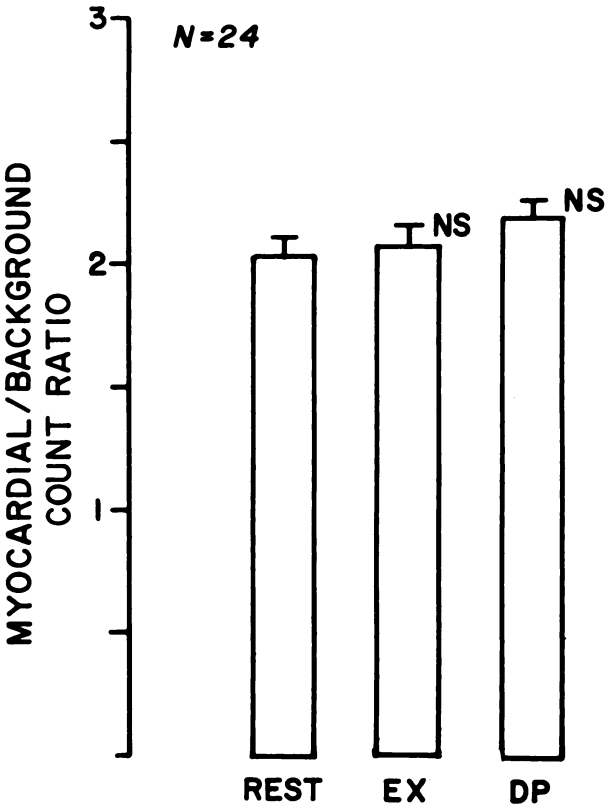

FIGURE 3
Normalized myocardial-to-background count ratios are shown for 24 patients undergoing computer analysis. Rest, exercise (EX), and oral dipyridamole (DP) studies do not demonstrate a significant difference in target-to-noise ratio

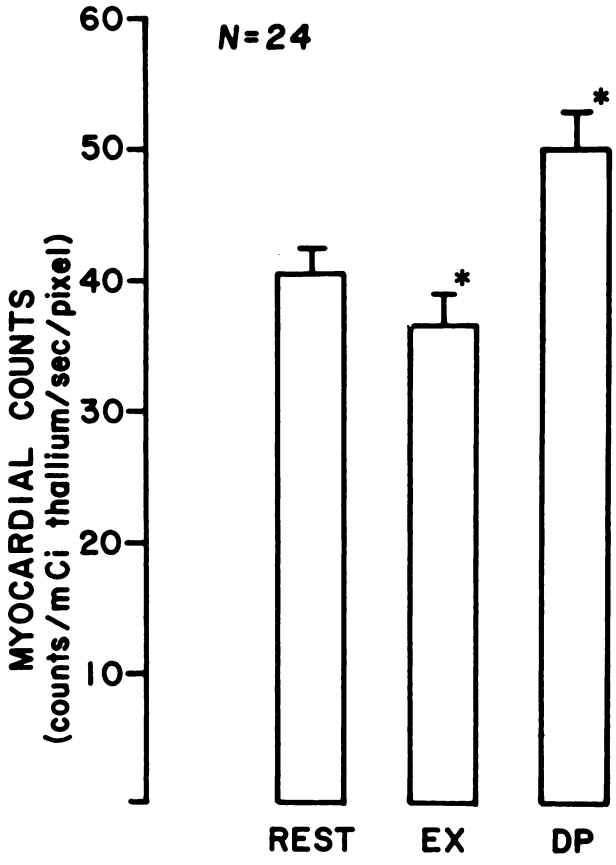

FIGURE 4
Normalized myocardial counts for rest, exercise (EX), and oral dipyridamole (DP) are shown. Statistically significant increase in myocardial counts is demonstrated after oral dipyridamole but not after exercise

ing the i.v. injection of 10–45 mg of dipyridamole and are somewhat lower than previously reported peak values reported for the oral ingestion of dipyridamole *(8)*, due most likely to dose differences.

Computer Analysis of Thallium Myocardial Perfusion Images

Normalized myocardial counts were obtained as described in the methods to obtain myocardial background count ratios and total myocardial counts. Figure 3 demonstrates the myocardial-to-background count ratio for the 24 patients undergoing this type of computer analysis. This figure demonstrates no statistical difference in myocardial-to-background count ratios for exercise or dipyridamole studies as compared with the resting study. A significant difference in target-to-noise ratio was, therefore, not demonstrated. Figure 4 demonstrates normalized myocardial counts in these same 24 patients for the rest, exercise, and oral dipyridamole studies. The reduction in total myocardial counts for the exercise study as compared with the rest study was significant ($p>0.05$). However, a statistically significant increase in myocardial counts is demonstrated for the oral dipyridamole study as compared with both exercise and resting studies ($p<0.001$). Since myocardial uptake of thallium is proportional to the ratio of coronary blood flow to cardiac output, the increase in myocardial uptake of thallium demonstrated in this figure suggests that coronary blood flow increased to a greater extent than cardiac output. This data suggests that oral dipyridamole had a significant pharmacologic effect as a coronary vasodilator for increasing coronary flow, more so than exercise in this group of patients.

DISCUSSION

In the current pilot study, we sought to determine whether thallium myocardial perfusion imaging after high dose oral ingestion of dipyridamole would yield diagnostically useful information. As the standard of reference, we used the demonstration of reversible ischemia during exercise thallium imaging, as evidenced by a new defect occurring with exercise or a defect which enlarged from rest to exercise imaging studies. Of the patients with demonstrable reversible ischemia by rest-exercise thallium imaging, 76% demonstrated reversible perfusion defects after oral dipyridamole. Thus, abnormal distribution of thallium uptake due to differences in coronary blood flow in patients with coronary artery stenoses may be demonstrated by oral dipyridamole imaging in the majority of patients with abnormal thallium exercise imaging. Of the patients given high dose oral dipyridamole, over 50% developed mild constitutional symtoms. Twenty percent of patients developed significant angina pectoris as compared with ~45% of patients developing angina with exercise testing. Two patients required i.v. aminophylline for control of anginal symptoms. Anginal destabilization or other untoward effects did not occur. This study also demonstrated an increase in myocardial counts following oral dipyridamole in comparison with exercise and resting studies. These data indicate that oral dipyridamole caused significant coronary arteriolar vasodilation.

There are several limitations to the current investigation. First, single-dose redistribution imaging, as is currently performed in most laboratories, was not used for this investigation due to uncertainty regarding the duration of action of oral dipyridamole. Kinetic studies *(8)* have indicated that peak levels of dipyridamole occur 45–60 min following the administration of oral dipyridamole, and decline to near base values at 3–4 hr. It is, therefore, possible that oral dipyridamole could be used in conjunction with single-dose redistribution imaging. Recent studies employing i.v. dipyridamole have indicated that thallium kinetics are similar to those observed with exercise *(9)* but the pharmacokinetics of

redistribution with oral dipyridamole are unknown. Second, computer quantitation of thallium washout was not performed since single-dose redistribution imaging was not employed. It may be that thallium washout occurring after oral dipyridamole would be as useful as it is after exercise. Third, the optimal oral dose of dipyridamole is unknown. A significant percentage of patients had moderate constitutional symptoms; of the patients developing angina pectoris and electrocardiographic changes, the administration of aminophylline provided immediate relief.

Our results show only mild changes in blood pressure and heart rate with oral dipyridamole; however, the increase in coronary blood flow may be limited due to slightly lower blood pressure after the drug. Recent studies would indicate that pressure augmentation by maneuvers such as hand grip may further increase coronary blood flow *(6)*.

This pilot study indicates that diagnostic thallium images may be obtained for the detection of coronary ischemia after oral dipyridamole as a consequence of it increasing coronary blood flow. Although our data indicate that oral dipyridamole causes coronary arteriolar vasodilation, it does not provide adequate sensitivity for diagnostic imaging for three possible reasons. The first may be due to the limitations of planar imaging of thallium-201. The second may be that serum levels of dipyridamole were lower than previously reported. However, serum levels were measured in only five patients, thereby subjecting these results to statistical variability, and more recent formulations of the oral preparation of dipyridamole have improved absorption. Finally, due to the variability of visual estimation of stenosis severity, we defined significant CAD as 50% or greater diameter narrowing. With more severe limits, such as 75% narrowing or greater, the sensitivity would undoubtedly be better. However, we chose conservative limits due to the fact that visual discrimination between 50% and 75% diameter narrowing is not likely to be valid. The comparison between results in the oral dipyridamole and exercise groups, however, is the important observation indicating that high dose oral dipyridamole causes significant coronary arteriolar vasodilation in most, 75% of patients. In a minority of patients, 25%, perfusion defects were not seen due to several possible reasons. In this minority of patients, the dipyridamole may have had less of an effect than exercise stress, suggesting some biological variability in effect of the drug. Other explanations may be the known variability of estimates of stenosis or the recognized problems of planar imaging. Boucher et al. have confirmed, in abstract form, the use of oral dipyridamole for purposes of diagnostic imaging *(11)*.

Improved diagnostic information might be obtained by redistribution imaging and computer analysis or by more complex interventions such as combining oral dipyridamole with exercise. In preliminary studies, combined dipyridamole and exercise appears to cause greater increases in coronary blood flow with better discrimination between normal and hemodynamically significant coronary artery stenosis *(10)*. Further studies using quantitative measurements of myocardial perfusion, such as positron emission tomography, will be necessary to better define the role of these vasodilatory stimuli in routine diagnostic imaging.

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