Effect of Exercise Supplementation on Dipyridamole Thallium-201 Image Quality

Sheryl Stern, I. David Greenberg, and Robert Corne

Sections of Nuclear Medicine and Cardiology, Health Sciences Centre, Winnipeg, Manitoba

To determine the effect of different types of exercise supplementation on dipyridamole thallium image quality, 78 patients were prospectively randomized to one of three protocols: dipyridamole infusion alone, dipyridamole supplemented with isometric handgrip, and dipyridamole with low-level treadmill exercise. Heart-to-lung, heart-to-liver, and heart-to-adjacent infradiaphragmatic activity ratios were generated from anterior images acquired immediately following the test. Additionally, heart-to-total infradiaphragmatic activity was graded semiquantitatively. Results showed a significantly higher ratio of heart to subdiaphragmatic activity in the treadmill group as compared with dipyridamole alone ($p < 0.001$) and dipyridamole supplemented with isometric handgrip exercise ($p < 0.001$). No significant difference was observed between patients receiving the dipyridamole infusion, and dipyridamole supplemented with isometric handgrip exercise. We conclude that low-level treadmill exercise supplementation of dipyridamole infusion is an effective means of improving image quality. Supplementation with isometric handgrip does not improve image quality over dipyridamole alone.

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Thallium-201 scintigraphy is a well accepted noninvasive method of assessing myocardial perfusion. When combined with a physiologic stress such as treadmill or bicycle exercise, inducible differences in regional myocardial flow allow discrimination between stenotic and non-stenotic coronary arteries. The sensitivity of this method for detecting coronary artery disease is dependent upon attaining a sufficient level of exercise (*1–4*). Unfortunately, a significant number of patients referred for diagnostic testing are limited in their exercise capacity by a variety of non-cardiac problems, and are unable to perform an adequate exercise test. Coronary vasodilatation with intravenous dipyridamole has become a valuable alternative to exercise testing in this subset of patients (*5–11*). The quality of these images has suffered from a high level of infradiaphragmatic activity making interpolative background subtraction and subjective assessment more difficult (*12*). Several investigators have proposed that the addition of low-level exercise, either in the form of isometric handgrip or low-level treadmill exercise, would improve image quality (*13,14*).

This study was designed to prospectively evaluate image quality in three patient groups: those receiving dipyridamole alone, dipyridamole in combination with isometric handgrip, and dipyridamole supplemented with low-level treadmill exercise.

MATERIALS AND METHODS

Patient Population

Seventy-eight consecutive patients referred to our department for dipyridamole thallium testing over a 5-mo period were entered into the study. Thirty-nine male and 39 female patients ranging from 28 to 86 yr of age were randomly assigned to one of three patient groups—those receiving dipyridamole alone (D), dipyridamole in combination with isometric handgrip (HG), and dipyridamole supplemented with low-level treadmill exercise (TM).

Test Protocols

Patients received 0.56 mg/kg of dipyridamole infused intravenously over 4 min. Two minutes following the infusion, patients assigned to Group HG began isometric handgrip exercise at 25% of their predetermined maximum and continued for a total of 4 min. Patients assigned to Group TM began treadmill exercise at either Bruce Stage 0 or Stage 1, depending on their exercise capacity. Treadmill exercise began 1 min following completion of the dipyridamole infusion, and continued to 1 min postinjection of thallium unless angina, hypotension, or patient fatigue intervened. Patients assigned to Group D lay supine for the duration of the test. Thallium-201 (74 MBq) was injected 8 min 30 sec after initiation of the dipyridamole infusion in all patients. Figure 1 summarizes the testing protocol.

Continuous electrocardiographic (ECG) monitoring, as well as recording of blood pressure and heart rate response was performed on all patients. Horizontal or downsloping ST-segment depression of ≥1 mm at 80 msec after the J point was noted. All side effects of the dipyridamole infusion were recorded, and those that were severe or sustained were treated with intravenous aminophylline at the discretion of the supervising physician. Sublingual nitroglycerine was administered when chest pain did not respond to intravenous aminophylline.

Thallium Imaging

Immediately following completion of the test protocol a single anterior image of the chest and upper abdomen was acquired with a wide field of view integrated gamma camera computer

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For reprints contact: Sheryl Stern, MD, Nuclear Medicine Section, Health Sciences Centre, 820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada.

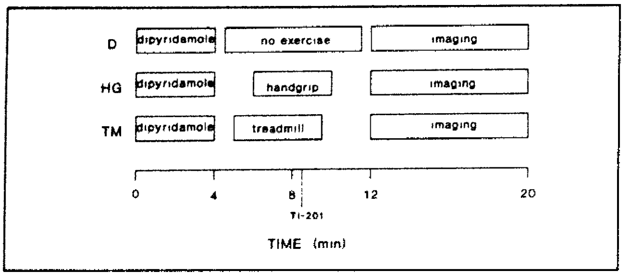

FIGURE 1. Protocols for the three patient groups. D = dipyridamole infusion alone; HG = dipyridamole infusion supplemented with isometric handgrip exercise; and TM = dipyridamole infusion supplemented with low-level treadmill exercise.

system equipped with a low-energy general purpose collimator (Elscint 409, Markham, Canada). Images were obtained in a 256 × 256 byte mode without zoom to a preset time of 480 sec. Routine myocardial images in three standard projections were then collected followed by redistribution images 4 hr later.

Image Analysis

Quantitative and semiquantitative analyses of the initial 256 × 256 computer images were performed as follows.

Quantitative Analysis. Circular ROIs were placed over peak anterior and inferior wall myocardial activity. The higher of the two values was used to represent peak heart activity. Circular ROIs were then placed over representative areas of both lung fields to generate the average counts per pixel of lung activity. A separate ROI was placed over peak liver activity, being careful to avoid overlap from bowel or kidney. Ratios of heart-to-lung (H/LUNG) and heart-to-liver (H/LIV) were generated. To generate the heart-to-adjacent infradiaphragmatic (H/ADJ) ratio, a circular ROI was placed over the entire myocardium, and a background ROI generated six pixels away from the inferior border of the heart. This background ROI was drawn six pixels wide in an arc extending from 15° to 105° from the myocardial apex. The ratio of peak H/ADJ was calculated. ROI placement are illustrated in Figure 2.

Semiquantitative Analysis. Images were assessed by two independent observers blinded to the test protocols. Heart-to-total infradiaphragmatic activity was graded semiquantitatively using a three-point scale as follows: 1 = poor, 2 = average, 3 = excellent.

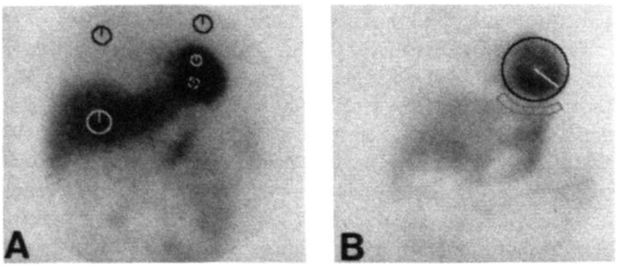

FIGURE 2. Quantitative image analysis. Sample ROIs generated for quantitative analysis of computer images. (A) ROIs placed over peak anterior and inferior myocardial activity, peak liver activity, and representative areas of both lung fields. (B) ROI drawn in an arc below the inferior border of the heart to generate the adjacent infradiaphragmatic activity.

Results from the two observers were averaged for each patient and the mean calculated for each group.

Statistical Analyses

Analyses of means were performed using the Student's t-test. Analysis of discrete quantitative data was accomplished using multiple chi-squared tests.

RESULTS

Seventy-eight patients were randomized to the three protocol groups, resulting in 26 patients assigned per group. Twenty-five of the 26 patients assigned to group HG were able to complete the full 4 min of isometric handgrip. One patient had difficulty in comprehending the instructions and was not able to sustain 25% of his maximum effort for the full time period. This patient was eliminated from the study. Twenty of the 26 patients assigned to Group TM were able to complete some degree of exercise. The six remaining patients were unable to perform treadmill exercise due to arthritis (three patients), claudication (one patient), foot ulcer (one patient), and significant chest pain during the dipyridamole infusion (one patient). These were excluded from the study.

The age and sex distribution of patients in each of the three protocol groups is presented in Table 1.

The hemodynamic response at various stages during each of the test protocols is presented graphically in Figure 3. To determine peak response, we examined hemodynamic data from completion of the dipyridamole infusion to completion of the test protocol. Peak heart rate response for all patients was defined as the maximum heart rate achieved during this time interval. Peak blood pressure response for patients receiving dipyridamole alone (in whom a decline in blood pressure was expected) was defined as the minimum blood pressure recorded during this time interval. For patients undergoing exercise intervention, peak blood pressure response was defined as the maximum blood pressure recorded during the designated exercise. The time at which the peak hemodynamic response was achieved differed among individual patients.

Following initiation of the dipyridamole infusion, heart rate rose in all three groups, but most notably in the group undergoing treadmill supplementation. Systolic blood

TABLE 1
Age and Sex Distribution

		Group		
		D	HG	TM
Age				
	Mean	61	61	64
	Range	28–83	32–86	44–81
Sex				
	Female	13	13	9
	Male	13	12	11

D = dipyridamole infusion alone; HG = dipyridamole + handgrip exercise; and TM = dipyridamole + treadmill exercise.

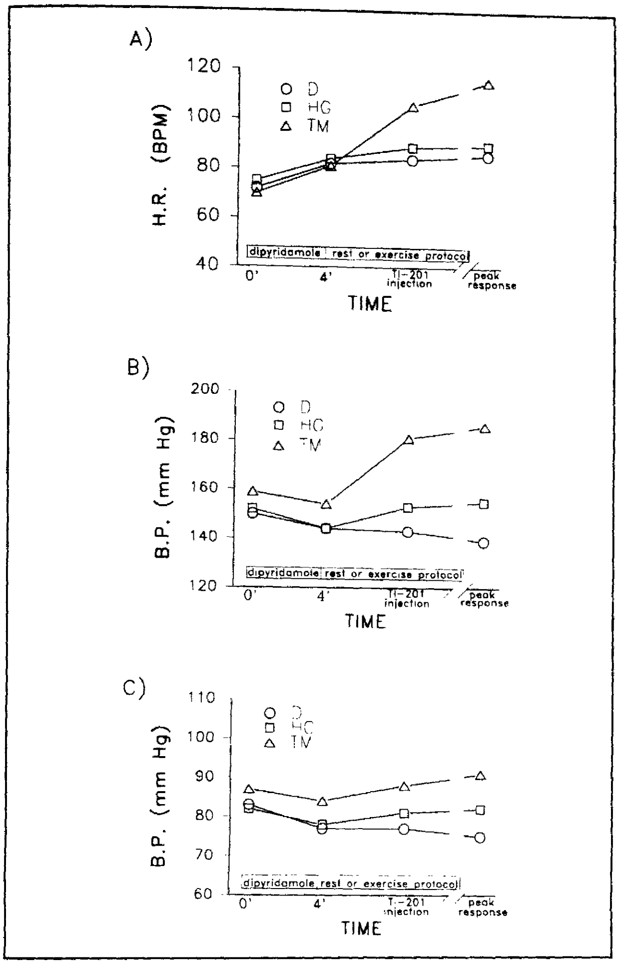

FIGURE 3. Hemodynamic response. The hemodynamic response at various stages during each of the test protocols is presented. (A) Heart rate response. (B) Systolic blood pressure response. (C) Diastolic blood pressure response. Thallium-201 was injected 8 min 30 sec after the start of the dipyridamole infusion.

pressure for all three groups was similar ($p > 0.1$) at rest and dropped initially in response to the dipyridamole infusion. Systolic pressure continued to decline in the group receiving dipyridamole without exercise supplementation, but rose significantly ($p < 0.001$) in response to treadmill intervention and remained essentially unchanged in the group undergoing handgrip exercise. Diastolic blood pressure followed a similar but more blunted pattern. None of the patients in our study experienced symptomatic hypotension during any of the protocols. The hemodynamic response at the time of ^{201}Tl injection was not significantly different from the peak hemodynamic response recorded in each of the three groups.

All side effects experienced during the test protocols were recorded. Whenever possible, differentiation was made between cardiac and non-cardiac chest pain, and the results of this and other side effects are presented in Table 2, including the number of patients requiring aminophylline. Chi-squared analysis of the data showed no significant difference in the incidence of side effects or in the administration of aminophylline between the three groups.

TABLE 2
Incidence of Side Effects

	Group		
	D (n = 26)	HG (n = 25)	TM (n = 20)
Angina	6 (23%)	6 (24%)	7 (35%)
Non-cardiac chest pain	2 (8%)	2 (8%)	0 (0%)
Headache	1 (3.8%)	0 (0%)	2 (10%)
Dizziness	0 (0%)	0 (0%)	1 (5%)
Nausea/flushed feeling	0 (0%)	0 (0%)	1 (5%)
Aminophylline administered	8 (31%)	10 (40%)	9 (45%)

ST depression of ≥1 mm during the procedure was recorded. Patients with resting ECG changes which precluded interpretation of the ST-segment were omitted from this analysis. The results are presented in Table 3. There was a significantly higher proportion of patients with ST depression in the TM group than in either of the other two categories ($p < 0.025$).

The results of the quantitative assessments of target-to-background ratios for each of the three groups are presented graphically in Figure 4. Mean values of the quantitative and semi-quantitative assessments were compared using the Student's t-test and are presented in Table 4. Semiquantitative assessment of heart-to-total infradiaphragmatic activity showed a significant improvement in image quality in Group TM over dipyridamole alone (D) ($p < 0.001$) and dipyridamole combined with isometric handgrip (HG) ($p < 0.001$). Quantitatively, treadmill exercise was associated with a significant increase in H/LIV and H/ADJ activity compared with dipyridamole alone ($p < 0.001$ for both) and dipyridamole supplemented with isometric handgrip ($p < 0.001$) for both). No difference in image quality was seen between dipyridamole alone, and dipyridamole combined with isometric handgrip when assessed quantitatively or semiquantitatively. The ratio of H/LUNG activity was similar in all three groups.

Examples of typical images obtained with the three protocols are presented in Figure 5.

The amount of treadmill exercise performed by patients assigned to this group varied from a minimum of 1 min 15 sec at Bruce Stage 0, to a maximum of 1 min 30 sec at Bruce Stage 2. Only 3 of 20 patients achieved their target heart rate of 85% predicted maximum for age and sex. We attempted to correlate various components of the exercise

TABLE 3
Incidence of ST-Segment Depression

Group	n	no.	%
D	25	3	(12%)
HG	24	4	(17%)
TM	17	9	(53%)

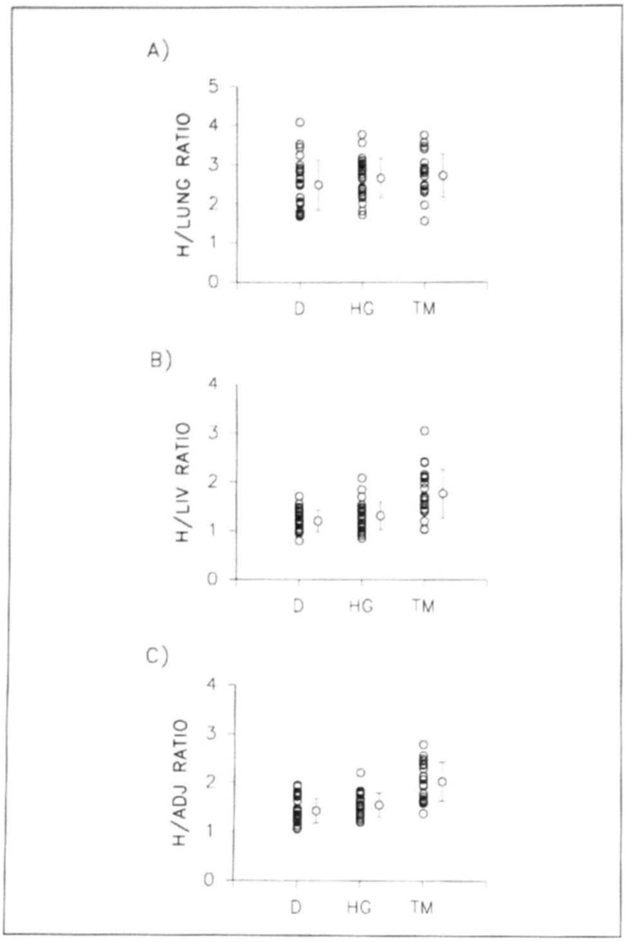

FIGURE 4. Target-to-background ratios. (A) Heart-to-lung (H/LUNG) ratio. (B) Heart-to-liver (H/LIV) ratio. (C) Heart-to-adjacent infradiaphragmatic activity (H/ADJ) ratio.

response with improvement in image quality as judged by the H/LIV and H/ADJ ratios. Peak heart rate and peak blood pressure were compared to image quality and showed no correlation.

The double product (heart rate × blood pressure) at the time of ^{201}Tl injection was also compared to these target-to-background ratios and showed a modest ($r = 0.41$) but not statistically significant ($p > 0.05$) correlation with H/LIV ratio. It was not possible to accurately quantitate the energy expenditure of individual patients for correlation with image quality since most did not reach a steady state. Instead, patients were ranked according to the maximum workload performed and compared (using rank correlation) to H/LIV and H/ADJ ratios. Using this method, there was a modest ($r = 0.41$), but not statistically significant ($p > 0.05$) correlation with H/LIV ratio.

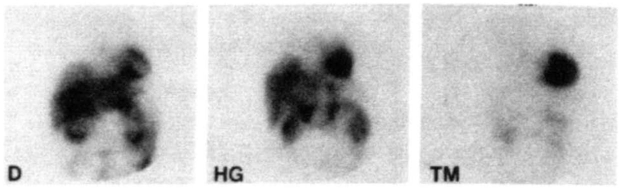

FIGURE 5. Representative images from each of the three groups.

DISCUSSION

Dipyridamole is a potent coronary vasodilator and enhances myocardial blood flow in regions supplied by normal coronary arteries, but not in myocardial regions perfused by coronary arteries with significant stenoses. This results in flow heterogeneity that can be imaged using ^{201}Tl providing a valuable alternative to exercise testing for patients unable to perform an adequate level of exercise (*5–10*). Nonspecific vasodilatation of systemic vessels, however, results in increased thallium uptake by the splanchnic bed, yielding images with high infradiaphragmatic background activity (*13*).

Several investigators have proposed the addition of low-level exercise to improve image quality. Gould et al. (*8*) were the first to describe a protocol for dipyridamole thallium imaging and demonstrated higher myocardial-to-lung ratios when patients stood upright or walked in place following the infusion. While our study also demonstrated improved target-to-background ratios with exercise, this improvement was limited to ratios of heart-to-abdominal

TABLE 4
Qualitative and Quantitative Assessment of Target-to-Background Ratios

	n	H/LUNG	H/LIV	H/ADJ	SQ*
D	26	2.48 ± .64	1.20 ± .22	1.43 ± .25	1.8 ± .43
HG	25	2.65 ± .51	1.31 ± .28	1.54 ± .25	1.9 ± .42
TM	20	2.71 ± .55	1.76 ± .50	2.03 ± .40	2.5 ± .35
p HG vs. D†		ns	ns	ns	ns
p TM vs. D†		ns	<0.001	<0.001	<0.001
p TM vs. HG†		ns	<0.001	<0.001	<0.001

All results are presented as mean ± s.d.
* Semiquantitative analysis.
† Statistical analyses of means performed using Student's t-test.

activity, with no significant improvement seen in the H/LUNG ratio with either isometric handgrip or treadmill exercise.

Brown et al. (*14*) examined coronary flow invasively during catheterization and reported increased coronary flow without significant effect on cardiac output when isometric exercise was combined with dipyridamole. Although not measured directly in their study, they proposed this combined protocol would optimize image quality by increasing target to background ratios. Recently, Rossen et al. (*15*) examined coronary flow using a Doppler catheter and reported no difference in flow between dipyridamole alone and dipyridamole supplemented with isometric handgrip. The patient populations as well as the methodology for assessing coronary flow differed in these studies, which may explain the discrepant results. In our study, the addition of isometric handgrip exercise did not improve target-to-background ratios.

Casale et al. (*13*) examined the effect of exercise supplementation using low-level treadmill exercise and reported higher H/LIV ratios in patients undergoing treadmill exercise supplementation compared with dipyridamole alone. They proposed that low-level treadmill exercise caused vasoconstriction of the splanchnic bed with perhaps improved myocardial uptake from higher aortic perfusion pressure. Their study however was not randomized and did not examine target-to-background regions outside the liver.

Our prospective study randomized patients to three test protocols—dipyridamole alone, dipyridamole with isometric handgrip, and dipyridamole supplemented with low-level treadmill exercise. We compared the effect of these exercise interventions on image quality using various measures of heart to abdominal activity, including H/LIV, H/ADJ activity, and a visual assessment of heart-to-total infradiaphragmatic activity. Supplementation of dipyridamole testing with low-level treadmill exercise improved image quality compared with either dipyridamole infusion alone or dipyridamole supplemented with isometric handgrip. No difference was seen between dipyridamole supplemented with isometric handgrip and dipyridamole alone. Because of the small number of patients in each of our study groups, no attempt was made to assess the impact of these exercise interventions on the diagnostic accuracy of the test.

Although patients are routinely referred for dipyridamole testing because of an inability to perform an adequate treadmill test, 77% of patients randomized to treadmill supplementation in our study were able to perform a modest degree of exercise, sufficient to produce significant improvement in image quality. While it is evident that a relationship exists between exercise performance and improved image quality, because of the small number of patients involved, further quantification of the amount of exercise necessary to produce this improvement was not possible. A more detailed study of this question—how much exercise is enough—is currently under investigation at our institution.

The incidence of cardiac and non-cardiac side effects did not differ between groups although there was a significantly higher percentage of ST-segment depression in the group of patients undergoing treadmill exercise. Since the incidence of angina was not significantly higher in this group, it is unclear whether this represents a truly higher incidence of inducible ischemia (presumably silent ischemia), or a nonspecific electrocardiographic response. As only 23 (29%) patients subsequently underwent coronary angiography, there were insufficient numbers to assess the sensitivity and specificity of the ST-segment depression.

In addition to exercise supplementation, two other approaches to improving results with dipyridamole thallium scintigraphy are high-dose dipyridamole infusion and tomographic imaging. The first modality involves increasing the dose of dipyridamole infused. It is recognized that there is a small subset of patients who will not have a maximal vasodilator response to the standard dipyridamole dose (*15,16*) and in these patients a higher dose regimen would be required to induce flow heterogeneity. There are no currently accepted criteria for the noninvasive identification of this subset. Furthermore, it is uncertain whether the target-to-background ratio would improve since the vasodilator response would likely affect the visceral and coronary vasculature similarly. Nevertheless, if subsequent studies document the safety of the higher dose regimen, a combined protocol using exercise supplementation with a high dose dipyridamole may optimize image quality and diagnostic accuracy.

A second approach to improving image quality would be through the use of tomographic imaging. This would allow better separation of heart from infradiaphragmatic structures on the reconstructed images. However, it has been shown that tomographic reconstruction may result in an apparent increase in count density in myocardial regions underlying increased visceral activity (*17*). Thus, exercise supplementation to decrease infradiaphragmatic activity would still appear to be worthwhile with SPECT dipyridamole thallium imaging.

We conclude that the addition of treadmill exercise is both a safe and effective means of improving image quality in patients undergoing dipyridamole testing. There is a small subset of patients unable to perform any treadmill exercise, and supplementation with isometric handgrip in this group does not provide any advantage in image quality over dipyridamole alone.

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EDITORIAL

Exercise Supplementation of Dipyridamole for Myocardial Perfusion Imaging

Intravenous dipyridamole provides a good alternative to treadmill exercise. Several studies have demonstrated that the diagnostic accuracy of ^{201}Tl scintigraphy performed with intravenous dipyridamole is equivalent to that performed in conjunction with treadmill exercise.

Dipyridamole infusion is technically simple and is associated with a low incidence of both cardiac and non-cardiac side effects. A threefold increase in coronary blood flow is achieved, comparable to that associated with maximal treadmill exercise (*1*). So why do some investigators feel that intravenous dipyridamole alone is insufficient and that supplementation with handgrip or treadmill exercise is advantageous? The following arguments have been offered:

1. The additive influence of exercise in further increasing coronary blood flow theoretically should allow for better differentiation of normal myocardium from vascular territories that are infarcted or supplied by stenotic coronary arteries. A similar argument has been offered to support the use of intravenous adenosine, a coronary vasodilator more potent than dipyridamole. However, at high coronary flow rates, exceeding 3.5 ml/min/gm of myocardial tissue, ^{201}Tl uptake begins to plateau despite further increases in blood flow, so the theoretical advantage of higher coronary flow rates might not be realized clinically with ^{201}Tl scintigraphy.

2. A minority of patients are dipyridamole "non-responders." In 12 patients in whom coronary blood flow reserve associated with dipyridamole infusion was measured, Rossen et al. demonstrated that two patients (17%) achieved peak flow rates of less than 2.0 ml/min/gm, compared to a mean ± s.d. of 3.7 ± 1.2 ml/min/g in the entire group (*2*). Poor coronary vasodilatory response to dipyridamole is also seen occasionally in routine ^{201}Tl studies and may be manifested by a poor myocardial-to-background ratio and diffusely diminished myocardial washout. The reason for such a poor coronary vasodilatory response in some patients is unknown. However, the addition of exercise to intravenous dipyridamole theoretically has the potential of improving test sensitivity by decreasing the number of "non-responders."

3. Dipyridamole decreases not only coronary but also systemic vascular resistance. Brown et al. measured systemic vascular resistance before and after dipyridamole infusion and measured a decrease from 15 ± 5 mmHg/liter/min to 10.9 ± 4.0 mmHg/liter/min ($p < 0.001$) mean ± s.d. (*1*). This results in increased ^{201}Tl uptake in tracer-avid organs other than the heart, including the liver. Since the liver lies immediately below the inferior wall of the left ventricle, myocardial image quality can be degraded due to Compton scatter and even actual overlap of the superior portion of the liver and the inferior wall of the left ventricle. Moreover, linear interpolative background subtraction algorithms used for exercise ^{201}Tl planar studies which demonstrate relatively little liver uptake may introduce error into dipyridamole studies. Because of the high count density in the liver, background will be oversubtracted from the inferior wall, resulting in artifactual inferior

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For reprints contact: E. Gordon DePuey, MD, St. Luke's-Roosevelt Hospital, Department of Nuclear Medicine, Amsterdam Avenue at 114th St., New York, N.Y. 10025.