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Comparing a High-Dose Dipyridamole SPECT Imaging Protocol with Dobutamine and Exercise Stress Testing Protocols

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ABSTRACT

Objective. To determine the safety, sensitivity, specificity, and accuracy of high-dose dipyridamole compared with treadmill and dobutamine stress imaging protocols.

Background. Nuclear imaging studies using standard dose dipyridamole provide similar results to those obtained when treadmill stress is used. Recently dobutamine tomography and planar imaging with high-dose dipyridamole have been shown to improve nuclear imaging results.

Methods. One hundred fifty-nine patients were imaged with thallium, teboroxime, or sestamibi per standard single photon emission computed tomography (SPECT) protocols. Pharmacologic stress was performed in 85 people with the remainder undergoing exercise testing by Bruce protocol. In this study, 0.852 mg dipyridamole was used per kilogram body weight and was infused over a four-minute period. Results from nuclear imaging were compared with those from coronary arteriograms.

Results. The sensitivity and specificity of high-dose dipyridamole was 100% and 88.9%, respectively, which is statistically greater ($P < 0.005$) than that achieved when patients were stressed by treadmill. Side effects with the higher dose of dipyridamole were easily reversed with aminophylline. The sensitivity and specificity of intravenous dobutamine was 100%, but it was used in a limited number of subjects. When patients were stressed by Bruce protocol the sensitivity was 92.5% and specificity was 42.8%. The differences were not attributable to inadequate exercise duration.

(continued on next page)

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(Abstract continued)

Conclusions. High-dose dipyridamole is safe and easily reversed with intravenous aminophylline. The sensitivity and specificity of dipyridamole and dobutamine stress testing were statistically more accurate than results obtained with treadmill protocols when SPECT is used to image the heart.

High-dose dipyridamole resulted in greater changes in heart rate and blood pressure response than seen with standard-dose dipyridamole. Associated side effects can be easily reversed with the administration of intravenous aminophylline without significant complications. The sensitivity, specificity, and accuracy of single photon emission computed tomography using high-dose dipyridamole are 100%, 88.9%, and 97.9%, respectively, for the overall presence or absence of disease when compared with coronary arteriography. This is significantly ($P < 0.005$) greater than that obtained by treadmill nuclear imaging protocols, independent of imaging agent.

Introduction

Conventional planar and single photon emission computed tomography (SPECT) imaging with thallium treadmill testing has yielded sensitivities between 75 and 90% with specificities of 45–85% since the mid-1970s. These results have not changed appreciably despite the introduction of techetium tracers in the late 1980s. Regardless of whether thallium,[1-6] teboroxime,[7-10] or sestamibi[11-13] is used, the results are similar and do not appear to be significantly influenced by observer variability.[10,14]

Previous work with pharmacologic stressors has primarily been used for subjects with limited exercise capacity, those with reactive airway disease, or those having positron emission tomography (PET) studies. The use of dipyridamole to increase coronary blood flow was first described[15] in 1978. At that time, it was shown that increases in blood flow were greater with dipyridamole infusion than with exercise. The results of standard dose (0.56 mg/kg body weight infused over four minutes) dipyridamole have been found to be similar[16] to those obtained with exercise stress nuclear imaging. Recent work in echocardiography[17-19] and planar imaging[20] demonstrated improved sensitivity and specificity by increasing the dose of dipyridamole. Work with intravenous (IV) dobutamine[21] revealed similar results.

The purpose of this study was to prospectively examine the results of SPECT in pharmacologically (dobutamine and high-dose dipyridamole) and nonpharmacologically (treadmill) stressed patients suspected of having coronary artery disease (CAD). Additionally, we wanted to assess the potential side effects of dobutamine and high-dose dipyridamole.

Methods

Study Patients

In total, 159 patients were studied between December 1992 and March 1993. Subjects were excluded from the study if they were deemed clinically unstable, had "severe" aortic stenosis or cardiomyopathy, or were pregnant. All individuals fasted for at least twelve hours prior to nuclear perfusion imaging. All medications affecting heart rate and blood pressure were discontinued for thirty-six hours prior to nuclear imaging. The study protocol was approved by the local ethics committee, and all patients consented to the study after having the risks and benefits explained. The selection of nuclear imaging agent and stressor was determined by the attending physician.

Coronary Arteriograms

One hundred and fifteen of the subjects underwent coronary arteriography prior to or immediately following the nuclear study without intervening changes in clinical status. The remaining subjects elected not to undergo invasive studies since they had either previously undergone coronary arteriography and were considered clinically stable or had no evidence of significant disease

by nuclear study and no further evaluation was deemed necessary by the referring physician.

Quantitative Coronary Arteriography

When available, quantitative coronary arteriography was used to define the extent of CAD for each of the three (left anterior descending [LAD], circumflex [CFX], and right coronary [RCA]) arterial beds. This was done in 45% of the 115 coronary arteriograms. Disease was reported as percent diameter stenosis of native or grafted vessels, depending upon the dominant source of blood supply to a given region. For the definition of this study an artery or graft was considered significantly diseased when the most severe narrowing met or exceeded 50% diameter stenosis. This method of quantitation has been described in detail previously.[10,22,23]

Visual Reporting of Coronary Arteriograms

The use of visual reporting was limited to those instances where quantitative coronary arteriography equipment was not available or cost was considered prohibitive; 55% of the coronary arteriograms were visually read for the overall presence or absence of "significant" disease as previously defined. Visual interpretation required agreement by both readers. In none of the instances was a third interpreter required. This method of reporting was considered acceptable only for the defining of the overall presence or absence of disease since visual and quantitative methods are not statistically different[22] when all three arterial beds are considered to be free of significant disease.

Pharmacologic Stress Testing

Eighty-five of the 159 studies were performed with the aid of pharmacologic stress, while 74 subjects were stressed by Bruce protocol.

Dipyridamole Infusion Protocol

Dipyridamole (0.852 mg/kg) was added to normal saline to make a 60 cc solution. This was administered continuously over four minutes. As noted in Figure 1, protocol A, thallium or sestamibi was injected at six minutes. Reversal of the dipyridamole with aminophylline was done at eight minutes and again if necessary at ten minutes. IV aminophylline was given for "chest discomfort/pressure/angina" or for ischemic (eg, ST depression of at least 1 mm in two contiguous leads) electrocardiographic (ECG) changes. In each case the aminophylline was given as a "bolus" over ten seconds. Thallium imaging was begun at twelve minutes and sestamibi imaging at one hour.

Teboroxime (Figure 1, protocol B) was injected at six minutes and immediately flushed with 20 cc of normal saline. Following this, aminophylline was immediately given to prevent "washout" as described previously.[24] Stress imaging with teboroxime was started at six and one-half minutes. Teboroxime rest imaging was started forty-five minutes later. Continuous ECG, blood pressure, and heart rate monitoring was performed from the beginning of dipyridamole infusion through the completion of imaging for both thallium and teboroxime studies. Patients receiving sestamibi were monitored until vital signs and electrocardiogram returned to prestress levels.

Exercise Physiology Study

Subjects were exercised by the "Bruce" protocol. Patients were exercised to 100% of their maximum predicted heart rate, until limited by symptoms (angina, dyspnea, fatigue, leg pain) or until ischemic changes were noted on the electrocardiogram, as defined above. The sequence for tracer injection and imaging times is shown in Figure 1, protocol C. Thallium or sestamibi was injected approximately one minute prior to peak exercise, and teboroxime was injected at peak exercise. Stress imaging for teboroxime was started two minutes after exercise was stopped, whereas thallium and sestamibi imaging was started at ten and thirty minutes, respectively. Sublingual nitroglycerin (NTG) was available for use as needed. ECG, blood pressure, and heart rate monitoring was done during the exercise and recovery periods until the patient returned to prestress levels.

Dobutamine Infusion Protocol

Figure 1, protocol D, depicts the sequence involved with dobutamine stress imaging of the heart. A mixture of 250 mg dobutamine was mixed in 250 mL of 5% dextrose. Infusion rates began at 5 μg/kg/minute and were titrated up every three minutes to 10, 20, 30, and finally 40 μg/kg/minute, as tolerated by the patient.

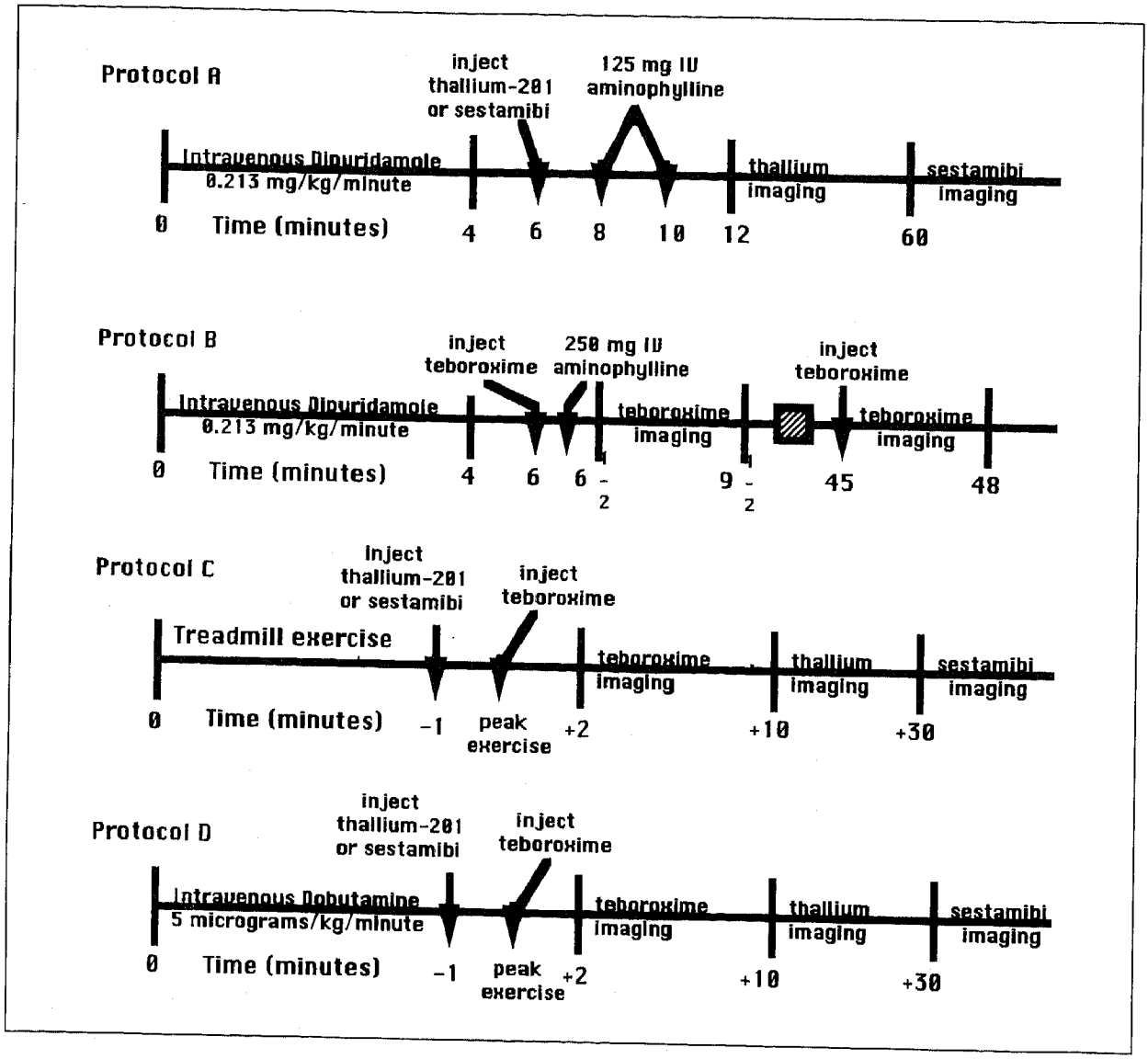

Figure 1. Fleming Protocols. Protocols A and B display the time sequence used for pharmacologic stress testing with high-dose dipyridamole. The time for injection of tracer, reversal of dipyridamole with aminophylline, and imaging times are depicted. Protocols C and D reveal the sequence of events used with treadmill and dobutamine stress respectively, for nuclear imaging with thallium, teboroxime, and sestamibi.

Infusion was discontinued for "chest discomfort/pressure/angina," dyspnea, an increase in ventricular ectopy, hypertensive response (systolic pressure > 220 mmHg, diastolic pressure > 110 mmHg), or for ischemic ECG changes as previously defined. No patient's heart rate reached 100% of the maximally predicted level, excluding this as a parameter for discontinuing dobutamine infusion.

Like treadmill testing, thallium and sestamibi were injected one minute prior to cessation of dobutamine, whereas teboroxime was injected at peak infusion rate. Sublingual NTG was available for angina as needed. The sequence for imaging was the same as noted for treadmill testing. ECG, blood pressure, and heart rate monitoring was carried out for the exercise and recovery periods until the patient returned to prestress levels.

Thallium 201 Imaging

Thallium 201 stress imaging was done with 3.0 mCi (±5%), and rest imaging used 1.0 mCi (±5%) of thallium. All patients undergoing thallium imaging were initially stressed with one of the previously described protocols. Imaging was completed using either of two commercially available cameras. In total, 32 acquisitions were obtained at forty seconds each, over 180 degrees beginning in the right anterior oblique (RAO) position with a 128 by 128 matrix. Images were processed with a filter and high-resolution collimator. Standard back-projection techniques were used for all three radionuclides regardless of camera, to obtain transaxial tomographic images. All patient images were displayed in conventional short-axis, horizontal, and vertical long-axis views. Reinjection for rest imaging was done four hours after stress. Images were acquired and processed in the same manner as that used for stress imaging.

Teboroxime Imaging

Teboroxime was prepared according to manufacturer specification[10] as described previously. All patients were stressed by one of the protocols described above. Both stress and rest injections consisted of 25 mCi (±5%) of teboroxime. When dipyridamole was used to stress the patient, a different camera was used, beginning six and one-half minutes after initiation of dipyridamole infusion. Continuous image acquisition began in the left posterior oblique (LPO) position and rotated to the RAO position over three minutes. A 64 by 64 matrix, filter, and general all-purpose collimator were used. Rest imaging was begun forty-five minutes after completion of the stress study, with the same parameters for acquisition and processing.

When dipyridamole was not used, images were obtained with either of two commercially available cameras. In total, 32 acquisitions at fifteen seconds each, over 180 degrees beginning in the RAO position was used. The matrix was 128 by 128. Images were processed with a filter and high-resolution collimator. Rest imaging was started one hour after the stress study using the same method for acquisition and processing.

Sestamibi Imaging

Sestamibi was prepared according to the specifications of the manufacturer[20] as previously described. Individuals were initially imaged at rest one hour after receiving 10 mCi (±5%) of sestamibi. Imaging was completed with a commercially available camera. In total, 32 acquisitions were obtained at forty seconds each in a manner identical to that described above for thallium. Stress images by one of the previously noted protocols was begun three to four hours after the rest image was completed. No food was given between the rest and stress images. Subjects were given a 30 mCi (±5%) injection of sestamibi and reimaged thirty minutes after exercise or dobutamine or one hour after dipyridamole. Stress image acquisition required only thirty seconds for each of the 32 frames .

Nuclear Image Interpretation

Reconstructed images were reviewed by three independent readers who rated 9 regions on a continuous scale from 0 to 5, where 0 was defined as normal and 5 defined as a severe defect. The results were averaged with values from 0–2 defined as negative and 3–5 as positive for perfusion defects consistent with disease. The regions of interest were matched in the following manner. The LAD artery distribution was defined as anterior, anteroseptal, and septal; the RCA as inferoposterior and posteroseptal; and the CFX as anterolateral, lateral, and posterolateral regions. The apex was matched from arteriograms to the appropriate artery.

Statistical Analysis

Cumulative ECG changes, symptoms, and changes in heart rate and blood pressure response were recorded for each of the pharmacologic stressors. Values and changes in hemodynamic parameters were reported as mean ±standard deviations. The two-tailed Student's t test was used to analyze differences between groups. Variance was analyzed by F-ratio testing. Chi-square analysis with continuity correction was used to determine whether differences between stressors existed.

Results

One hundred and fifty-nine patients were studied with use of three different radionuclides over a four-month period. Table I displays the breakdown by age and sex for each of the three stres-

Table I

Distribution of Patients for Each of the Three Stressors

	Dipyridamole	Dobutamine	Treadmill
Age (mean years)	64.7	67.9	56.1
Men	41	6	50
Women	34	4	24

Table II

Changes in Hemodynamic Parameters for the Different Stressors

	Percent Change in Heart Rate	Percent Change in Systolic Pressure	Percent Change in Diastolic Pressure
Dipyridamole	45.5 ±22.2	−8.3 ±11.3	−9.6 ±8.0
Dobutamine	77.0 ±28.8	19.4 ±31.4	−8.9 ±14.3
Treadmill	89.5 ±35.1	31.3 ±18.5	4.22 ±11.3

Values are displayed as mean ±standard deviation.

sors. Younger people tended to be selected more commonly for treadmill studies, although no difference in group assignment by sex or prevalence of disease was noted. The results of the different tracers were similar and did not display statistically significant differences despite differences in their physical and biological properties. Almost equal numbers of patients were stressed by dipyridamole as by treadmill. Ten patients (6 men, 4 women) were stressed by dobutamine. All 10 patients had limited exercise endurance and/or significant lung disease.

The percent changes in heart rate and blood pressure seen with exercise, dobutamine, and high-dose dipyridamole are shown in Table II. With high-dose dipyridamole, increases in heart rate averaged 45%, while decreases in both systolic and diastolic blood pressure averaged 8% to 10%.

There was a statistically ($P < 0.01$) significant difference in changes in heart rate achieved with dipyridamole as compared with either dobutamine or treadmill exercise; however, there was no significant difference between dobutamine and exercise. There was greater variability ($P < 0.01$) in heart rate response seen with treadmill stress than with dipyridamole. There was no significant difference between changes noted in systolic pressure with dobutamine and exercise stress. However, there was a significant ($P < 0.01$) decrease in systolic pressure when dipyridamole was used. A wider variability ($P < 0.01$) in systolic pressure response was seen with dobutamine and treadmill stress when compared with dipyridamole. Both dobutamine ($P < 0.02$) and dipyridamole ($P < 0.01$) exhibited significant decreases in diastolic pressure when compared with changes seen with treadmill studies. As with systolic pressure, dobutamine and treadmill were associated with wider ranges ($P < 0.01$) in diastolic response than seen with dipyridamole .

The frequency of reported side effects for the pharmacologic stressors is shown in Table III.

Table III

Percent Reported Side Effects from Dobutamine and High-Dose Dipyridamole

	Dipyridamole	Dobutamine
Chest pressure	41.3	20.0
ST depression	25.3	20.0
Headache	9.3	0.0
Nonspecific ST changes	6.7	0.0
Nausea	6.7	0.0
Dyspnea	5.3	0.0
Increased ventricular ectopy	4.0	40.0
Flushing	2.7	0.0

When dobutamine was used, the most frequent side effect was an increase in ventricular ectopy, which resolved within minutes of discontinuing the infusion. No patient receiving dobutamine required sublingual NTG for relief of angina. Both symptoms and ECG changes returned to baseline within two to three minutes of discontinuing the infusion. The incidence of side effects for high-dose dipyridamole is consistent with that previously reported.[20] The most common side effect was angina, with or without ECG changes. When symptoms without ECG changes were reported, a single bolus of 125 mg aminophylline given over ten seconds completely reversed symptoms within one to two minutes. Those individuals having ECG changes consistent with ischemia as defined above and still present after the initial dose of aminophylline were given a second bolus of aminophylline two minutes after the initial dose. This led to resolution of the ECG changes in all but 1 case. This patient was given one sublingual NTG tablet, resulting in resolution of angina and ECG changes without further problems. Followup coronary arteriography demonstrated a 90% narrowing of her proximal LAD artery, which was successfully angioplastied. No patient suffered significant side effects from the aminophylline bolus, although 2 subjects reported a metallic taste that spontaneously resolved.

When the results of SPECT images were compared with results obtained by coronary arteriography, no statistical difference between nuclear tracers was detectable. When the overall presence or absence of disease was compared by visual and quantitative method, results did not change. When results of different stressors were compared, there was a statistical difference between results obtained when people were stressed by treadmill as compared with pharmacologic stress. The resulting sensitivity and specificity for dobutamine were 100% each, although it was only used in 10 patients. The sensitivity and specificity were 100% and 88.9%, respectively, for dipyridamole. Both dobutamine and high-dose dipyridamole produced statistically significantly ($P < 0.005$) better results than stress by treadmill, which yielded a sensitivity of 92.5% and specificity of 42.8%. Only 1 patient with a false-nega-

Table IV

Chi-Square Analysis of Nuclear Results Following Pharmacologic Stress vs Treadmill Stress

	Chi-Square Value	Level of Significance
Dobutamine vs treadmill	29.6	$P < 0.005$
Dipyridamole vs treadmill	17.0	$P < 0.005$

tive exercise study was unable to reach 85% of his maximally predicted heart rate. Table IV shows the results of chi-square analysis used to assess differences between nuclear results obtained after dobutamine and dipyridamole stress and after treadmill stress.

Discussion

One hundred fifty-nine patients were studied by use of one of three available forms of physiologic stress prior to receiving one of three equally diagnostic imaging agents currently used for SPECT imaging of the heart. Younger patients tended to be stressed by treadmill, whereas older patients were stressed with pharmacologic agents. Patients with limited exercise endurance and significant lung disease were stressed by dobutamine. Women and men were equally stressed by each of the three approaches. No adverse side effects were associated with any of the three forms of stress.

High-dose dipyridamole can be safely used, even with angina occurring in approximately 40% of the cases. This can be easily controlled and reversed with a single bolus injection of 125 mg IV aminophylline in most cases. In those instances where significant ST changes are seen on the electrocardiogram, a second dose of aminophylline is usually required two minutes after the first. Sublingual NTG may rarely be required but should be available if needed.

With high-dose dipyridamole, an average increase in heart rate of 45% can be expected. This is greater than that seen at standard infusions where increases of 20% are common. While treadmill and dobutamine stress result in higher increases in heart rate, there is considerably more variability in what these increases might be. All patients undergoing dipyridamole infusion were stressed for four minutes without need to stop prematurely. The predictability of discontinuing treadmill and dobutamine stress could not be determined in advance, regardless of the patient's age, weight, or number of diseased vessels, thereby complicating the timing of injection of nuclear tracer and imaging. Average decreases in systolic and diastolic pressures were greater with high-dose dipyridamole than typically seen with the standard dose. Like heart rate changes, there was less variability associated with high-dose dipyridamole infusion than with either dobutamine or treadmill stress.

Both dobutamine and high-dose dipyridamole gave 100% sensitivity when the overall presence or absence of disease was analyzed by both quantitative and visual methods of interpreting coronary arteriograms. While the limited number of studies performed with dobutamine makes it impossible to draw general conclusions, those patients studied here had excellent results. Dobutamine provided a safe and alternative method for studying those individuals with limited exercise capacity and significant lung disease. Like treadmill stress, however, dobutamine is associated with a wide range of hemodynamic response. Additionally, dobutamine resulted in an increased frequency in ventricular activity in approximately 40% of the cases, although no ventricular tachycardia occurred. Side effects were easily handled by discontinuing the dobutamine infusion.

When high-dose dipyridamole was used in 75 studies, the resultant sensitivity was 100%. The specificity was 88.9%, with an overall accuracy of 97.9%. This is statistically better than results seen

from 74 treadmill stress imaging studies, where the sensitivity was 92.5% and specificity 42.8%. Only 1 of the false-negative results obtained with treadmill stress was associated with an inadequate heart rate response.

Conclusions

Results of planar and SPECT studies have routinely yielded sensitivities and specificities of 75–90% and 45–85%, respectively, despite the use of quantitative approaches, reinjection techniques, and the advent of technetium tracers. Given this information it is logical to conclude that either inadequate changes in heart rate and blood pressure occur, resulting in limited changes in coronary flow reserve, or these values represent the limitations of the technology, or both. The use of high-dose dipyridamole demonstrated significant improvement[20] with planar imaging but has not previously been reported for SPECT imaging. This study demonstrates that significantly better results can be obtained with a slightly higher dose of dipyridamole than that recently reported for planar imaging. The use of this higher dose dipyridamole infusion might also be expected to increase the sensitivity and specificity of other imaging modalities, such as echocardiography and positron emission tomography.

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