Effects of Modified Pharmacologic Stress Approaches on Hyperemic Myocardial Blood Flow

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Pharmacologic stress testing with 0.56 mg/kg of intravenous dipyridamole is frequently used to noninvasively detect coronary artery disease (CAD). However, high-dose dipyridamole (0.80 mg/kg) or the combination of standard-dose dipyridamole (0.56 mg/kg) with the isometric handgrip maneuver might evoke a greater coronary hyperemic response. **Methods:** To evaluate the effect of modified pharmacologic stress tests, myocardial blood flow was quantified in 11 male subjects (mean age: 27 ± 7 yr) during standard-dose dipyridamole (0.56 mg/kg), high-dose dipyridamole (0.80 mg/kg) and standard-dose dipyridamole combined with the isometric handgrip exercise using dynamic PET and a two-compartment model for ^{13}N-ammonia. **Results:** Systolic blood pressure, heart rate and rate pressure product remained unchanged from standard to high-dose dipyridamole but increased with the addition of the isometric handgrip. Myocardial blood flow was unchanged from standard to high-dose dipyridamole but was lower with the addition of the isometric handgrip. **Conclusion:** The hyperemic response induced by standard-dose dipyridamole cannot be further enhanced by high-dose dipyridamole. The addition of the isometric handgrip exercise results in a modest, but significant decline in hyperemic blood flow possibly due to increased extravascular resistive forces or an increase in a mediated coronary vasoconstriction associated with exercise.

Key Words: myocardial blood flow; pharmacologic stress testing; isometric handgrip exercise; positron emission tomography; coronary artery disease

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Myocardial perfusion imaging during pharmacologic vasodilation with dipyridamole is used frequently for the noninvasive detection of coronary artery disease (CAD) with SPECT (*1,2*) or PET (*3–5*). Currently, 0.56 mg/kg of dipyridamole are infused intravenously over 4 min to induce coronary vasodilation and hyperemic myocardial blood flow. This dose schedule is based on findings in animal experiments (*2*). On the other hand, studies with intracoronary flow velocity probes have suggested that higher doses of intravenous dipyridamole might be required in some individuals to induce maximal coronary flow velocity (*6,7*). However, the effect of high-dose dipyridamole on hyperemic myocardial blood flow has not been evaluated systematically in humans.

Studies in isolated dog hearts have demonstrated the dependency of coronary flow during maximal vasodilation on the pressure gradient between the aorta and the right atrium and thus, on the coronary perfusion pressure (*8*). Therefore, increases in mean aortic blood pressure in response to isometric handgrip exercise have been reported to increase myocardial blood flow during pharmacologic vasodilation (*9*). On the other hand, increases in extravascular resistive forces or an increase in alpha-adrenergically mediated coronary vasoconstriction during exercise might attenuate the pharmacologically induced hyperemia (*10,11*).

The effects of such modifications on pharmacologic stress remain to be explored systematically. This can now be accomplished through noninvasive measurements of blood flow in the human myocardium with dynamic PET, ^{13}N-ammonia and an appropriate tracer kinetic model (*12–15*). Accordingly, it was the aim of this study to quantify the response of myocardial blood flow to standard-dose dipyridamole (0.56 mg/kg), high-dose dipyridamole (0.80 mg/kg), and standard-dose dipyridamole combined with isometric handgrip exercise.

METHODS

Study Population

The study population consisted of 11 healthy male volunteers (mean age 27 ± 7 yr). No patient had a history of smoking or elevated serum cholesterol, diabetes, hypertension or cardiac disease. The study participants were therefore at low risk for CAD. None of the participants were on any medication and all refrained from intake of caffeine-containing food or beverages for at least 12 hr prior to the PET study. Each participant signed an informed consent form approved by the UCLA Human Subject Protection Committee.

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Study Protocol

Myocardial blood flow was quantified during standard-dose dipyridamole (0.56 mg/kg), high-dose dipyridamole (0.80 mg/kg) and during standard-dose dipyridamole combined with the isometric handgrip exercise. All participants underwent three PET studies on three different days (within 10 ± 3 days) using ^{13}N-ammonia as a tracer of myocardial blood flow. The sequence of the studies was altered randomly between individuals.

Dipyridamole (both standard and high-dose) was infused intravenously over 4 min with a Harvard infusion pump. Four minutes after the end of the infusion, 10–15 mCi of ^{13}N-ammonia were injected intravenously while serial image acquisition was started. For the hyperemia plus handgrip study, the participants were asked to perform and maintain the isometric handgrip for 4 min as vigorously as possible. This is similar to the handgrip stress as performed in most laboratories for clinical diagnostic dipyridamole studies. The isometric handgrip began 2 min after the end of the dipyridamole infusion and was maintained during the initial 2 min of serial PET image acquisition. This protocol was chosen to ascertain steady-state conditions during the initial 2 min of the tracer delivery and trapping in the myocardium.

Throughout each of the three studies, the electrocardiogram was monitored continuously while heart rate and blood pressure (cuff measurements) were measured at 1-min intervals.

Image Acquisition

All studies were performed on a Siemens/CTI 931/08-12 tomograph which acquires 15 transaxial images simultaneously. The tomograph has an intrinsic in-plane spatial resolution of 6.5 mm FWHM, an inter-plane spacing of 6.7 mm and an axial field of view of 10 cm (*16*). The tomographic images were reconstructed using a Shepp filter with a cut-off frequency of 0.3 Nyquist, resulting in an effective in-plane resolution of 11 mm FWHM.

To correct for photon attenuation, a 20-min transmission image was acquired prior to each of the three blood flow studies. Ten to 15 mCi of ^{13}N-ammonia were then injected intravenously over 30 sec while serial image acquisition commenced. The images were recorded in the following sequence: twelve 10-sec images, two 30-sec images and one 900-sec image amounting to a total imaging time of 18 min.

Semiquantitative Image Analysis

Each of the serially acquired transaxial image sets were reoriented into six short-axis planes as described previously (*17*). To rule out the presence of resting or hyperemia-induced regional flow defects, the short-axis images were assembled into polar maps of the ^{13}N-ammonia activity distribution and compared to a database of normals, established in 11 healthy volunteers (*18*).

Region of Interest Placement and Time-Activity Generation Curve

Three, 70°–90° sectorial regions of interest (ROIs) were assigned to the anterior, lateral and inferior wall on a basilar, midventricular and apical short-axis cross section of the left ventricular myocardium as described previously (*19*). The three sectorial ROIs corresponded to the myocardial territories subtended by the left anterior descending, the left circumflex and the right coronary artery.

The ROIs assigned to the reoriented images of all three flow studies were identical. This was achieved by using the same anatomical landmark (the insertion of the right ventricle into the intraventricular septum) as the starting point for the placement of regions in all three studies. They were then copied to the first 120 sec (12 frames) of the dynamic imaging sequence to obtain tissue time-activity curves. Because the myocardial activity concentrations did not differ between vascular territories on short-axis planes, the time activity data were averaged and a single time-activity curve was obtained for each study.

The arterial input function was derived from a small ROI (25 mm^2) which was centered in the left ventricular blood pool and copied to the serially acquired images (*20*).

The tissue time-activity curves were corrected for partial volume effects by assuming a uniform wall thickness of 1 cm. They were also corrected for activity spillover of the left ventricular blood pool to the left ventricular myocardium and for physical decay of the ^{13}N-ammonia activity (*21*). The blood-pool time-activity curve was only corrected for physical decay of ^{13}N-ammonia.

A previously validated two-compartment model for ^{13}N-ammonia (*14*) was then fitted to the corrected myocardial and blood-pool time-activity curves in order to obtain estimates of myocardial blood flow in ml/g/min.

Statistical Analysis

Mean values are given with standard deviations. Analysis of variance for repeated measurements was used to examine differences in hemodynamic parameters and hyperemic responses to the three interventions. Probability levels of less than 0.05 were considered statistically significant.

RESULTS

Semiquantitative Polar Map Analysis

Polar map analysis of the reoriented short-axis images indicated that the myocardial uptake of ^{13}N-ammonia was homogeneous in each of the three hyperemic studies in all participants. The absence of regional flow defects provided additional evidence that the participants in this study were indeed free of significant CAD.

Hemodynamic Findings

The rate pressure products averaged 6750 ± 1280, 6410 ± 1460 and 6770 ± 1040 prior to the standard-dose, the high-dose and the standard-dose plus handgrip study (p = ns). Thus, baseline cardiac work did not differ between the three study conditions suggesting that rest blood flows were similar.

The hemodynamic findings during the three hyperemic blood flow studies are listed in Table 1. Systolic blood pressure, diastolic blood pressure and heart rate were similar during the standard and high-dose dipyridamole study but increased significantly with the addition of the isometric handgrip exercise ($p < 0.001$). Accordingly, the rate pressure product increased from 11076 ± 1300 during standard and 11380 ± 2010 during high-dose dipyridamole to 14760 ± 1526 during the handgrip plus standard-dose dipyridamole infusion ($p < 0.0001$).

Myocardial Blood Flow

Table 1 lists the myocardial blood flow for each individual during the three study conditions. Hyperemic myocardial blood flow was similar after the standard and the high-dose dipyridamole infusion (2.13 ± 0.28 versus 2.08 ± 0.20 ml/g/min; p = ns). However, it was lower when the iso-

TABLE 1
Measurements of Myocardial Blood Flow and Hemodynamics

Volunteer	MBF standard	MBF high	MBF standard + HG	BP syst standard	BP syst high	BP syst standard + HG	HR standard	HR high	HR standard + HG
1	1.80	2.08	1.95	125	114	140	88	92	108
2	2.05	1.85	1.50	120	121	140	84	86	93
3	2.00	1.85	1.93	112	122	136	100	95	104
4	1.83	2.10	1.95	110	113	142	101	110	102
5	2.40	1.80	2.20	131	134	158	94	106	104
6	2.50	2.21	1.65	140	139	165	100	103	104
7	1.75	1.95	1.40	125	112	150	86	98	90
8	2.30	2.07	1.55	125	122	140	94	96	102
9	2.09	2.25	1.98	124	134	142	86	94	116
10	2.25	2.32	2.10	120	115	164	80	72	94
11	2.50	2.37	2.42	125	122	145	75	68	85
mean ± s.d.	2.13 ± 0.28	2.08 ± 0.20	1.87* ± 0.32	123 ± 8	123 ± 9	147† ± 10	90 ± 9	93 ± 13	100† ± 9

*$p < 0.05$ vs. standard-dose dipyridamole.
†$p < 0.01$ vs. standard and high-dose dipyridamole.
MBF = myocardial blood flow (ml/g/min); standard = 0.56 mg/kg of intravenous dipyridamole; high = 0.80 mg/kg of intravenous dipyridamole; HG = isometric handgrip exercise; BP = blood pressure (mmHg); Syst = systolic; and HR = heart rate (bpm).

metric handgrip was added to standard-dose dipyridamole (1.88 ± 0.30 ml/g/min; $p < 0.05$ versus standard-dose; p = ns versus high-dose; Fig. 1).

Coronary Vascular Resistance

During pharmacologically induced coronary vasodilation, myocardial blood flow depends on the coronary driving pressure. To account for inter-individual and inter-study differences in coronary perfusion pressure, an index of coronary vascular resistance was derived from the ratio of mean aortic blood pressure (mmHg)-to-myocardial blood flow (ml/g/min). The coronary vascular resistance index was similar for the high-dose and low-dose dipyridamole hyperemic study (42 ± 6 versus 41 ± 5 mmHg/ml/g/min) but increased when isometric handgrip exercise was added to the standard-dose dipyridamole hyperemia (57 ± 12 mmHg/ml/g/min; $p < 0.01$ versus standard and high-dose dipyridamole; Figure 2).

DISCUSSION

The findings of this study indicate that high-dose dipyridamole (0.80 mg/kg) does not enhance the coronary vasodilatory effect of the standard dose of 0.56 mg/kg nor does high-dose dipyridamole produce a more consistent hyperemic response. Although the addition of the isometric handgrip exercise to standard-dose dipyridamole raised the mean arterial, and thus, the coronary driving pressure, it resulted in a modest yet statistically significant 10% decline in hyperemic blood flow. Thus, modification of the

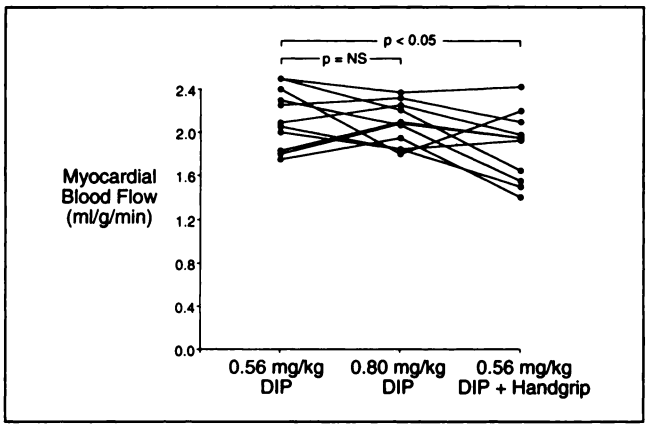

FIGURE 1. Changes in hyperemic myocardial blood flow from standard-dose dipyridamole (0.56 mg/kg DIP) to high-dose dipyridamole (0.80 mg/kg DIP) to 0.56 mg/kg plus isometric handgrip. High-dose dipyridamole failed to further increase hyperemic blood flow. Moreover, high-dose dipyridamole did not evoke a more consistent hyperemic response than the standard dose.

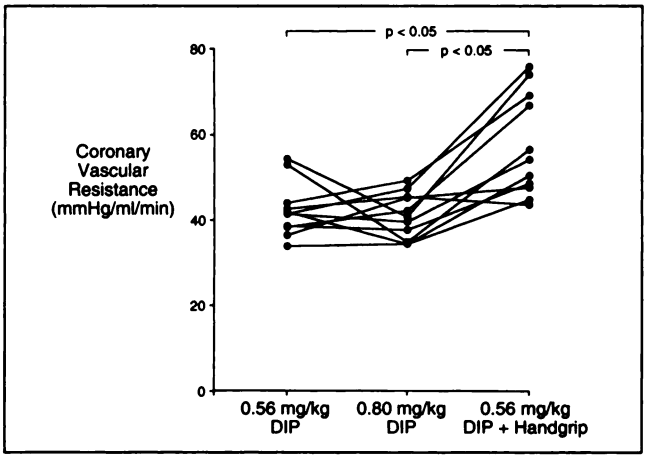

FIGURE 2. Changes in index of coronary vascular resistance. This index, derived from the ratio of mean aortic blood pressure-to-hyperemic blood flow, remained unchanged from standard-dose to high-dose dipyridamole but increased significantly with the addition of the isometric handgrip.

standard pharmacologic stress either by increasing the dipyridamole dose or by adding the isometric handgrip is unlikely to enhance the diagnostic accuracy of noninvasive stress testing for the detection of CAD.

Standard-Dose versus High-Dose Dipyridamole

Only a few animal experimental studies have attempted to establish the dose response characteristics of intravenous dipyridamole. Using the microsphere technique in anesthetized open chest dogs, Jolly et al. (*22*) failed to observe significant changes in myocardial blood flow when the intravenous dipyridamole dose was increased from 0.25 to 0.50 mg/kg. In contrast, Rembert et al. (*23*) reported significant flow increases when the same regimen was employed in chronically instrumented awake dogs. The different study conditions might account for these disparate findings. However, the two studies did not explore the coronary dilatory response to high-dose dipyridamole.

A dose of 0.56 mg/kg of dipyridamole infused intravenously over 4 min has now been widely accepted as the standard for inducing pharmacologically coronary hyperemia. However, the approach initially established in dog experiments (*2*), produces variable flow responses and does not appear to produce maximal hyperemia consistently. Careful review of the literature indicates that the effect of higher dose dipyridamole has been demonstrated thus far in only three individuals (*6,7*). Addition of 0.25 mg/kg of intravenous dipyridamole in these three individuals with poor hyperemic responses to the standard-dose dipyridamole increased coronary flow velocities by 10%–170%. While these preliminary observations suggested that higher dipyridamole doses produced greater myocardial flow responses, this possibility has not been explored more systematically. Consistent with a possible augmented flow response to higher doses of dipyridamole are recent observations with echocardiography in patients with CAD (*24–26*). In these investigations, wall motion abnormalities not observed during standard-dose dipyridamole were noted after high-dose dipyridamole. The occurrence of new wall motion abnormalities cannot be ascribed to demand induced myocardial ischemia because standard-dose and high-dose dipyridamole produced comparable increases in cardiac work as evidenced by similar changes in the rate pressure product in the current study. Similarly, because high-dose dipyridamole in the current study failed to augment hyperemic flows, an enhanced coronary steal effect appears unlikely. Thus, the mechanism underlying these observations remains uncertain. Consistent with the findings of the current study are however preliminary observations with intracoronary Doppler flow velocity measurements which failed to observe a significant difference in flow velocity between standard-dose and high-dose dipyridamole in seven subjects with angiographically normal coronary arteries (*27*).

In the current study, blood flow increased in five of the eleven volunteers from standard to high-dose dipyridamole (45%). However, the mean increase was only 10% ± 5% with a maximal increase of 0.28 ml/g/min. Conversely, in six of the eleven volunteers (55%), blood flow was lower after high-dose than after standard-dose dipyridamole resulting in an average decline of 12% ± 7% and a maximal flow reduction of 0.60 ml/g/min. None of the hemodynamic parameters was useful in predicting the direction of the blood flow changes. The changes in blood flow are within the expected variability of about 10% for sequential hyperemic blood flow studies (*28*). Thus, the apparent changes may reflect method-related inaccuracies rather than true changes in hyperemic myocardial blood flow.

Pharmacologic Vasodilation Combined with the Isometric Handgrip Exercise

During near maximal coronary hyperemia, myocardial blood flow is determined, among other factors, by the coronary perfusion pressure (*8*). Increases in coronary perfusion pressure as induced by the isometric handgrip would therefore be expected to produce further increases in hyperemic blood flow. On the other hand, increases in extravascular resistive forces or an increase in the alpha-adrenergically mediated vasomotor tone during exercise might attenuate the hyperemic response to dipyridamole (*10,11*).

Four studies have quantified the response of coronary flow velocity or of myocardial blood flow to combined physical and pharmacologic stress and have yielded conflicting results. Using the coronary sinus thermodilution technique, Brown et al. reported proportional increases in mean aortic blood pressure and flow velocity of 25% and 34%, respectively (*9*). Using intracoronary Doppler measurements during intracoronary application of papaverine McGinn et al. found a modest, 10% increase in flow velocity for a 25% increase in mean aortic blood pressure (*29*). In contrast, Rossen et al. failed to observe an increase in hyperemic coronary flow velocity during the isometric handgrip with the intracoronary Doppler technique (*7*). Lastly, Müller et al. increased mean arterial blood pressure with supine bicycle exercise during standard-dose dipyridamole and found that hyperemic blood decreased rather than increased (*30*).

To clarify these conflicting results, Rossen et al. monitored changes in coronary flow velocity with the intracoronary Doppler technique and measured simultaneously coronary blood flow velocity with the coronary sinus thermodilution technique in two individuals (*7*). Intracoronary Doppler measurements showed a constant flow velocity throughout the entire handgrip maneuver. In contrast, coronary sinus thermodilution flow was initially unchanged but increased with the beginning of labored respirations. This increase was attributed to catheter movement or reflux of right atrial blood into the coronary sinus due to the labored respirations.

In the current study, addition of the isometric handgrip exercise raised mean aortic blood pressure by about 15% while myocardial blood flow declined by an average of about 10%. This decline was observed in all but two par-

ticipants. The observed decrease in hyperemic blood flow is not necessarily in disagreement with the above discussed findings. Intracoronary flow velocity measurements are confined to only one vascular territory. More importantly, changes in flow velocities do not fully reflect changes in absolute myocardial flow. Conversely, measurements of coronary sinus blood flow may be subject to errors such as catheter placement or catheter movement.

It is possible that the observed decline in hyperemic myocardial blood flow during isometric handgrip exercise resulted from an increase in extravascular resistive forces related to an increase in myocardial contractility and higher LV pressures (*11*). Alternatively, it is also possible that in addition to the mechanical compression of the small resistance vessels an alpha-adrenergically mediated vasoconstriction occurred due to local and systemic release of norepinephrine. However, as a limitation, catecholamine levels were not measured in the current study.

Limitations of the Study

Both high-dose dipyridamole and the combination of standard-dose with the isometric handgrip exercise were tested only in young healthy subjects, who were at a low risk for CAD. Thus, the effect of these modified protocols on blood flow in significantly stenosed coronary arteries may differ. For instance, high-dose dipyridamole might reduce the mean arterial blood pressure in patients with CAD, thereby lowering the coronary perfusion pressure, and in turn, coronary blood flow across a coronary stenosis. Such distal flow reduction would result in a more severe reduction in tracer activity in the dependent myocardial territories.

As another limitation, a uniform wall thickness of 1 cm was assumed for correction of partial volume effects (*31*). Obviously, such assumption represents a simplification and might not hold for all conditions. Marked differences in LV wall thickness from standard-dose to high-dose dipyridamole are unlikely to have occurred since LV workload did not differ between both conditions. However, the likely increase in myocardial contractility during isometric handgrip exercise might have been associated with an increase in LV wall thickness. To appropriately correct for such possible increase, a higher recovery coefficient would have been required, which in turn would have lowered the blood flow estimates. Thus, more appropriate corrections for partial volume effects would have further attenuated the increase in blood flow during standard-dose dipyridamole combined with the handgrip exercise.

Further, no corrections for contamination of the time-activity data by ^{13}N-ammonia metabolites were performed. Thus, true hyperemic blood flow, if corrected appropriately, might have been higher by 5%–10%. However, the lack of such correction would have affected all three blood flow measurements in a similar fashion and, thus, does not invalidate the findings of the current study.

As another limitation, myocardial blood flow was not quantified under baseline conditions. Radiation safety concerns precluded such measurements which would have been required to assess myocardial flow reserve. However, resting myocardial blood flow, which is linearly related to cardiac work, would be expected to range from 0.5 to 0.7 ml/g/min for the baseline rate pressure products of about 6500 (*19*). Thus, as expected in healthy humans, the myocardial flow reserve likely would have ranged from 3 to 4.

Clinical Implications

The current study demonstrates that myocardial hyperemia induced by the standard-dose of 0.56 mg/kg of intravenous dipyridamole cannot be increased further by the administration of a higher dose (0.80 mg/kg). Moreover, the isometric handgrip reduced rather than increased myocardial blood flow in all but two subjects. This is in agreement with a previous study in which a decline in hyperemic blood flow when adenosine hyperemia was combined with supine treadmill exercise was observed (*30*). It is therefore unlikely that modified pharmacologic stress approaches will improve the accuracy of noninvasive stress tests for detecting CAD.

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REFERENCES

1. Strauss HW, Pitt B. Noninvasive detection of subcritical coronary arterial narrowings with a coronary vasodilator and myocardial perfusion imaging. *Am J Cardiol* 1977;39:403–406.
2. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic vasodilation. I. Physiologic basis and experimental validation. *Am J Cardiol* 1978;42:761–768.
3. Go R, Marwick T, MacIntyre W, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990;31:1899–1905.
4. Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission tomography. Comparison with quantitative arteriography in 193 patients. *Circulation* 1989;79:825–835.
5. Stewart R, Schwaiger M, Molina E, et al. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. *Am J Cardiol* 1991;67:1303–1310.
6. Wilson R, Laughlin D, Ackell P, et al. Transluminal subselective measurement of coronary blood flow velocity and vasodilator reserve in man. *Circulation* 1985;72:82–92.
7. Rossen J, Simonetti I, Marcus M, Winniford M. Coronary dilation with standard dose dipyridamole combined with handgrip. *Circulation* 1989;79:566–572.
8. Hoffman E. Maximal coronary flow and the concept of coronary vascular reserve. *Circulation* 1984;70:153–165.
9. Brown BG, Josephson MA, Peterson RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in cor-

onary flow in patients with coronary artery disease. *Am J Cardiol* 1981;48: 1077–1085.
10. McRaven D, Abboud F, Mayer H. Responses of coronary vessels to adrenergic stimuli. *J Clin Invest* 1971;50:773–781.
11. Marzilli M, Goldstein S, Sabbah H, Lee T, Stein P. Modulating effect of regional myocardial performance on local myocardial perfusion in the dog. *Circ Res* 1979;45:634–643.
12. Krivokapich J, Smith GT, Huang SC, et al. Nitrogen-13-ammonia myocardial imaging at rest and with exercise in normal volunteers. Quantification of absolute myocardial perfusion with dynamic positron emission tomography. *Circulation* 1989;80:1328–1337.
13. Hutchins G, Schwaiger M, Rosenspire K, Krivokapich J, Schelbert H, Kuhl D. Noninvasive quantification of regional blood flow in the human heart using ^{13}N-ammonia and dynamic positron emission tomographic imaging. *J Am Coll Cardiol* 1990;15:1032–1042.
14. Kuhle W, Porenta G, Huang S-C, et al. Quantification of regional myocardial blood flow using ^{13}N-ammonia and reoriented dynamic positron emission tomographic imaging. *Circulation* 1992;86:1004–1017.
15. Schelbert HR, Phelps ME, Hoffman EJ, Huang SC, Selin CE, Kuhl DE. Regional myocardial perfusion assessed with ^{13}N-labeled ammonia and positron emission computerized axial tomography. *Am J Cardiol* 1979;43: 209–218.
16. Spinks TJ, Guzzardi R, Bellina CR. Performance characteristics of a whole-body positron tomograph. *J Nucl Med* 1988;29:1833–1841.
17. Kuhle W, Porenta G, Huang S-C, Phelps M, Schelbert H. Issues in the quantitation of reoriented cardiac PET images. *J Nucl Med* 1992;33:1235–1242.
18. Porenta G, Kuhle W, Czernin J, et al. Semiquantitative assessment of myocardial viability and perfusion utilizing polar map displays of cardiac PET images. *J Nucl Med* 1992;33:1623–1631.
19. Czernin J, Müller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993;88:62–69.
20. Weinberg IN, Huang SC, Hoffman EJ, et al. Validation of PET-acquired functions for cardiac studies. *J Nucl Med* 1988;29:241–247.
21. Gambhir SS, Schwaiger M, Huang SC, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18-deoxyglucose. *J Nucl Med* 1989;30:359–366.
22. Jolly S, Gross G. Improvement in ischemic myocardial blood flow following a new calcium antagonist. *Am J Physiol* 1980;239:H163–H171.
23. Rembert J, Boyd L, Watkinson W, Greenfield JR. Effect of adenosine on transmural myocardial blood flow distribution in the awake dog. *Am J Physiol* 1980;239:H7–H13.
24. Smits P, Thien T, van't Laar A. Circulatory effects of coffee in relation to the pharmacokinetics of caffeine. *Am J Cardiol* 1985;56:958–963.
25. Picano E, Simonetti I, Masini M, et al. Transient myocardial dysfunction during pharmacologic vasodilation as an index of reduced coronary reserve: a coronary hemodynamic and echocardiographic study. *J Am Coll Cardiol* 1986;8:84–90.
26. Picano E, Simonetti I, Carpeggiani C. Regional and global biventricular function during dipyridamole stress testing. *Am J Cardiol* 1989;63:429–433.
27. Bach RG, Al-Joundi B, Kern M, et al. High-dose dipyridamole compared with standard infusion fails to further augment coronary hyperemia in patients. *J Am Coll Cardiol* 1994;1A:127A.
28. Czernin J, Kim A, Dominguez V, Phelps M, Schelbert H. How reproducible are measurements of myocardial blood flow by ^{13}N-ammonia and PET [Abstract]? *J Nucl Med* 1994;35:24P.
29. McGinn A, White C, Wilson R. Interstudy variability of coronary flow reserve: influence of heart rate, arterial pressure, and ventricular preload. *Circulation* 1990;81:1319–1330.
30. Müller P, Czernin J, Choi Y, et al. Effect of exercise supplementation during adenosine infusion on hyperemic blood flow and flow reserve. *Am Heart J* 1994;128:52–60.
31. Hoffman EJ, Huang SC, Phelps ME. Quantitation in positron emission computed tomography. *J Comput Assist Tomogr* 1979;3:299–308.