JACC Vol. 20, No. 4
October 1992:979–85

Comparison of Maximal Myocardial Blood Flow During Adenosine Infusion With That of Intravenous Dipyridamole in Normal Men

SAMMY Y. CHAN, MD, RICHARD C. BRUNKEN, MD, FACC, JOHANNES CZERNIN, MD, GEROLD PORENTA, MD, WILLIAM KUHLE, MD, JANINE KRIVOKAPICH, MD, FACC, MICHAEL E. PHELPS, PHD, HEINRICH R. SCHELBERT, MD, FACC

Los Angeles, California

Objective. This study compared quantitatively the efficacy of intravenous adenosine and dipyridamole for pharmacologic induction of myocardial hyperemia.

Background. Pharmacologic vasodilation is used increasingly for induction of myocardial hyperemia in conjunction with radionuclide imaging of myocardial blood flow. Although both intravenous dipyridamole and adenosine have been used, the magnitude of hyperemia induced by these agents and the hyperemia to baseline blood flow ratios have not been quantified and compared.

Methods. Twenty normal volunteers were studied with dynamic positron emission tomography (PET) and intravenous nitrogen-13 ammonia. Myocardial blood flow was quantified with a two-compartment tracer kinetic model.

Results. Myocardial blood flow at rest averaged 1.1 ± 0.2 ml/min per g and increased significantly to 4.4 ± 0.9 ml/min per g during adenosine and 4.3 ± 1.3 ml/min per g after dipyridamole administration. Hyperemia to baseline flow ratios averaged 4.3 ± 1.6 for adenosine and 4.0 ± 1.3 for dipyridamole. The average flow ratios and the maximal flows achieved were similar for both agents, but there was considerable variation in the individual response to these agents, as indicated by the range of hyperemia to baseline flow ratios (from 2.0 to 8.4 for adenosine and from 1.5 to 5.8 for dipyridamole). In addition, the hyperemic responses to dipyridamole and to adenosine differed by >1 ml/min per g in nine subjects.

Conclusions. Despite these inter- and intraindividual differences, we conclude that both agents are equally effective in producing myocardial hyperemia.

(J Am Coll Cardiol 1992;20:979–85)

Evaluation of regional myocardial blood flow with radionuclide techniques plays an important role in the diagnosis and management of coronary artery disease. The presence of a segmental defect on stress images of myocardial blood flow depends on a differential flow reserve between normal myocardium and myocardium supplied by a critically stenosed coronary artery. Maximal exercise usually serves as the stimulus for myocardial hyperemia. In patients unable to exercise, pharmacologic vasodilation offers an alternative. The agent most commonly used for this purpose is intravenous dipyridamole.

Dipyridamole thallium-201 scintigraphy has been shown to have a sensitivity and specificity comparable to those of exercise scintigraphy for the detection of coronary artery disease and it provides important prognostic information in patients with such disease (1). The mechanism of action of dipyridamole is indirect and appears to be related to an increased interstitial concentration of adenosine, a potent coronary vasodilator. Dipyridamole inhibits the cellular reuptake of adenosine and metabolism by adenosine deaminase. Other modes of action of dipyridamole include inhibition of phosphodiesterase and an increase in prostacyclin synthesis (2,3).

Intravenous adenosine has recently become available as an alternative agent for pharmacologic stress imaging. Adenosine activates specific receptors at the membranes of the smooth muscles of the coronary circulation (4) that initiate production of cyclic adenosine monophosphate, smooth muscle relaxation and a decrease in slow inward calcium current. Intravenous adenosine has a rapid onset of action and a biologic half-life of <2 s (5). These properties make

From the Division of Nuclear Medicine and Biophysics, Department of Radiological Sciences, University of California, Los Angeles School of Medicine and the Laboratory of Nuclear Medicine, Laboratory of Biomedical and Environmental Sciences, University of California, Los Angeles, Los Angeles, California. The Laboratory of Biomedical and Environmental Sciences is operated for the United States Department of Energy by the University of California under contract DE-FC03-87ER60615. This work was supported in part by the Director of the Office of Energy Research, Office of Health and Environmental Research, Washington, D.C., by Research Grants HL 29845, HL 33171 and HL 36232 from the National Institutes of Health, Bethesda, Maryland, and by an Investigative Group Award, Greater Los Angeles Affiliate, American Heart Association, Los Angeles, California. Dr. Brunken is the recipient of a Clinical Investigator Award (HL 02022-02) from the National Institutes of Health, and Dr. Kuhle the recipient of a Medical Student Research Fellowship from the American Heart Association, Greater Los Angeles Affiliate, Los Angeles, California. The study drugs were supplied by Medco Research, Inc., Los Angeles, California and Boehringer Ingelheim, Ingelheim, Germany.

Manuscript received December 26, 1991; revised manuscript received February 14, 1992, accepted March 13, 1992.

Address for correspondence: Heinrich R. Schelbert, MD, Division of Nuclear Medicine and Biophysics, University of California, Los Angeles School of Medicine, Los Angeles, California 90024-1721.

0735-1097/92/$5.00

Table I. Hemodynamic Variables and Side Effects During Pharmacologic Vasodilation in 20 Normal Men

Subject No.	Age (yr)	Baseline		Adenosine		Dipyridamole		Systemic Effects	
		Heart Rate (beats/min)	Blood Pressure (mm Hg)	Heart Rate (beats/min)	Blood Pressure (mm Hg)	Heart Rate (beats/min)	Blood Pressure (mm Hg)	Adenosine	Dipyridamole
1	36	80	115/72	115	116/72	92	144/92	F, SOB	
2	37	56	111/67	99	128/68	88	129/68	F, N, SOB	F, HA
3	39	68	116/72	104	137/72	84	132/64	N, SOB, CL	—
4	38	64	121/71	111	137/83	112	135/75	HA, N	HA, N
5	38	70	102/68	107	110/75	92	107/66	F, HA	HA
6	24	64	112/63	92	113/85	104	121/67	—	Diaphoresis
7	40	44	112/64	118	103/65	103	119/84	F, N, SOB, AP	—
8	27	59	112/67	71	108/59	92	113/64	F	—
9	84	62	132/62	69	139/57	71	133/72	F, HA	—
10	32	61	128/74	95	148/96	87	145/84	SOB, HA	—
11	30	61	123/71	86	125/64	91	141/64	F, HA, TP	F, SOB, TP
12	22	51	101/56	87	109/55	90	120/58	N	—
13	25	62	97/62	95	88/46	113	99/56	F, HA	—
14	29	60	124/64	106	124/80	108	132/82	F, HA	F, HA, N, EP
15	18	47	115/54	96	128/59	97	122/68	F, HA, N	N, S, DT
16	23	89	120/81	107	144/60	96	144/75	F, SOB	HA, N
17	42	52	96/63	70	104/68	70	115/60	F, HA	—
18	18	60	119/60	96	113/59	106	136/52	F, N	—
19	64	78	120/75	101	109/62	99	116/70	F, HA, SOB	—
20	23	66	130/85	76	131/80	88	124/73	F, TP, AP	F, HA, SOB
Mean ± SD		63 ± 11	115 ± 10/67 ± 8	95 ± 15*	121 ± 16/68 ± 12	94 ± 12*	126 ± 13/70 ± 10		

*$p < 0.001$ versus rest values. AP = arm pain; CL = cold leg; DT = dry throat; EP = eye pain; F = flushing; HA = headache; N = nausea; S = sweating; SOB = shortness of breath; TP = throat pain.

intravenous adenosine an attractive agent for use with myocardial blood flow imaging.

Although both dipyridamole and adenosine have been reported to be similarly effective in detecting coronary artery disease (6), no information exists as to whether the magnitude of hyperemia achieved with the two agents is comparable. The purpose of this study was to quantify in normal subjects the increase in myocardial blood flow in response to intravenous adenosine and dipyridamole by using dynamic positron emission tomography and intravenous nitrogen-13 (N-13) ammonia as a tracer of myocardial perfusion.

Methods

Study group. Twenty normal male volunteers with an average age of 34.5 ± 15.8 years (range 18 to 84) were studied (Table 1). After the rationale, investigative nature and risks of the study were explained, each subject signed an informed consent form approved by the Human Subject Protection Committee at the University of California, Los Angeles. Beverages containing caffeine were withheld for at least 12 h before the study. None of the men had a history of cardiovascular disease, and each had normal findings on physical examination and a 12-lead electrocardiogram (ECG) at rest and normal exercise tolerance. In addition, men >35 years of age underwent a symptom-limited submaximal treadmill exercise stress test to rule out silent ischemia. None developed chest pain or ECG evidence of myocardial ischemia during the exercise stress test. Therefore all subjects had <7% probability of silent coronary artery disease by Bayesian analysis (7).

Study protocol. All subjects were studied with dynamic positron emission tomography and intravenous N-13 ammonia at rest, during intravenous adenosine infusion and after intravenous dipyridamole infusion. Intravenous adenosine (Adenoscan) was supplied by Medco Research, Inc. Intravenous dipyridamole (Persantine) was supplied by Boehringer Ingelheim.

Nitrogen-13 ammonia was produced at the University of California, Los Angeles Medical Cyclotron as described previously (8). Imaging was performed with a whole body positron emission tomograph (model 931/8, CTI/Siemens Gammasonics), which simultaneously acquires 15 transverse slices spaced 6.75 mm apart and covers a 10.8-cm axial field of view (9).

Appropriate positioning of the subject's heart within the actual field of view of the tomograph was first confirmed on a 4-min rectilinear transmission scan. Twenty-minute transaxial transmission images were then acquired and used for subsequent correction for photon attenuation. An intravenous bolus of 12 mCi of N-13 ammonia was administered over 30 s while acquisition of serial transaxial emission images for 23 min was started. Forty-five minutes later, after physical decay of the N-13 activity to nearly undetectable

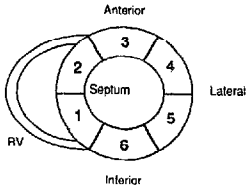


Figure 1. Schematic depiction of the assignment of sectorial regions of interest to the left ventricular myocardium on a reoriented, myocardial short-axis image. RV = right ventricle.

levels, adenosine was administered intravenously at a rate of 140 μg/kg body weight per min for 6 min. Three minutes after the start of adenosine infusion, N-13 ammonia was again administered and a second set of serial transaxial images was acquired. After another 45 min and after dissipation of the pharmacologic effects of adenosine and physical decay of the N-13 activity, dipyridamole was infused intravenously at a rate of 0.56 mg/kg over 4 min. Four minutes after the end of the infusion, a third dose of N-13 ammonia was administered with acquisition of serial transaxial images.

Subject movement within the tomograph was minimized by wrapping a Velcro strap across the chest. Heart rate, blood pressure and a 12-lead ECG were monitored regularly during the procedure. The estimated total body radiation exposure resulting from the cumulative dose of 36 mCi of N-13 ammonia during the procedure was 0.036 rad (10).

Images were acquired serially to determine noninvasively the arterial tracer input function and the myocardial tissue response. The image acquisition sequences were 12 frames of 10 s each, followed by 2 frames of 30 s each, 5 frames of 60 s each and 1 frame of 900 s.

Image analysis and calculation of myocardial blood flow. The serially acquired transaxial images were transferred to a Macintosh II personal computer and reoriented into left ventricular short-axis views using a computer software program described previously (11). A midventricular short-axis image was used for quantitative analysis. The left ventricular myocardium on this short-axis cross section was outlined with a semiautomatic computer program (11) and divided into six sectors (Fig. 1). Myocardial sectors ranged in area from 119 to 173 mm^2. The outline and sectorial regions of interest were copied to all the serial images and average tissue activity concentrations for each region in counts/mm^2 were calculated.

Estimates of sectorial wall thicknesses were obtained by a model-based and previously validated profile-fitting algorithm that was applied to radial myocardial activity profiles with the use of nonlinear regression algorithms (12,13). Regional recovery coefficients for each of the six sectorial regions of interest were then derived from the wall thickness estimates and from correction factors to compensate for the measured tissue activity concentrations for partial volume effects. A small blood pool region of interest (area 5 to 79 mm^2) corresponding to the left ventricular cavity was defined manually on each serial image and the arterial input function was generated.

Myocardial and blood pool time-activity curves were corrected for physical decay to the time of injection. Myocardial blood flow was calculated for each myocardial sector by using the 1st 120 s of the corrected myocardial time-activity curves and the arterial input function and a previously validated two-compartment tracer kinetic model (8,11). A mean myocardial blood flow value was obtained for each study by averaging the values of the six myocardial sectors. The coefficient of variation for each study was determined by dividing the standard deviations of the sectorial flow values by the average flow value.

Statistical analysis of the data. Statistics were calculated with a commercially available personal computer software program (Statview 512+, Abacus Concepts, Inc.). Values are expressed as mean value ± SD. Two-way analysis of variance with repeated measures and the Scheffé F test were used to determine statistically significant differences between groups. The Student t test for paired data and the chi-square test were used to compare values between two groups. A probability value < 0.05 was considered significant.

Results

Hemodynamic measurements. Hemodynamic variables at baseline, during intravenous adenosine infusion and after intravenous dipyridamole infusion are shown in Table 1. The heart rate increased significantly during adenosine infusion and was similar for the adenosine and dipyridamole studies. Although systolic pressures initially decreased after dipyridamole and adenosine infusions, they returned to control values at the time of tracer injection. Thus systolic and diastolic blood pressures did not differ significantly between the three studies. No subject reported a major adverse reaction (chest pain, heart block or acute asthmatic attack) to either of the two drugs (Table 1). Minor adverse events occurred in 19 subjects during adenosine infusion but in only 9 subjects after dipyridamole infusion (chi-square = 11.92, $p < 0.001$).

Homogeneity of myocardial blood flow at baseline and during pharmacologic vasodilation. Myocardial blood flow at baseline was homogeneous throughout the left ventricular myocardium and remained homogeneous during both hyperemic studies in all subjects. None of the images revealed segmental defects of tracer uptake on visual inspection at baseline or new hyperemia-induced defects on the adenosine or dipyridamole images (Fig. 2). The coefficients of variation of myocardial blood flow for each subject at rest and during intravenous adenosine and after intravenous dipyridamole administration are listed in Table 2. There were no signifi-

JACC Vol. 20, No. 4
October 1992:979–85

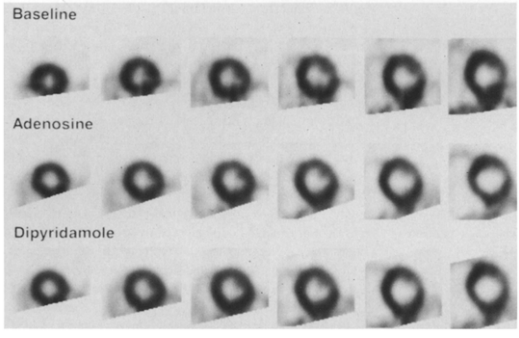


Figure 2. Subject 9. Example of six contiguous short-axis images of myocardial N-13 ammonia uptake at baseline (**upper row**), during adenosine infusion (**middle row**) and after dipyridamole infusion (**bottom row**). The images were reoriented from the transaxial images recorded from 5 to 20 min after tracer injection and are displayed from the apex to the base of the left ventricle. Note the homogeneous N-13 ammonia uptake at all three study conditions.

cant differences between the mean coefficient of variation of perfusion at rest (0.17 ± 0.05) or during intravenous adenosine (0.21 ± 0.08) or after intravenous dipyridamole (0.19 ± 0.09).

Myocardial blood flows at baseline and during pharmacologic vasodilation. Mean values of myocardial blood flow at baseline and during intravenous adenosine and intravenous dipyridamole administration are given for each subject in Table 2 and illustrated in Figure 3. Myocardial blood flow at baseline ranged from 0.6 to 1.4 ml/min per g (average 1.1 ± 0.2). During intravenous adenosine, myocardial blood flow ranged from 2.5 to 5.8 ml/min per g (average 4.4 ± 0.9). With intravenous dipyridamole, myocardial blood flow ranged from 1.5 to 6.2 ml/min per g (average 4.3 ± 1.3). Thus mean myocardial blood flow increased significantly with intravenous adenosine ($p < 0.0001$) and with dipyridamole ($p < 0.0001$) but did not differ significantly between the adenosine and the dipyridamole studies (p = NS).

Table 2. Myocardial Blood Flow at Baseline and During Pharmacologic Vasodilation

Subject No.	Myocardial Blood Flow (ml/min per g)			Coefficient of Variation		
	Baseline	Adenosine	Dipyridamole	Baseline	Adenosine	Dipyridamole
1	1.4 ± 0.1	5.5 ± 0.5	4.8 ± 0.2	0.07	0.09	0.04
2	0.7 ± 0.1	5.5 ± 1.1	3.8 ± 0.5	0.15	0.21	0.13
3	1.4 ± 0.2	4.6 ± 1.0	6.0 ± 1.0	0.17	0.22	0.17
4	1.1 ± 0.2	5.2 ± 1.9	1.5 ± 0.4	0.22	0.37	0.26
5	1.4 ± 0.2	4.8 ± 0.9	5.0 ± 1.5	0.17	0.20	0.30
6	0.9 ± 0.1	4.5 ± 0.6	3.1 ± 0.8	0.15	0.13	0.27
7	1.0 ± 0.1	2.6 ± 0.7	4.8 ± 1.0	0.15	0.26	0.21
8	1.3 ± 0.2	2.5 ± 0.6	4.1 ± 0.6	0.19	0.26	0.14
9	1.3 ± 0.3	3.0 ± 0.7	2.4 ± 0.7	0.24	0.23	0.30
10	0.9 ± 0.2	4.1 ± 1.3	2.0 ± 0.6	0.26	0.32	0.31
11	1.2 ± 0.3	4.4 ± 1.5	5.2 ± 1.7	0.22	0.34	0.32
12	0.9 ± 0.1	4.7 ± 0.6	4.5 ± 0.6	0.11	0.14	0.13
13	1.2 ± 0.3	3.7 ± 0.7	3.7 ± 0.4	0.24	0.18	0.12
14	0.8 ± 0.1	4.6 ± 0.7	4.7 ± 0.5	0.13	0.14	0.11
15	0.7 ± 0.1	4.0 ± 0.8	4.2 ± 0.6	0.15	0.19	0.13
16	1.1 ± 0.2	5.8 ± 1.1	5.1 ± 0.8	0.18	0.18	0.16
17	1.1 ± 0.1	5.4 ± 0.8	5.6 ± 0.7	0.13	0.15	0.13
18	0.6 ± 0.1	4.0 ± 1.0	6.2 ± 1.8	0.17	0.29	0.30
19	1.2 ± 0.2	4.5 ± 0.6	3.6 ± 0.9	0.16	0.14	0.24
20	1.1 ± 0.2	3.9 ± 0.4	6.0 ± 0.7	0.19	0.09	0.12
Mean ± SD	1.1 ± 0.2	4.4 ± 0.9*	4.3 ± 1.3*	0.17 ± 0.07	0.21 ± 0.08	0.19 ± 0.09

*$p < 0.0001$ versus baseline

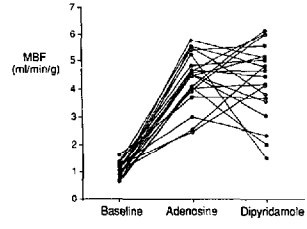


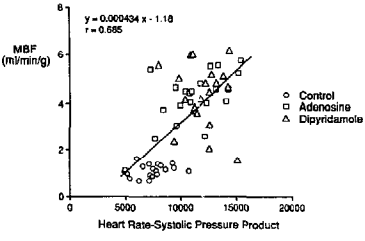
Figure 3. Individual values of average myocardial blood flow (MBF) at baseline, during adenosine infusion and after dipyridamole infusion. Note the individual variability in the response to pharmacologic vasodilation, although the mean values for the group of 20 volunteers are similar for both hyperemic conditions.

Myocardial perfusion reserve, defined as the ratio of hyperemic to baseline blood flow, ranged from 2.0 to 8.4 with adenosine and averaged 4.3 ± 1.6; for dipyridamole, it ranged from 1.5 to 5.8 and averaged 4.0 ± 1.3 (p = NS vs. adenosine).

There were substantial variations in the individual responses to both agents. In four subjects, myocardial blood flow during intravenous adenosine administration was more than 1 ml/min per g higher than after intravenous dipyridamole administration. Conversely, in five subjects, mean myocardial blood flows after intravenous dipyridamole were >1 ml/min per g higher than during intravenous adenosine. In the remaining subjects, blood flow differed by <1 ml/min per g between the adenosine and the dipyridamole studies.

The relation between the heart rate-systolic blood pressure product and myocardial perfusion is shown in Figure 4. There is an overall trend between higher rate-pressure products and mean myocardial blood flows. However, the considerable scatter about the regression line suggests the importance of other factors.

Figure 4. Relation between mean myocardial blood flows (MBF) and the rate-pressure product.



Discussion

Standard doses and intravenous infusion rates of adenosine (140 μg/kg per min) and dipyridamole (0.56 mg/kg over 4 min) increased myocardial blood flow significantly above levels at rest. The increase was homogeneous throughout the left ventricular myocardium, as evidenced by visual inspection of the contiguous transaxial images and the constant coefficient of variations. However, there were substantial variations in the response to the two agents in individual subjects. On average, both adenosine and dipyridamole infusions achieved similar levels of myocardial hyperemia.

Methodologic considerations. Myocardial blood flow was quantified by high temporal resolution positron emission tomography with intravenous N-13 ammonia and a tracer kinetic model that has been validated in animal experiments (11,14) and used in humans (8). Only the initial 120 s of image data was used for model fitting because this procedure minimizes contamination of the arterial input function by N-13–labeled metabolites of N-13 ammonia. In humans, N-13 ammonia metabolites have been reported to constitute only 6% of the total N-13 blood activity at 2 min (15). Quantification of myocardial blood flow further relied on reoriented short-axis cross sections of the left ventricular myocardium, a factor that permitted accurate estimates of regional myocardial wall thickness, which is important for accurate correction for regional partial volume effects (11). Such corrections are problematic on transaxial images because the anterobasal and inferior regions of the left ventricular myocardium traverse the image planes in an oblique or even tangential fashion. This pattern precludes adequate measurements of regional tracer activity concentrations as well as appropriate corrections for partial volume effect in these regions. Although the baseline and hyperemic estimates of blood flow in this study are comparable to those obtained previously with N-13 ammonia from transaxial tomographic images (16), these measurements were confined largely to mid-ventricular image slices that traverse the image plane in a more perpendicular fashion.

Randomization of the order in which the vasodilator agents were administered was not possible because the longer half-life of intravenous dipyridamole (3) would have interfered with the action of adenosine. Although the study group included older subjects, care was taken to rule out the presence of coronary artery disease. Its absence was confirmed by the homogeneous distribution of blood flow at rest as well as during both hyperemic studies which, in view of the previously reported high sensitivities and specificities of positron emission tomography for the detection of coronary artery disease (17,18), argued against the presence of this disease.

Comparison with invasive measurements. In this group of healthy men, intravenous adenosine resulted in an average

hyperemia to baseline blood flow ratio of 4.3 ± 1.6, although individual responses varied. For example, the flow ratio was <1 SD below the mean value in 3 (15%) of the 20 subjects. The results are similar to changes in coronary flow velocities determined with intercoronary Doppler catheters before and after intravenous adenosine administration (19). Flow velocities in normal coronary arteries increased on average by >400%. They increased maximally in 84% of the coronary arteries. In comparison, intravenous dipyridamole in the current study resulted in a hyperemia to baseline blood flow ratio of 4.0 ± 1.3. Individual responses varied, and flow ratios ranged from 1.5 to 5.8 and were <1 SD below the mean in three (15%) of the volunteers. Studies with intracoronary Doppler catheters (6) revealed a range of coronary flow responses to intravenous dipyridamole from 1.9 to 5.4 (mean 3.7 ± 1.2). A flow reserve >3.0 was seen in only 66.7% of the subjects studied (6).

The variable response of myocardial blood flow to either intravenous adenosine or dipyridamole is therefore similar to that observed with intracoronary Doppler probes. The relatively small number of subjects with suboptimal responses precludes elucidation of hemodynamic criteria that would distinguish between suboptimal and optimal flow responses. Although intravenous infusion by both adenosine and dipyridamole invariably affected the heart rate, the agents did exert a pharmacologic effect. Further, the rate-pressure product correlated significantly with myocardial blood flows. Although we are not implying a direct relation between hyperemic blood flows and heart rate or aortic pressure, the correlation might reflect a primary response of the systemic circulation to the vasodilator. Although this correlation might serve as an index of the pharmacologic effect on the coronary circulation, its value appears limited because of the relatively large data scatter about the regression line. Furthermore, the mean hyperemia to baseline flow ratios were similar for intravenous adenosine and for intravenous dipyridamole. Nevertheless, the responses to the two agents differed considerably in some subjects.

Possible causes of variable flow responses. Several reasons might account for the variations in flow response. Intravenous adenosine has been shown in animals and humans to be a potent, direct-acting coronary vasodilator (4–6). In contrast, the effect of dipyridamole is indirect because it is mediated in part through the inhibition of uptake and metabolism of adenosine (3). However, five of our subjects had higher myocardial blood flows in response to dipyridamole than to adenosine. The pharmacologic effects of adenosine in these subjects are evidenced by the associated hemodynamic changes as well as by the high incidence of minor adverse reactions to adenosine. The differential effects of intravenous adenosine and intravenous dipyridamole in these subjects may be related to differences in metabolism of the two compounds. Adenosine has a very short (<2.0 s) half-life in vivo. Exogenous adenosine is primarily metabolized through incorporation into the cellular adenine nucleotide pool, a process that takes place mainly at the vascular endothelium (5). Wilson et al. (19) demonstrated that a fraction of adenosine was metabolized during its transit from the peripheral venous infusion site to the myocardium. It is possible that in some persons, exogenous adenosine is rapidly metabolized by peripheral venous vascular endothelium. Concentrations of adenosine in the coronary circulation might therefore be inadequate to produce maximal coronary vasodilation. In contrast, dipyridamole is bound to an acidic alpha$_1$-glycoprotein in plasma and metabolized mainly through conjugation to glucuronide in the liver (3). An enterohepatic circulation of dipyridamole has been demonstrated in humans. The multiple steps of dipyridamole metabolism imply that after intravenous infusion, dipyridamole plasma concentrations may vary widely among individual subjects. It is conceivable that dipyridamole concentrations in some persons may achieve levels that result in supranormal elevations of endogenous adenosine. Either one or both of these mechanisms may result in myocardial blood flows that are higher with intravenous dipyridamole than with intravenous adenosine. Additional factors might be related to age (20). Although the age of our subjects ranged from 18 to 84 years, the study group was too small to reveal any significant age-related trend, even though the oldest participant, 84 years of age, had a somewhat blunted hyperemic response.

Conclusions. Our results suggest that intravenous adenosine and intravenous dipyridamole are equally effective in inducing myocardial hyperemia.

In contrast to previously reported findings with invasive approaches such as intracoronary Doppler flow probes (6,19,21), the current study demonstrates that rest and hyperemic myocardial blood flow can be quantified noninvasively with positron emission tomography, N-13 ammonia and an appropriate tracer kinetic model. Substantial variations in individual responses to these two agents were noted and suboptimal responses could not be accurately predicted from the hemodynamic effects of the agent. Nevertheless, the average magnitude of hyperemia and the proportion of subjects with a maximal response induced by these two agents were found to be similar.

We thank Wendy Wilson for preparing the illustrations and Eileen Rosenfeld for skillful secretarial assistance in preparing the manuscript.

References

1. Beller GA. Dipyridamole thallium-201 scintigraphy: an excellent alternative to exercise scintigraphy. J Am Coll Cardiol 1989;14:1642–4.
2. Knabb RM, Gidday JM, Ely SW, Rubio R, Berne RM. Effects of dipyridamole on myocardial adenosine and active hyperemia. Am J Physiol 1984;247:H804–10.
3. Fitzgerald GA. Dipyridamole. N Engl J Med 1987;316:1247–56.
4. Olsson RA, Davis DJ, Khouri EM, Patterson RE. Evidence for an adenosine receptor on the surface of dog coronary myocytes. Circ Res 1976;39:93–8.
5. Olsson RA, Pearson JD. Cardiovascular purinoceptors. Physiol Rev 1990;70:761–845.

6. Rossen JD, Quillen JE, Lopez AG, Stenberg RG, Talman CL, Winniford MD. Comparison of coronary vasodilation with intravenous dipyridamole and adenosine. J Am Coll Cardiol 1991;18:485–91.
7. Detrano R. Optimal use of literature knowledge to improve the Bayesian diagnosis of coronary artery disease. J Clin Epidemiol 1989;42:1021–7.
8. Krivokapich J, Smith GT, Huang SC, et al. 13N-Ammonia myocardial imaging at rest and with exercise in normal volunteers. Quantification of absolute myocardial perfusion with dynamic positron emission tomography. Circulation 1989;80:1328–37.
9. Spinks TJ, Jones T, Gilardi MC, Heather JD. Physical performance of the latest generation of commercial positron scanner. Trans Nucl Sci 1988; 35:721–5.
10. Lockwood AH. Absorbed doses of radiation after an intravenous injection of N-13 ammonia. J Nucl Med 1980;21:276–8.
11. Kuhle W, Porenta G, Buxton D, et al. Quantification of myocardial blood flow using N-13 ammonia and reoriented dynamic positron emission tomographic imaging. Circulation (in press).
12. Porenta G, Kuhle W, Czernin J, et al. Semiquantitative assessment of myocardial viability and flow from cardiac PET polar maps (abstr). J Nucl Med 1991;32:927.
13. Gambhir S. Quantitation of the physical factors affecting the tracer kinetic modeling of cardiac positron emission tomography data. PhD thesis. University of California, Los Angeles, 1990.
14. Smith GT, Huang SC, Wu Y, Hubner KF, Schelbert HR. Error analysis of myocardial perfusion calculations with N-13 ammonia and dynamic positron emission tomography (abstr). J Nucl Med 1990;31:862.
15. Rosenspire KC, Schwaiger M, Mangner TJ, Hutchins GD, Satorik A, Kuhl D. Metabolic fate of 13N ammonia in human and canine blood. J Nucl Med 1990;31:163–7.
16. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990;15:1032–42.
17. Schelbert HR, Wisenberg G, Phelps ME, et al. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. VI. Detection of coronary artery disease in human beings with intravenous N-13 ammonia and positron computed tomography. Am J Cardiol 1982;49:1197–207.
18. 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;79:825–35.
19. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990;82: 1595–606.
20. Sennoff MJ, Geltman EM, Bergmann SR, Hartman J. Noninvasive delineation of the effects of moderate aging on myocardial perfusion. J Nucl Med 1991;32:2037–42.
21. Rossen JD, Simonetti I, Marcus ML, Winniford MD. Coronary dilation with standard dose dipyridamole and dipyridamole combined with handgrip. Circulation 1989;79:566–72.