Effect of Caffeine on Myocardial Blood Flow at Rest and During Pharmacological Vasodilation

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Stress testing with intravenous injection of dipyridamole is frequently used for noninvasive detection of coronary artery disease (CAD) with PET or SPECT. Dietary intake of caffeinated food, beverages or medication might alter both resting and dipyridamole-induced hyperemic blood flow, thereby compromising the diagnostic sensitivity of dipyridamole stress testing. **Methods:** To quantify the effect on myocardial blood flow at rest and during intravenous injection of dipyridamole, 12 healthy volunteers (mean age 27 ± 6 yr) with low risk for CAD were studied with dynamic PET and a tracer kinetic model for ^{13}N-ammonia after 24 hr of caffeine abstinence and after caffeine intake. **Results:** Caffeine tended to increase the rate pressure product from 6873 ± 1494 to 7566 ± 1102 ($p = 0.051$), whereas resting myocardial blood flow remained unchanged (0.61 ± 0.13 versus 0.58 ± 0.07 ml/g/min, p = ns). The heart rate response to dipyridamole was inversely related to serum caffeine levels. Hyperemic blood flow (2.01 ± 0.46 versus 1.31 ± 0.0.38 ml/g/min; $p < 0.001$) and flow reserve (3.4 ± 0.8 versus 2.3 ± 0.7; $p < 0.001$) were inversely related to the caffeine dose. Coronary vascular resistance at rest tended to increase (132 ± 32 versus 147 ± 25 mmHg/ml/g/min; $p = 0.06$), whereas minimal coronary vascular resistance was significantly higher after caffeine (41 ± 9 to 69 ± 25 mmHg/ml/g/min; $p < 0.01$). **Conclusion:** Caffeine intake alters the coronary vasomotor tone at rest, which might lower the threshold for ischemic events in patients with CAD. It reduces hyperemic blood flow and flow reserve and the dipyridamole-induced increase in heart rate in a dose-dependent fashion. These findings emphasize the importance of carefully screening patients for intake of caffeinated food, beverages or medication prior to dipyridamole stress testing.

Key Words: positron emission tomography; myocardial blood flow; caffeine; dipyridamole

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Pharmacologic stress with dipyridamole is frequently used for the noninvasive detection of coronary artery disease (CAD) with radionuclide imaging (*1–4*). Intake of theophylline or its derivatives contained in food, beverages or medications, however, might modify myocardial blood flow at rest as well as its response to the vasodilator dipyridamole (*5*). For example, caffeine is known to increase heart rate and blood pressure at rest (*6*). Tolerance to caffeine might develop and thus blunt its hemodynamic effects (*7*). In addition to a modest effect on myocardial contractility, caffeine might directly increase the coronary vasomotor tone by blocking coronary adenosine A2 receptors (*8*) or, indirectly, by stimulating local and/or systemic catecholamine release causing an $\alpha 2$ receptor-mediated coronary vasoconstriction (*9,10*). These increases in coronary vasomotor tone might affect both myocardial blood flow at rest, by blocking the effects of endogenously produced adenosine, and during pharmacologic stress, by blocking the effects of a dipyridamole induced increase in circulating adenosine (*11,12*). Thus, caffeine intake prior to pharmacologic stress testing is likely to substantially lower the hyperemic response, which, in turn, would reduce the sensitivity of dipyridamole stress testing for detecting CAD (*1–4*).

The effect of caffeine or theophylline on myocardial blood flow and/or the coronary vasodilator capacity during dipyridamole-induced hyperemia can now be quantified noninvasively with intravenous ^{13}N-ammonia, PET and an appropriate tracer compartment model (*13*). Therefore, the aims of this study were: (a) to quantify the effect of caffeine intake on resting coronary vasomotor tone, hyperemic blood flow and on myocardial flow reserve and (b) to examine a possible dose-response relationship between caffeine intake or caffeine blood concentrations, resting blood flow and the hyperemic response to dipyridamole.

METHODS

Subjects

The study population consisted of 12 healthy volunteers (5 women, 7 men; mean age 27 ± 6 yr) with no history of cardiac or pulmonary disease, diabetes mellitus, hypertension, elevated cholesterol levels or cigarette smoking. All had a normal EKG at rest and during intravenous dipyridamole infusion. None of the volunteers was on any medication prior to or at the time of the myocardial flow measurements. Thus, all participants were at low risk for CAD (*14*). All volunteers gave informed consent as approved by the UCLA Human Subject Protection Committee.

Study Protocol

Myocardial blood flow at rest and during dipyridamole-induced hyperemia (0.56 mg dipyridamole/kg body weight intravenous) was

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TABLE 1
Hemodynamic Findings

Subject no.	Systolic BP (mmHg)				Diastolic BP (mmHg)				Heart rate (bpm)			
	Baseline	Coffee	DIP	DIP + Coffee	Baseline	Coffee	DIP	DIP + Coffee	Baseline	Coffee	DIP	DIP + Coffee
1	122	135	129	140	68	90	70	85	61	63	95	71
2	95	110	102	105	58	75	59	70	51	55	77	77
3	111	125	114	136	55	64	53	62	66	72	100	98
4	131	138	133	141	67	67	62	67	59	60	90	85
5	107	124	123	133	54	60	62	58	60	60	87	70
6	107	103	117	109	60	67	65	68	65	69	88	83
7	105	103	109	115	62	64	66	61	50	58	84	77
8	115	115	115	110	62	67	64	61	75	79	97	83
9	112	122	129	113	60	64	54	52	45	50	83	64
10	115	128	108	133	55	57	43	50	56	64	85	72
11	106	121	121	122	52	65	61	63	94	62	118	77
12	115	128	120	111	73	58	64	65	56	59	85	77
Mean ± s.d.	112 ± 9	121* ± 11	118 ± 9	122 ± 13	61 ± 6	61 ± 6	60 ± 7	64 ± 9	62 ± 13	63 ± 8	91 ± 11	78* ± 9

*$p < 0.05$ versus baseline.
BP = blood pressure; DIP = dipyridamole.

quantified in all study participants at baseline (baseline study) and after caffeine consumption (caffeine study). The time interval between the two study sessions averaged 7 ± 2 days. One of the two paired rest/hyperemic blood flow studies was performed after the participants refrained from caffeine intake for at least 24 hr. The other paired study was performed 1–4 hr after intake of one or two cups of coffee. One of the investigators scheduled caffeine studies randomly, while another investigator analyzed the myocardial blood flow studies without knowledge of the particular type of study performed.

Throughout each flow measurement, the EKG was monitored continuously and heart rate and arterial blood pressure (cuff measurements) were measured at 1-min intervals.

Venous blood samples to determine serum caffeine levels were drawn at the beginning of each of the four dynamic blood flow studies and were analyzed using a standard HPLC method (*15*).

Myocardial Blood Flow Measurements

Myocardial blood flow was quantified at rest and during dipyridamole-induced hyperemia (0.56 mg/kg) with intravenous ^{13}N-ammonia, dynamic PET and a two-compartment tracer kinetic model as previously described (*13,16,17*). Briefly, after intravenous injection of ^{13}N-ammonia (10 mCi–15 mCi), serial transaxial images were acquired with a whole-body positron emission tomograph (Model 931/8, CTI-Siemens, Knoxville, TN). For the hyperemic blood flow study, 0.56 mg/kg of dipyridamole was infused intravenously over 4 min. Four minutes after the end of the dipyridamole infusion, ^{13}N-ammonia (10 mCi–15 mCi) was injected intravenously and acquisition of serial images started. The transaxial image sets were reoriented into six short-axis images of the left ventricle, assembled into polar maps of myocardial blood flow and compared to a reference database of normal (*18*).

Three 90° circumferential regions of interest (ROIs) were placed in the territories of the three major coronary arteries, and a fourth ROI was assigned to the center of the left ventricular blood pool. The ROIs were copied to the first 2 min of serially acquired images to derive time-activity curves for the left ventricular myocardium and arterial blood (*17*). The myocardial time-activity curves were corrected for partial volume effects by assuming a uniform left ventricular wall thickness of 1 cm (*19–21*). Because regional time-activity data did not differ (*17*), they were averaged and one value of myocardial blood flow was obtained for each participant.

The decay-corrected myocardial and blood-pool time-activity data were then fitted with a previously validated, two-compartment model for ^{13}N-ammonia and quantitative estimates of myocardial blood flow were obtained (*13,22*).

Statistical Analysis

Mean values are given with their standard deviations. For comparison of blood flow, coronary resistance and hemodynamics between the different study conditions, the Student's paired t-test was used. Correlations were sought using least square regression analysis. Probability values less than 0.05 were considered statistically significant.

RESULTS

Hemodynamic Findings

The hemodynamic findings are summarized in Table 1. At rest, caffeine intake tended to increase the rate pressure product from 6873 ± 1494 to 7566 ± 1102 ($p = 0.051$) mainly because of a statistically significant increase in systolic blood pressure (from 112 ± 9 to 121 ± 11 mmHg; $p < 0.01$), whereas heart rate remained unchanged.

During the baseline study, dipyridamole increased the rate pressure product by 59% ± 21% to 10763 ± 1670. During the caffeine study, dipyridamole induced an increase in the rate pressure product by only 26% ± 15% to 9536 ± 1648 ($p < 0.05$ versus baseline dipyridamole). The blunted heart rate response to dipyridamole during caffeine primarily accounted for this attenuated increase. The dipyridamole-induced increase in heart rate was inversely related to serum caffeine levels ($y = -0.03x + 1.37$; $r = 0.68$; $p < 0.05$; Fig. 1).

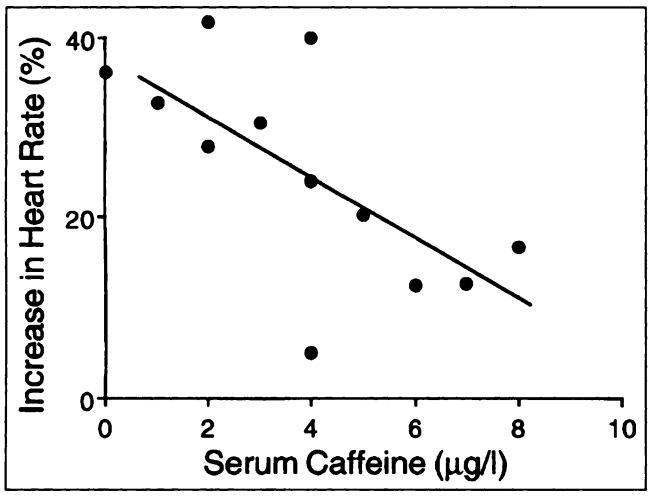

FIGURE 1. Dipyridamole-induced increases in heart rate (%) and serum caffeine levels (μg/liter) were inversely related by $y = -0.03x + 1.37$; $r = 0.68$; $p < 0.05$.

Serum Caffeine Levels

For the caffeine studies, the serum caffeine concentrations ranged from 0 to 8 μg/liter, suggesting that one of the participants consumed decaffeinated coffee. No caffeine was detected in the serum at the time of the baseline study. No significant relationship between time of caffeine intake or number of cups and serum caffeine levels was observed.

Myocardial Blood Flow and Flow Reserve

The individual measurements of blood flow and flow reserve are listed in Table 2. At rest, caffeine remained without significant effect on myocardial blood flow (0.61 ± 0.13 versus 0.58 ± 0.07 ml/g/min; p = ns; Fig. 2A). Yet, as mentioned above, caffeine did alter hemodynamic parameters. Further, myocardial blood flow normalized to the rate pressure product × (10^5) as an index of cardiac work was lower after caffeine than at baseline (7.77 ± 1.06 versus 9.05 ± 1.40; $p < 0.001$). Also, myocardial blood flow was correlated significantly to the rate pressure product at baseline ($y = 0.0001x + 0.15$; $r = 0.77$; $p < 0.01$; Fig. 3A) but no longer after caffeine intake ($y = 0.00026x + 0.37$; $r = 0.43$; p = ns; Fig. 3B).

Caffeine therefore altered the relationship between cardiac work and blood flow. In fact, it reduced blood flow relative to cardiac work as implied by the lower ratio of flow to the rate pressure product. During caffeine, dipyridamole-induced increases in myocardial blood flow were 37% ± 51% lower than at baseline (2.01 ± 0.46 to 1.31 ± 0.38 ml/g/min; $p < 0.01$; Fig. 2B). Moreover, hyperemic flows were correlated inversely with serum caffeine concentrations ($y = -0.12x + 1.78$; $r = 0.79$; $p < 0.01$; Fig. 4A).

The reduction in hyperemic blood flow after caffeine resulted in a 36% decline of the myocardial flow reserve defined as the ratio of hyperemic to resting myocardial blood flow (3.4 ± 0.8 versus 2.3 ± 0.7; $p < 0.001$; Fig. 2C). Furthermore, myocardial flow reserve was correlated inversely to the serum caffeine concentration ($y = -0.23x + 3.15$; $r = 0.74$; $p < 0.01$; Fig. 4B).

Coronary Vascular Resistance Index

An index of coronary vascular resistance was derived from the ratio of mean arterial blood pressure to myocardial blood flow. At rest, this index tended to be higher after caffeine than at baseline (147 ± 25 versus 132 ± 32 mmHg/ml/g/min; p = 0.06). In contrast, the minimal coronary vascular resistance after dipyridamole was higher after caffeine intake than under baseline conditions (69 ± 25 versus 41 ± 9 mmHg/ml/g/min; $p < 0.01$).

DISCUSSION

The results of this study indicate that caffeine alters coronary vasomotor tone at rest and causes dose-depen-

TABLE 2
Myocardial Blood Flow and Flow Reserve

	Rest MBF (ml/g/min)		MBF/RPP (× 10^5)		Hyperemic MBF (ml/g/min)		Flow reserve		Caffeine
Subject no.	Baseline	Coffee	Baseline	Coffee	Baseline	Coffee	Baseline	Coffee	(μg/liter)
1	0.64	0.57	8.64	6.66	2.37	0.85	3.68	1.50	7.00
2	0.45	0.50	9.22	8.26	1.89	1.03	4.23	2.07	4.00
3	0.69	0.65	9.42	7.22	3.02	1.96	4.38	3.02	0.00
4	0.58	0.57	7.46	6.92	1.64	1.94	2.84	3.38	2.00
5	0.66	0.66	10.28	8.87	1.46	0.72	2.21	1.08	8.00
6	0.63	0.59	9.06	8.35	2.10	1.42	3.33	2.39	5.00
7	0.55	0.59	10.48	9.93	1.67	1.29	3.03	2.17	1.00
8	0.68	0.62	7.88	6.82	1.91	1.16	2.81	1.87	4.00
9	0.61	0.53	12.10	8.69	2.38	1.30	3.90	2.45	2.00
10	0.52	0.65	8.07	7.89	1.47	1.20	2.83	1.86	6.00
11	0.93	0.59	9.33	7.86	2.36	1.29	2.54	2.19	4.00
12	0.43	0.43	6.68	5.69	1.89	1.54	4.40	3.58	3.00
Mean ± s.d.	0.61 ± 0.13	0.58 ± 0.07	9.05 ± 1.47	7.77* ± 1.16	2.01 ± 0.46	1.31* ± 0.38	3.35 ± 0.75	2.30* ± 0.75	3.83 ± 2.41

*$p < 0.01$.
MBF = myocardial blood flow; MBF/RPP = myocardial blood flow normalized to the rate pressure product; Caffeine = serum caffeine levels.

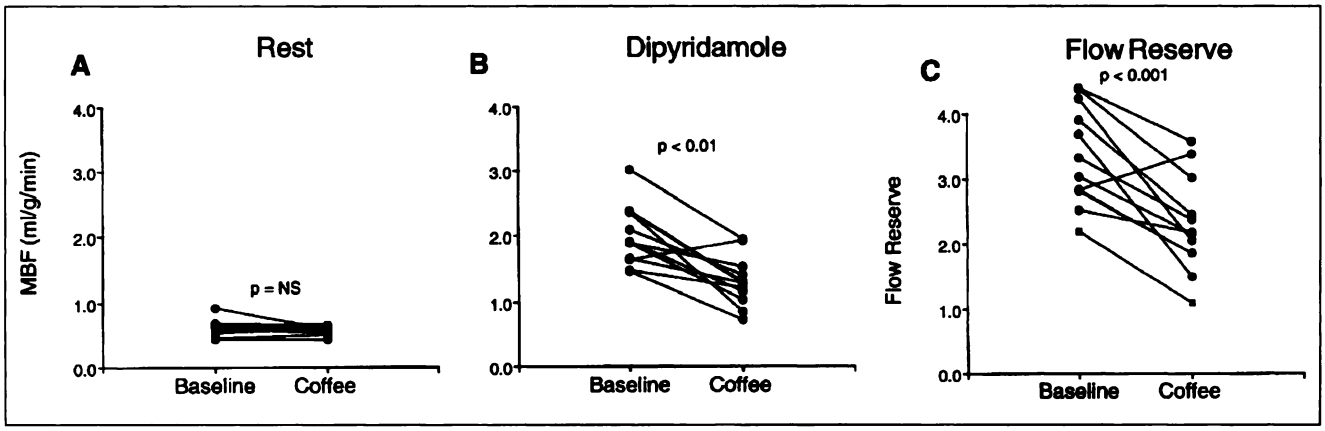

FIGURE 2. (A) Changes in resting blood flow (0.61 ± 0.13 versus 0.58 ± 0.07 ml/g/min), (B) dipyridamole-induced hyperemic blood flow (2.01 ± 0.46 versus 1.31 ± 0.38 ml/g/min) and (C) flow reserve (3.35 ± 0.75 versus 2.30 ± 0.75) from baseline to the caffeine study. Resting blood flow remained unchanged despite a tendency to higher rate pressure products during caffeine ingestion.

dent attenuation of the dipyridamole-induced hyperemic response.

Effect of Caffeine on Dipyridamole-Induced Hyperemia

Dipyridamole and adenosine induce an increase in heart rate, presumably by stimulation of carotid body chemoreceptors (*6*) and vagal withdrawal in response to a fall in blood pressure as a consequence of its systemic vasodilatory effect (*23*). Accordingly, Smits et al. observed a blunted heart rate response to dipyridamole which depended on serum caffeine levels, suggesting that caffeine attenuates the adenosine-mediated stimulation of carotid body chemoreceptors (*6*). This finding is consistent with the inverse relationship between serum caffeine levels and the heart rate response in the current study.

Dipyridamole increases the level of circulating adenosine by inhibiting phospodiesterase, activating adenylate cyclase and by preventing its cellular re-uptake (*11,12*). The increase in circulating adenosine induces near maximal coronary vasodilation through coronary A2 receptors. Methylxanthines, like caffeine, are competitive adenosine

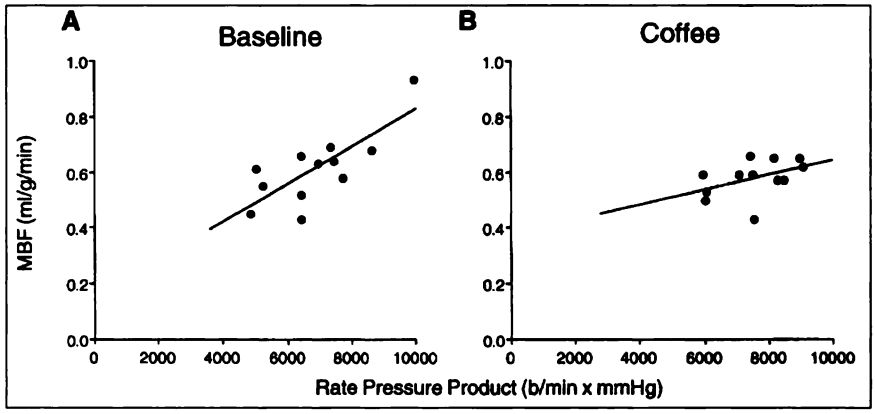

FIGURE 3. Relationship between resting myocardial blood flow and rate pressure product under (A) baseline conditions and (B) during caffeine intake. The relationship was only significant at baseline ($y = 0.0001x + 0.15$; s.e.e.: 0.12; $r = 0.77$; $p < 0.01$) but not during caffeine ingestion ($y = 0.00026x + 0.37$; s.e.e.: 0.13; $r = 0.43$; p = ns).

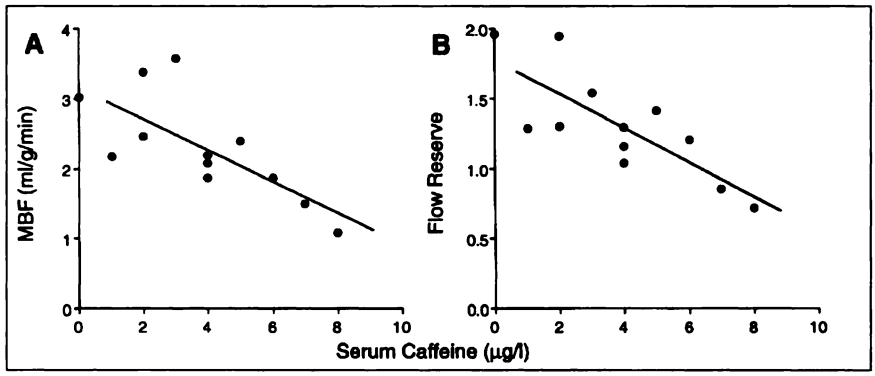

FIGURE 4. (A) Hyperemic blood flow and (B) flow reserve were inversely related to serum caffeine levels by $y = -0.12x + 1.78$; $r = 0.79$; $p < 0.01$ and $y = -0.23x + 3.15$; $r = 0.74$; $p < 0.01$.

antagonists and offset, in part, dipyridamole- and adenosine-induced coronary vasodilation (*24,25*). Caffeine-induced adrenal catecholamine release might contribute further to an increase in coronary vasomotor tone via $\alpha 2$ receptor-mediated coronary vasoconstriction (*26*). Thus, the antagonistic effects of methylxanthine on coronary A2 receptors and, to a smaller degree, the increase in adrenal catecholamine release with subsequent $\alpha 2$-mediated vasoconstriction might contribute to the observed reduction in hyperemic blood flow.

The inhibitory effect of caffeine on adenosine-induced hyperemia has been quantified only in the peripheral vascular bed but not in the human coronary system. Smits et al. studied the effect of caffeine on adenosine-induced forearm vasodilation and found a reduction of the flow reserve from 3.3 to 1.5 (*27*). These results are consistent with the current findings of a caffeine-induced reduction in dipyridamole-induced hyperemic myocardial blood flow and flow reserve by as much as 70%. The antagonistic effect of caffeine at the A2 receptor level suggests that methylxanthines are likely to attenuate coronary vasodilation induced by intravenous adenosine in a similar fashion.

A previous study demonstrated good reproducibility of hyperemic blood flow as measured quantitatively with ^{13}N-ammonia PET with an interstudy variability of less than 15% (*28*). Thus, method-related inaccuracies or a variable physiologic response to pharmacologic vasodilation do not explain the significant reduction in hyperemic blood flow following caffeine intake.

The reduction in hyperemic blood flow accounts for the reduced sensitivity of dipyridamole stress testing for detecting CAD and the low reproducibility of dipyridamole-induced blood flow defects following caffeine intake (*29*). The effect of caffeine intake on myocardial perfusion imaging, however, has not been evaluated systematically. A recent experimental animal study demonstrated that extraction of ^{201}Tl and ^{99m}Tc-sestamibi was attenuated at high flow rates but relatively enhanced in hypoperfused myocardium, thereby reducing the activity ratio between normal and ischemic myocardium. Such reduction might lead to an underestimation of true defect extent and severity by relative perfusion imaging with any extractable flow tracer (*30*). Consequently, the caffeine-induced reduction in hyperemic blood flow would be expected to limit further the accuracy of relative myocardial perfusion imaging. It should be noted, however, that 8 of the 12 participants in the current study had a flow reserve in excess of 2 despite caffeine intake. Thus, the diagnostic accuracy of pharmacologic stress testing might not be altered in the majority of patients.

Effect of Caffeine on Cardiac Work and Myocardial Blood Flow at Rest

Less anticipated though intriguing were the observed effects of caffeine on myocardial blood flow at rest. As noted in this study and as reported previously, caffeine has been found to increase systolic blood pressure and thus, cardiac work (*5,6,31*). Hemodynamic responses varied, however, between individuals, possibly because of a development of tolerance to caffeine (*7*). The caffeine-related increase in cardiac work would be expected to prompt a proportional increase in myocardial blood flow (*17,32,33*), which, however, did not occur. In fact, after caffeine intake, myocardial blood flow was no longer significantly correlated with the rate pressure product. Furthermore, blood flow normalized to the rate pressure product declined with caffeine intake.

Different mechanisms might account for this finding. For example, caffeine might have inhibited the vasodilatory effect of endogenous adenosine (*34*). This possibility has been suggested by an earlier invasive study; intravenous theophylline infusion produced a subtle decrease in coronary sinus blood flow despite an increase in the rate pressure product, suggesting a moderate inhibition of endogenously formed adenosine by xanthine derivatives (*35*). As an alternative or additional explanation, a caffeine-induced release of adrenal norepinephrine might have increased the coronary vasomotor tone by coronary $\alpha 2$ receptor stimulation, which may partly have offset demand-induced coronary vasodilation (*9,10*). The observed (~10%) increase in resting coronary vascular resistance and the decline in blood flow normalized to cardiac work might be attributed to both an adrenergic $\alpha 2$ receptor stimulation and/or blockade of the A2 adenosine receptors.

Study Limitations

The time dependence of caffeine-induced reductions in hyperemic blood flow was not assessed in this study. Thus, the study offers no information on the time of caffeine abstinence necessary to achieve a maximal hyperemic response. A previous report, however, suggests that significant serum caffeine levels might persist as long as 24 hr after caffeine intake (*5*). Thus, rigorous adherence to a 24-hr abstinence from caffeinated food, beverages or medication would presumably increase the reliability and accuracy of pharmacologic stress testing with dipyridamole.

Another limitation is that coffee and not pure caffeine was used. Other unknown substances might also have affected myocardial blood flow and flow reserve. Furthermore, we did not explore the effects of caffeine on resting and hyperemic blood flow in patients with CAD. Indirect evidence suggests, however, that caffeine affects blood flow and flow reserve in a similar fashion (*6,25,27,29*).

Lastly, as a technical limitation, left ventricular wall thickness was assumed to be uniformly 1 cm thick for correction of partial volume effects. It is acknowledged that such simplification might result in systematic errors of flow estimates. Yet, because each participant served as his/her own control, this assumption does not invalidate the finding of marked reduction in hyperemic blood flow following caffeine ingestion.

CONCLUSION

The attenuated hyperemic response to dipyridamole demonstrates that careful dietary instructions and screen-

ing of patients prior to pharmacologic stress testing is important to obtain conclusive results.

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