JACC Vol. 16, No. 3
September 1990:586–95

Increased Myocardial Perfusion at Rest and Diminished Perfusion Reserve in Patients With Angina and Angiographically Normal Coronary Arteries

EDWARD M. GELTMAN, MD, FACC, C. GREGORY HENES, MD, MARTHA J. SENNEFF, MD, BURTON E. SOBEL, MD, FACC, STEVEN R. BERGMANN, MD, PhD, FACC

St. Louis, Missouri

Angiographically normal coronary arteries are found in a substantial number of patients evaluated for angina pectoris. One third to one half of such patients demonstrate abnormalities of myocardial perfusion or metabolism when evaluated with invasive techniques. This study was designed to determine whether angina in such patients is attributable to abnormalities of perfusion at rest, maximal perfusion or vasodilator reserve and whether any identified abnormalities were global or regional in nature.

Positron emission tomography was performed with oxygen-15–labeled water ($H_2{}^{15}O$) and oxygen-15–labeled carbon monoxide ($C^{15}O$) before and after intravenous dipyridamole to assess regional myocardial perfusion and perfusion reserve in absolute terms in 16 normal subjects and 17 patients with chest pain and angiographically normal coronary arteries. Eight of the 17 patients had a myocardial perfusion reserve <2.5 (the lower limit of normal in studies with positron emission tomography, as well as with other techniques) and 9 of 17 patients had a normal response. In the patients with an impaired perfusion reserve, perfusion at rest was significantly higher than that measured in normal subjects (1.61 ± 0.38 versus 1.25 ± 0.28 ml/g per min, $p < 0.02$) and maximal flow and perfusion reserve were significantly reduced (2.26 ± 0.92 versus 4.62 ± 1.58 ml/g per min and 1.4 ± 0.5 versus 3.8 ± 1.1, respectively; $p < 0.001$ for both comparisons). Abnormalities of perfusion and perfusion reserve were spatially homogeneous without detectable regional disparities.

Thus, nearly half of patients with chest pain and normal coronary arteries have abnormalities of myocardial perfusion that are detectable noninvasively with positron emission tomography and $H_2{}^{15}O$.

(J Am Coll Cardiol 1990;16:586–95)

Angiographically normal epicardial coronary arteries are seen in a substantial subset of patients evaluated for angina pectoris. Despite their low mortality rate, some patients experience frequent episodes of severe chest pain, precipitating repeated and extensive medical evaluations. When left ventricular hypertrophy is present, angina may reflect increased wall stress, intramyocardial deposition of collagen that limits access of myocytes to substrates and oxygen or impaired subendocardial perfusion. However, in most patients with chest pain and angiographically normal coronary arteries, ventricular mass is normal. When pain is not associated with mitral valve prolapse, myocardial coronary bridging or noncardiac processes (such as musculoskeletal abnormalities, costochondritis, esophageal dysmotility and psychosomatic disorders), the pain has been attributed to microvascular abnormalities (1–6). In some patients, increases in great cardiac vein blood flow are limited in response to cardiac pacing or dipyridamole (1,3,5). Microvascular spasm has been implicated in some patients by observed attenuation of the increase in great cardiac vein flow induced by pacing or dipyridamole after infusion of ergonovine (4,6).

Despite these intriguing and suggestive observations, the pathogenesis of angina with normal coronary arteries has remained somewhat controversial. Coronary sinus or great cardiac vein flow may not reflect nutritive perfusion for several reasons, including its inability to distinguish regional alterations in flow. Increases appear to underestimate coronary flow reserve. Great cardiac vein flow increases only

From the Cardiovascular Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by Specialized Center of Research Grant HL17646 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Manuscript received December 6, 1989; revised manuscript received February 13, 1990, accepted March 14, 1990.

Address for reprints: Edward M. Geltman, MD, Box 8086, Cardiology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110.

0735-1097/90/$3.50

two- to threefold in response to dipyridamole in normal subjects compared with the three- to fivefold increases in reserve detectable with intracoronary or epicardial Doppler flow velocity measurements and positron emission tomography with oxygen-15–labeled water ($H_2{}^{15}O$) (5,7–9). Furthermore, coronary sinus or great cardiac vein flow may vary despite maintenance of nutritive perfusion in any given region of the left ventricle because of admixture of blood from its diverse tributaries. Doppler flow velocity catheter techniques appear to be more accurate in measuring flow reserve, but only interrogate limited vascular territories and provide measurement of flow velocity rather than nutritive perfusion (10).

Our laboratory (9,11–14) has recently developed and validated a method for quantification of regional myocardial nutritive perfusion in human subjects. We did this to better characterize the pathogenesis of several cardiac disorders with obscure etiology and to evaluate therapeutic approaches directed against the derangements identified. The present study was performed to determine whether angina with angiographically normal coronary arteries is attributable to altered myocardial perfusion at rest or with pharmacologic stress, and if so, whether reduced nutritive perfusion reserve is attributable to high rest flow or reduction of maximal perfusion in specific regions of the left ventricle or in the ventricle as a whole.

Methods

Patients studied. Patients with normal coronary arteriograms and no structural heart disease were selected by review of records from the cardiac catheterization laboratory at Barnes Hospital at Washington University Medical Center. Coronary arteriograms were considered normal if reductions in luminal diameter of ≥50% were absent on the basis of visual inspection by two experienced observers. Patients with a history of asthma, obstructive pulmonary disease or an allergic response to dipyridamole, aspirin or nonsteroid anti-inflammatory drugs were excluded. Those with documented vasospasm of epicardial coronary vessels occurring spontaneously or in response to ergonovine were also excluded. Patients were included only if they reported a history of chest pain highly suggestive of angina pectoris (that is, exercise-induced, relieved by nitrates or associated with an abnormal exercise electrocardiographic [ECG] or scintigraphic response). Seventeen patients were studied comprising 13 men and 4 women 40 to 73 years of age (mean ± SD 53 ± 10). Their clinical characteristics are delineated in Table 1.

Control group. Sixteen healthy, presumably normal volunteers were also studied. Myocardial perfusion in 11 of these normal subjects was reported previously (9) as part of our initial validation studies. Each had had no symptoms suggestive of heart disease. Physical examination and the rest ECG were normal in each. The normal volunteers included seven men and nine women ranging in age from 20 to 35 years (mean 25 ± 4).

The study protocol was approved by the Human Studies Committee of the Washington University School of Medicine. Each subject provided informed written consent.

Tomography protocol. Subjects were instructed to refrain from ingestion of food and beverages containing caffeine or other methylxanthines for at least 16 h before study because ingestion of these substances can attenuate the effects of dipyridamole. They were also instructed to withhold cardiac medications for at least 12 h before study and for 5 half-lives if feasible, deemed safe and permitted by the patient's personal physician.

All subjects were studied with a whole body, time of flight positron emission tomograph (Super PETT I) that permits simultaneous list mode acquisition of seven transaxial slices with a center to center separation of 1.5 cm and a slice thickness of 1.14 cm, with a reconstructed transaxial full-width half-maximal (FWHM) resolution of 13.5 mm in the high resolution mode (15). Polyurethane molds were made for each subject before study and used to stabilize the head, neck and upper torso so that patient movement was minimized and reference points in serial tomograms would be congruent. The patients were positioned within the Super PETT I such that the heart was centered within the field of view. A brief attenuation data collection study was performed, with rapid reconstruction of selected tomographic sections to ensure proper positioning. Subsequently, transmission data were collected for 12 min with an external ring of germanium-68/gallium-68, used to define parameters for correction for attenuation of emitted photons.

After collection of attenuation data, approximately 0.3 to 0.4 mCi/kg body weight of $H_2{}^{15}O$ was injected as a bolus through a large-bore catheter inserted into an antecubital vein, followed by a rapid flush with 5 to 10 ml of normal saline solution. List mode data were collected beginning with the onset of injection for 150 s. After a 5 min interval to allow for decay of tracer activity to baseline levels, 40 to 50 mCi of oxygen-15–labeled carbon monoxide ($C^{15}O$) was administered by inhalation to label the blood pool. After a brief delay to allow residual tracer to clear from the lungs, data were collected for 5 min. After collection of baseline data was complete, 0.14 mg/kg per min, dipyridamole (Persantine, Boehringer-Ingelheim) was administered intravenously for 4 min (0.56 mg/kg total dose) with a calibrated infusion pump. After an interval of 4 to 5 min after the completion of the infusion to permit sufficient time for occurrence of the peak flow response, the imaging sequence was repeated after repeat administration of $H_2{}^{15}O$ and $C^{15}O$.

The ECG was monitored continuously throughout the procedure. Serial seven lead ECGs (the six limb leads and an anterior precordial lead) were recorded at baseline, before and after the first imaging sequence, at the initiation of the infusion of dipyridamole and every 2 min thereafter until

Table 1. Demographic and Clinical Characteristics of the Patients Studied

Case No.	Age (yr)/ Gender	Chest Pain	HTN	LVH	ECG	ETT	Tl-201	Medication	Chest Pain With Dipyridamole	LVEF	Angiographic Coronary Disease
Patients With Normal Myocardial Perfusion Reserve (Group I)											
1	50/M	R TNG	–	–	NL	–	–	Nit	–	0.63	None
2	64/M	Ex R	+	+	NL	–	–	BB HCTZ	–	0.83	None
3	56/F	Ex R TNG	+	–	LBBB	UI CP	+	Nit Ver	+	0.72	40% LAD
4	52/M	Ex R TNG	+	–	NL	– CP	+	Dilt BB	+	0.61	20%–30% LCx
5	52/F	Ex R	+	–	NT	0	0	Nit Dilt	–	0.71	None
6	42/M	R TNG	–	–	NST	0	0	0	+	0.80	None
7	58/M	Ex R TNG	–	–	NL	– CP	0	Dilt Nit	+	0.65	None
8	40/M	Ex R	–	–	NL	0	0	0	–	0.60	RCA PLQ
9	73/M	Ex R	+	–	NSTT	+	0	Ver	–	0.74	LAD PLQ
Patients With Reduced Myocardial Perfusion Reserve (Group II)											
10	59/M	Ex R TNG	+	–	NL	–	0	Dig Nit	–	0.81	None
11	41/M	Ex R TNG	–	–	NT	0	0	Nit Dilt	+	0.63	None
12	43/M	Ex	–	–	NL	+	0	0	–	0.72	None
13	45/F	Ex R TNG	–	–	NL	0	0	0	+	0.53	PLQ LAD PLQ LCx
14	71/M	R	–	–	NL	–	+	Dilt Nif Nit	–	0.74	PLQ LAD PLQ LCx PLQ RCA
15	50/M	Ex R	–	–	PRWP	+	+	0	–	0.68	None
16	63/M	Ex TNG	+	–	Paced	0	0	Nif Fur	+	0.72	PLQ LAD PLQ LCx PLQ RCA
17	49/F	Ex R TNG	–	–	PRWP	+	0	Dilt	+	0.65	None

BB = beta-adrenergic blocker; CP = chest pain; Dilt = diltiazem; ECG = electrocardiography; ETT = exercise tolerance test; Ex = exercise; F = female; Fur = furosemide; HCTZ = hydrochlorothiazide; HTN = hypertension; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LCx = left circumflex coronary artery; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; M = male; Nif = nifedipine; Nit = long-acting nitrates; NL = normal; NST = nonspecific ST segment abnormalities; NSTT = nonspecific ST-T wave abnormalities; NT = nonspecific T wave abnormalities; PLQ = minor plaquing or luminal irregularity (<20% stenosis); PRWP = poor precordial R wave progression; R = angina at rest; RCA = right coronary artery; Tl-201 = thallium-201 scintigraphy; TNG = pain relieved by nitrates; UI = uninterpretable; Ver = verapamil; 0 = not performed; + = positive findings; – = negative (normal) findings.

termination of the second $C^{15}O$ data collection study. If the patient developed symptoms, an additional ECG was recorded until symptoms had abated and the ECG had returned to baseline. Blood pressure was monitored with a sphygmomanometer at 1 min intervals during the infusion of dipyridamole and at 2 min intervals during imaging.

The effects of dipyridamole were reversed with aminophylline (125 to 250 mg intravenously) at the conclusion of the second $C^{15}O$ data collection study or earlier if symptoms warranted. In five patients, aminophylline was administered after the conclusion of the data collection study performed after the second injection of $H_2{}^{15}O$. In no patient was aminophylline administered before or during the data collection study performed after the second injection of $H_2{}^{15}O$. The $H_2{}^{15}O$ and $C^{15}O$ were prepared as previously described (16,17).

Analysis of tomographic data. Data collected after inhalation of $C^{15}O$ were reconstructed as single composite images for each of the seven tomographic sections. Each reconstruction comprised a 128 × 128 matrix of voxels, each of which represented a 3.5 × 3.5 mm area and a slice thickness of 1.14 cm. The $C^{15}O$ reconstructions aided in the definition of cardiac anatomy and in the placement of blood pool regions of interest. The first 30 s of each $H_2{}^{15}O$ data collection study was reconstructed as a series of 15 sequential 2 s frames. A 3 × 3 voxel region of interest was positioned interactively in the center of the left atrial blood pool and decay-corrected counts for the region of interest selected were plotted for the first 30 s after injection of $H_2{}^{15}O$. The time of arrival of the bolus of $H_2{}^{15}O$ in the left atrial blood pool was determined from the time-activity curve. Beginning with the time of arrival of radioactivity ($H_2{}^{15}O$) in the left atrial blood, a single composite image was reconstructed from 120 s of data for each ventricular level. In the composite $H_2{}^{15}O$ images, radioactivity attributable to tracer in the cardiac blood pool was corrected on a pixel by pixel basis as previously described (11–13). The composite spillover-corrected images were employed for positioning of regions of interest in left ventricular myocardium. With the use of an interactive cursor, a 3 × 3 voxel region of interest was centered in the left atrial blood pool for determination of the arterial input function. Larger irregular regions of interest were placed over the septum and anterior, lateral and posterior wall at multiple levels for determination of tissue time-activity curves.

Calculation of myocardial perfusion. For calculation of myocardial perfusion in absolute terms, data were reformatted into a sequence of 18 consecutive 5 s tomographic reconstructions. Regional, nutritive myocardial blood flow at rest and after dipyridamole injection was determined in absolute terms with a kinetic modification of the Kety one compartment model as previously described and validated in our laboratory (9,14). The method requires knowledge of the arterial input function, the time-activity curve of the flow tracer in the myocardium and the tissue/blood partition coefficient for the tracer. Previous studies in our laboratory (9) have demonstrated that time-activity curves obtained from regions placed in the left atrial blood pool closely approximate arterial input functions measured directly.

The model assumes that the arterial input function is not subject to partial volume effects (9,14) and that the spillover of myocardial activity into the blood pool region of interest does not contaminate the arterial input curve. Both of these assumptions are valid because the left atrium is more than twice the size of the resolution of the positron emission tomographic system used (18) and because the left atrial time-activity curves were acquired at levels above and posterior to the left ventricle sufficiently removed to preclude spillover of radioactivity from the myocardium to the left atrial region of interest.

A tissue/blood partition coefficient of 0.92 ml/g was employed in the calculations. The model used (9,14) employs a three variable fitting technique to estimate myocardial blood flow, the recovery coefficient of myocardium and the effects of spillover of blood radioactivity into the myocardium. Calculation of the myocardial recovery coefficient and spillover fraction with use of the operational flow equation eliminates the need to estimate these variables by employing independent measures of ventricular chamber dimensions and wall thickness, with their unavoidable inherent limitations and difficulties in indexing to ungated tomographic data (19). Because blood flow was homogeneous (see Results), flow values from all regions that could be analyzed in all sections were averaged for each subject. Myocardial perfusion reserve was defined as the ratio of myocardial blood flow after dipyridamole infusion to myocardial blood flow at rest in the same region of interest.

Statistics. All data are presented as mean values ± SD. For comparisons of differences, Student's *t* test for independent or paired samples as appropriate was employed. Chi-square analysis was employed for comparison of proportions. Differences with a p value <0.05 were considered to be significant.

Results

Patient characteristics (Table 1). The patients' age averaged 53 ± 10 years. On coronary angiography, minor luminal irregularities or plaquing was observed in 5 of the 17 patients. Two additional patients each demonstrated a single, subcritical coronary lesion demonstrating luminal narrowings of 20% to 40% of the vessel diameter. Thirty-five percent had a history of hypertension, but no subject had ECG evidence of left ventricular hypertrophy and only one had mild left ventricular hypertrophy noted at left ventriculography. Forty-seven percent had an abnormal rest ECG, including nonspecific ST-T wave abnormalities in four, poor precordial R wave transition in two, left bundle branch block in one and a permanent pacemaker in one patient. Seventy-six percent were taking one or more antianginal medications. Eight of the 17 patients had typical angina characterized as exertional substernal chest pain sometimes relieved by nitrates. Six other patients had exercise-induced chest pain not promptly relieved by nitrates. Atypical features were seen in

JACC Vol. 16, No. 3
September 1990:586–95

Table 2. Hemodynamics at Rest and After Dipyridamole

	Rest					Dipyridamole					
Case No.	HR (beats/min)	SBP (torr)	DBP (torr)	MAP (torr)	MBF (ml/g per min)	HR (beats/min)	SBP (torr)	DBP (torr)	MAP (torr)	MBF (ml/g per min)	MPR
Patients With Normal Myocardial Perfusion Reserve (Group I)											
1	56	119	80	93	1.12	76	120	79	93	3.69	3.2
2	52	123	85	98	0.86	66	121	82	95	2.55	3.0
3	68	140	72	95	1.03	94	131	68	89	5.98	5.8
4	73	140	93	109	0.85	107	141	89	106	4.13	4.9
5	62	127	80	96	0.46	76	124	74	91	3.28	7.1
6	60	133	83	100	1.84	85	144	83	103	8.35	4.5
7	62	124	83	97	1.56	96	126	77	93	6.15	3.9
8	77	112	69	83	1.71	100	123	69	87	7.03	4.1
9	55	153	86	108	1.07	57	152	86	108	3.21	3.0
Patients With Reduced Myocardial Perfusion Reserve (Group II)											
10	51	173	89	116	1.92	63	165	78	106	2.21	[illegible]
11	70	115	75	88	1.49	87	115	72	86	3.59	2.4
12	70	128	90	103	1.50	81	[illegible]	93	109	1.81	1.2
13	87	101	67	78	1.43	99	111	68	82	2.20	1.5
14	62	114	50	71	1.92	71	89	40	56	1.22	0.6
15	72	142	75	97	0.88	87	145	82	103	0.87	1.0
16	60	154	102	119	1.54	78	149	98	115	2.73	1.8
17	85	135	89	104	2.23	95	118	81	93	3.48	1.6
Combined Results for All Patients											
Normal subjects	69 ± 11	111 ± 10	73 ± 6	85 ± 6	1.25 ± 0.28	94 ± 14	118 ± 12	68 ± 7	85 ± 5	4.62 ± 1.58	3.8 ± 1.1
All patients	65 ± 11	132 ± 16*	80 ± 12†	97 ± 13*	1.38 ± 0.46	83 ± 14	135 ± 20†	78 ± 13†	95 ± 14†	3.68 ± 2.01	3.0 ± 1.8
Group I	63 ± 8	130 ± 13*	81 ± 7†	98 ± 8*	1.17 ± 0.43‡	85 ± 15	131 ± 12*	79 ± 7*	96 ± 7*	4.93 ± 1.89§	4.4 ± 1.3§
Group II	70 ± 12	133 ± 24*	80 ± 6	97 ± 17†	1.61 ± 0.38†	83 ± 12	129 ± 25	77 ± 18	93 ± 19	2.26 ± 0.92*	1.4 ± 0.5*

*$p < 0.01$ versus normal; †$p < 0.05$ versus normal; ‡$p < 0.05$ versus Group II; §$p < 0.01$ versus Group II. DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; SBP = systolic blood pressure.

many patients, including occasional chest pain at rest or atypical radiation of pain. Five patients had been admitted to the coronary care unit for the evaluation of severe chest pain on at least one occasion. Exercise ECGs or exercise thallium scintigrams were abnormal in 7 of the 10 patients in whom these tests were performed.

The mean time of coronary angiography to positron emission tomography was 79 days (range 1 day to 1 year). Eight patients were studied tomographically within 48 h of catheterization. There were no major clinical events between catheterization and tomography in any patient, with one exception. Patient 16 had a long history of syncopal episodes and had a permanent pacemaker in place. A single syncopal episode occurred between cardiac catheterization and his initial tomographic study, but there were no sequelae of this event and no evidence of interim myocardial infarction. The patient was studied tomographically on a second occasion 4 months after his initial study, without a significant interim event and without a significant change in tomographic findings.

Hemodynamic and clinical responses to dipyridamole (Table 2). The interval from initiation of infusion of dipyridamole to injection of $H_2{}^{15}O$ was 8.5 ± 0.7 min in normal control subjects and 9.0 ± 1.3 min in patients (p = NS). In the normal subjects, heart rate increased from 69 ± 11 to 94 ± 14 beats/min ($p < 0.001$) accompanied by a slight increase in systolic and mean blood pressure and a slight decline in diastolic blood pressure. In the patients, heart rate increased from 65 ± 11 to 83 ± 14 beats/min. Neither systolic nor diastolic pressure changed significantly. However, rest and postdipyridamole blood pressures were significantly higher in patients than in normal subjects under the same conditions. Nine patients experienced chest pain during or after infusion of dipyridamole; in each, the pain was similar to that experienced spontaneously. Five of the nine patients exhibited reversible ST segment depression with infusion of dipyridamole, but ST segment depression was <0.1 mV in all.

For purposes of data analysis, all patients were compared with all normal volunteers. In addition, patients were separated into two groups with respect to estimates of myocardial perfusion reserve. One group (Group I) comprised patients in whom myocardial perfusion increased ≥2.5-fold (a normal response, based on our experience [9]

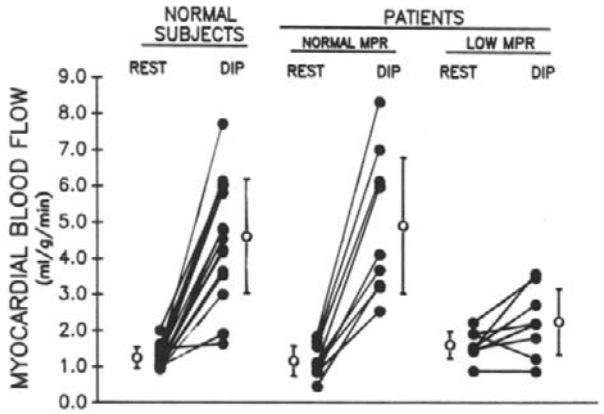


Figure 1. Individual values for myocardial perfusion at rest and after dipyridamole (DIP) for normal subjects, patients with normal myocardial perfusion reserve (MPR) (Group I) and those with reduced myocardial perfusion reserve (Group II). **Open circles** indicate group means and **brackets** indicate standard deviations.

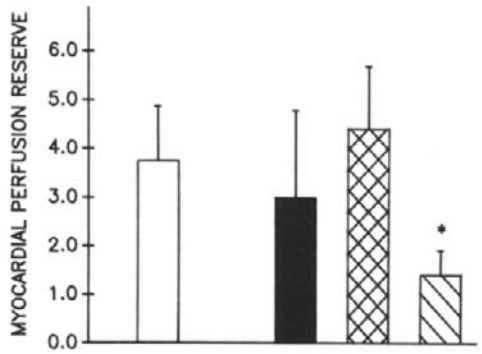


Figure 2. Average data for myocardial perfusion reserve (MPR) in normal subjects (n = 16) (**open bar**), all patients (n = 17) (**solid bar**), patients in Group I, myocardial perfusion reserve ≥2.5, (n = 9) (**cross-hatched bar**) and patients in Group II, myocardial perfusion reserve <2.5, (n = 8) (**slashed bar**). **Brackets** indicate standard deviations and the **asterisk** indicates $p < 0.001$ compared with normal subjects or with patients with normal myocardial perfusion reserve.

with normal subjects studied with positron emission tomography and $H_2{}^{15}O$ and from results of others [8,10,20] who assessed coronary flow reserve with intracoronary Doppler probes). The other group of patients (Group II) comprised those in whom the response to dipyridamole was blunted (myocardial perfusion reserve <2.5) (Fig. 1). The increase in heart rate after dipyridamole averaged 13 ± 3 beats/min in patients in Group II compared with 25 ± 7 beats/min in normal subjects ($p < 0.001$) and 22 ± 8 beats/min in patients with chest pain, angiographically normal coronary arteries and normal flow responses (Group I) ($p < 0.001$). The responses of systolic and diastolic blood pressure to dipyridamole were similar in the two groups of patients (that is, those with normal and those with attenuated responses of myocardial perfusion to dipyridamole). Maximal myocardial work loads reflected by the rate-pressure product (heart rate × systolic blood pressure) induced by dipyridamole were similar in normal subjects and both groups of patients. The proportion of men and the characteristics of the chest pain were similar in the two groups of patients, as was the incidence of induction of chest pain with dipyridamole (Table 1).

Myocardial perfusion. Patients differed from normal subjects with respect to myocardial nutritive perfusion at rest and after dipyridamole and with respect to calculated myocardial perfusion reserve (Table 2, Fig. 2). At rest, myocardial perfusion in normal subjects averaged 1.25 ± 0.28 ml/g per min; it increased to 4.62 ± 1.58 ml/g per min ($p < 0.001$) after dipyridamole. Average myocardial perfusion reserve was 3.8 ± 1.1. With all 17 patients considered as a group, blood flow at rest was higher (1.38 ± 0.46 ml/g per min) and maximal myocardial blood flow lower (3.68 ± 2.02 ml/g per min) than in normal subjects. Although these differences were not significant, they were directionally consistent. Myocardial perfusion reserve averaged 3.0 ± 1.8 in patients, a value somewhat lower than that in normal subjects.

When the response to dipyridamole among patients was analyzed with respect to normal responses delineated previously by us (9) and others (8,21), 8 of the 17 patients exhibited reduced myocardial perfusion reserve (<2.5) in contrast to only 2 of 16 normal volunteers ($p < 0.03$ by chi-square analysis) (Fig. 1). Striking differences were apparent in comparisons of patients in Groups I and II. Blood flow at rest in patients in Group II averaged 1.61 ± 0.38 compared with 1.25 ± 0.28 ml/g per min in normal subjects ($p < 0.02$) and 1.17 ± 0.42 ml/g per min in patients in Group I ($p < 0.05$) (Table 2). Maximal myocardial blood flow was markedly lower (2.26 ± 0.92 ml/g per min) in patients in Group II compared with values in normal subjects (4.62 ± 1.58 ml/g per min, $p = 0.001$) and patients in Group I (4.93 ± 1.89 ml/g per min, $p = 0.004$). Myocardial perfusion reserve in patients in Group II averaged only 1.4 ± 0.5 compared with 3.8 ± 1.1 in normal subjects ($p < 0.001$) and 4.4 ± 1.3 in Group I ($p < 0.001$).

Myocardial perfusion reserve in patients in whom chest pain was induced by dipyridamole was not significantly different from values in patients in whom it was not (3.0 ± 1.7 versus 2.9 ± 2.0, p = NS). The percent of patients in Groups I and II with abnormal treadmill or thallium scintigraphic studies was comparable (Table 1). Myocardial perfusion reserve in patients with a positive treadmill or thallium exercise stress test was not significantly different from that in those in whom results of these tests were normal (2.6 ± 2.0 versus 3.3 ± 1.7, p = NS). The prevalence of minor irregularities of the coronary vasculature was similar in Groups I and II, and the presence of plaquing did not affect rest or maximal myocardial blood flow or myocardial perfusion reserve. Myocardial perfusion reserve in patients with

JACC Vol. 16, No. 3
September 1990:586-95

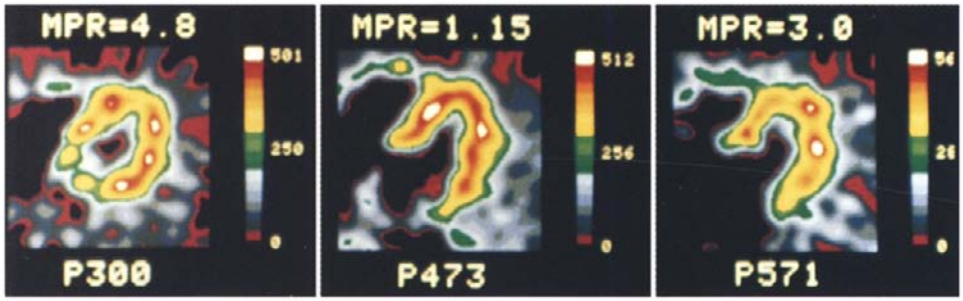


Figure 3. Midventricular reconstructions depicting relative flow for a normal subject (P300), Patient 10 (P473) from Group II with reduced myocardial perfusion reserve (MPR) and Patient 9 (P571) from Group I with normal myocardial perfusion reserve. Values for perfusion reserve are shown above each image. The top of each image is anterior and the right of each image is the patient's left. Areas of white and red indicate zones of highest flow and areas of blue and black signify lowest flow. In each image, the discontinuity posteriorly is due to the mitral apparatus, which is below the resolution of the instrument. In each patient, subjective and objective assessment indicated that myocardial perfusion was homogeneous despite wide differences in myocardial perfusion reserve among the patients. Thus, simple static imaging of relative perfusion does not permit assessment of quantitative differences in myocardial perfusion or perfusion reserve.

coronary artery plaquing was 3.1 ± 1.9 compared with 2.9 ± 1.9 (p = NS) in patients without coronary luminal irregularities.

Nearly half of the patients in each of the two groups had been given nitrates recently, and half of those in each group had been given a calcium channel blocker. There was no significant difference in perfusion at rest between patients with and without calcium channel blockade (1.35 ± 0.55 versus 1.40 ± 0.41 ml/g per min, p = NS), and there was no difference in maximal perfusion (3.75 ± 1.54 versus 3.59 ± 2.67 ml/g per min) or in myocardial perfusion reserve (3.5 ± 2.2 versus 2.3 ± 1.2, p = NS). These data suggest that patients had indeed not taken their medication during the 12 to 18 h before tomography as instructed or that these agents did not significantly affect the variables assessed. Recent work by Rossen et al. (21) demonstrated that treatment with diltiazem did not alter coronary flow reserve measured with an intracoronary Doppler flow probe in a group of patients undergoing diagnostic cardiac catheterization. Similarly, there were no differences in rest or maximal myocardial blood flow or myocardial perfusion reserve between patients who had or had not been receiving long-term nitrate therapy. Overall left ventricular function was comparable between patients in Groups I and II (Table 1).

Regional flow responses. Myocardial perfusion was homogeneous in normal subjects and patients. No discrete perfusion defects were apparent on composite tomographic images (Fig. 3). When myocardial perfusion was assessed regionally in three to four regions per tomographic reconstruction, responses were relatively uniform within each subject and patient (Fig. 4). The coefficients of variation for myocardial perfusion with hyperemia were 26 ± 17 for normal subjects, 22 ± 15 for patients in Group II with reduced myocardial perfusion reserve and 14 ± 10 for the patients in Group I with normal myocardial perfusion reserve (p = NS). No systematic differences in perfusion were noted among anterior, septal, lateral and posterior regions with regard to rest flow, peak flow or myocardial perfusion reserve in normal subjects or either group of patients (Fig. 4).

Reproducibility of flow estimates. To define the reproducibility of the tomographic end points and the persistence of impaired perfusion over time, 10 patients were studied on two occasions an average of 5.2 months apart (range 3 h to 10 months). No significant differences were observed between results of initial and follow-up studies with regard to perfusion at rest or after dipyridamole or with regard to myocardial perfusion reserve. Initial and repeat measurements of perfusion correlated closely ($r = 0.93$, $p < 0.001$) (Fig. 5).

Discussion

Myocardial perfusion reserve. Our results indicate that myocardial perfusion reserve is limited in a substantial number of patients with chest pain and angiographically normal coronary arteries. The limitation of perfusion reserve reflects both increased flow at rest and decreased maximal

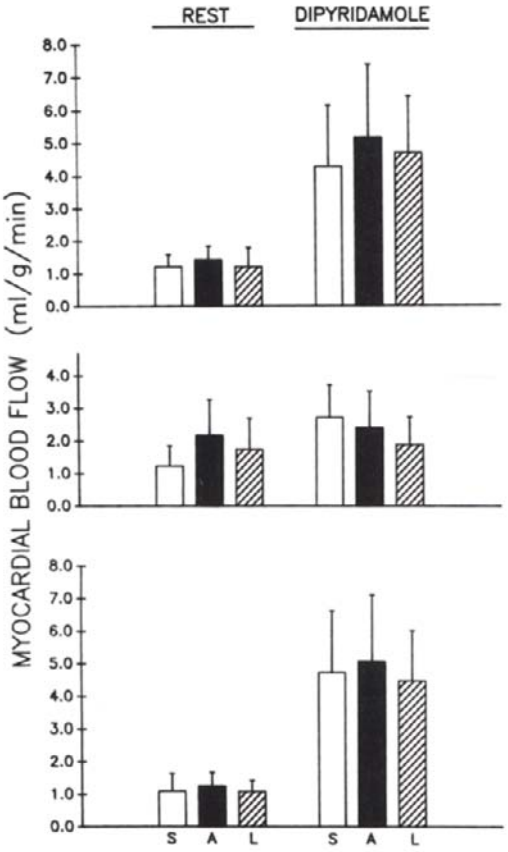
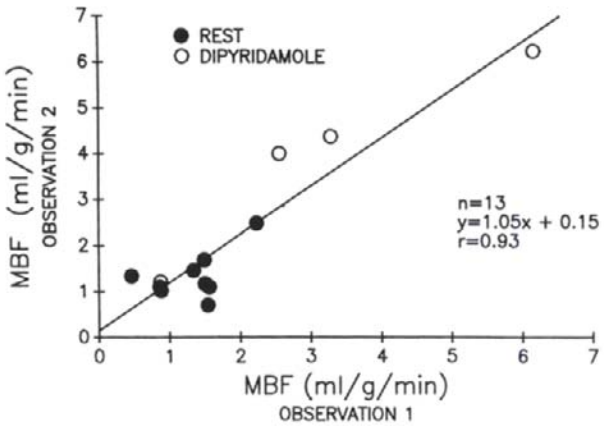


Figure 4. Regional values of myocardial perfusion at rest and after dipyridamole for normal subjects (**top**), patients in Group I (**bottom**) and patients in Group II (**middle**). No regional disparities were observed. A = anterior; L = lateral; S = septum.

myocardial perfusion induced by the vasodilator dipyridamole. These abnormalities of perfusion appear to be global, throughout the left ventricle. Thus, variability of regional perfusion in the patients studied is comparable with that in normal subjects. This is the first noninvasive study to demonstrate absolute changes in myocardial perfusion, both at rest and with vasodilator stress, in patients with this syndrome. Previous studies that provided quantitative data were invasive. Prior noninvasive studies were limited to evaluation of relative perfusion, employing thallium (22,23) or indirect measures of ischemia such as the development of regional wall motion abnormalities (24,25).

Figure 5. Myocardial blood flow (MBF) was assessed twice at rest or with dipyridamole stress, or both, in 10 patients. Data acquired at rest are indicated by **solid circles** and those acquired after dipyridamole by **open circles**. Results of the duplicate studies correlated closely.



Role of blood pressure elevation. Although the cause of the increased perfusion at rest has not been determined conclusively, blood pressure at rest was significantly higher than in normal control subjects, possibly reflecting a modest incidence of hypertension, although it was within the generally defined normal range at the time of study in 11 of the 17 patients. Judging from results of studies performed in experimental animals (26), one would expect autoregulation at the blood pressure observed, with maintenance of myocardial perfusion at a virtually constant level. However, such studies have generally been performed in the arrested heart or under conditions in which myocardial work is held constant (26). In the heart of intact animals, increased systemic arterial blood pressure increases myocardial work and oxygen consumption, thereby increasing the demand for perfusion, which increases to meet the demand (27). In previous studies (28) of patients with single vessel coronary artery disease, we observed high rest perfusion in zones supplied by angiographically normal coronary arteries. Blood pressure at rest in patients who exhibited this phenomenon was similar to blood pressure in the patients in the present study and higher than that in the normal control subjects. Accordingly, increased rest myocardial oxygen requirements are the likely cause of the observed increased blood flow at rest.

Reduced maximal perfusion and perfusion reserve induced by dipyridamole. The limitation of myocardial perfusion reserve was also attributable, however, not only to increased rest flow, but also to a significant diminution of maximal perfusion induced by dipyridamole. Reduced maximal myocardial perfusion and reduced myocardial perfusion reserve were evident in 8 (47%) of the 17 patients we studied. Patients with reduced maximal myocardial perfusion and perfusion reserve were indistinguishable from those patients with normal perfusion reserve based on gender, clinical history, characteristics of the chest pain, rest hemodynamics (heart rate, systolic blood pressure, rate-pressure product), ECG responses to dipyridamole or exercise stress and prior medication. Patients in both Groups I and II were older than our normal volunteers, but there was no significant difference in age between patients in Groups I and II. In recent preliminary studies in our laboratory (unpublished observations), myocardial perfusion at rest and perfusion reserve in healthy subjects >40 years of age without evidence or history of heart disease appeared to be comparable with those of younger individuals. The minor degrees of coronary

JACC Vol. 16, No. 3
September 1990:586–95

atherosclerosis observed in some patients in this study did not appear to affect the results substantially because myocardial perfusion at rest and perfusion reserve in patients with minor degrees of plaquing were comparable with those in patients who did not demonstrate such luminal irregularities. Despite some overlap, increases in heart rate induced by dipyridamole were less in patients with depressed myocardial perfusion reserve compared with changes in the other patients or in normal volunteers. Visual assessment of tomographic images of relative perfusion did not permit differentiation of patients with and without blunted responses to dipyridamole.

Previous studies. Our observations are concordant with prior observations by others who employed invasive techniques. Opherk et al. (5) studied 36 patients with chest pain and normal coronary arteriograms and demonstrated reduced coronary sinus blood flow reserve in 21, most of whom had episodes of severe chest pain and abnormal exercise stress tests. Observations by Cannon et al. (1) demonstrated attenuation of the increase in great cardiac vein flow induced by rapid atrial pacing in 13 (59%) of 22 patients, with relative preservation of the response in the remainder despite similar presenting symptoms.

Metabolic studies in patients with chest pain and angiographically normal coronary arteries have been performed by several investigators (1,3,5,29) employing great cardiac vein or coronary sinus catheterization. Abnormal flow or metabolic responses were found in 34% to 46% of patients with chest pain and angiographically normal coronary arteries.

Wall motion at rest was normal in our patients and those studied by Cannon et al. (24). However, they observed focal wall motion abnormalities after exercise stress in 46% of patients and other abnormalities of global or regional ejection fraction in 79% of patients undergoing exercise stress. Conversely, although Picano et al. (25) observed ST segment depression in 84% of patients studied after high doses of intravenous dipyridamole, no wall motion abnormalities were detected.

Thallium scintigraphy has been employed extensively in the diagnostic evaluation of patients with chest pain and angiographically normal coronary arteries. Abnormalities have been observed in the regional distribution or kinetics of thallium-201 after exercise in 15% to 45% of patients (22,23).

The limitation of myocardial perfusion reserve observed in the present study was remarkably homogeneous. Regional information is not available from the analysis of coronary sinus or great cardiac vein flow by catheterization. Wall motion abnormalities have been found in 0% to 79% of patients with angina and angiographically normal coronary arteries (24,25,30) and regional abnormalities of the distribution of thallium-201 in 15% to 45% (22,23). The low incidence of regional abnormalities of myocardial perfusion reserve observed in our study is consistent with observations by Picano et al. (25), who used dipyridamole (as did we), an intervention that accentuates regional differences in perfusion without necessarily inducing ischemia. In contrast, most studies (22–24) reporting a high incidence of regional wall motion or thallium distribution abnormalities are those in which exercise stress was employed.

Technical considerations. Positron emission tomography provides quantification of regional tissue content of tracer not attainable with single photon imaging techniques, including single photon emission computed tomography. Oxygen-15–labeled water behaves essentially as a freely diffusible tracer in the heart and permits accurate measurement of myocardial perfusion despite hyperemia (9,11–14).

The tomographic data in the present study were acquired in an ungated mode. Thus, significant spatial averaging was unavoidable (19). Although ECG gating is feasible with positron emission tomography and has been employed in some studies (19,31), its implementation with dynamic acquisitions including individual time frames as brief as 5 s is impractical because of limitations in counting statistics. Because of the lack of gating and because of volume averaging, small regional abnormalities of myocardial perfusion might have been missed, particularly if they involved the inferoposterior wall or apex, regions with data most prone to distortion from partial volume averaging. Perfusion abnormalities observed in other patients may have involved primarily subendocardium. Unfortunately, the spatial resolution of current generation positron emission tomographic instruments does not permit independent assessment of subendocardial and subepicardial perfusion.

A fixed dose of dipyridamole (0.56 mg/kg) was used in our study. Previous studies (8,32) with coronary artery Doppler catheterization have demonstrated that the coronary blood flow response to dipyridamole is variable. Some patients respond to only large doses of dipyridamole. Dipyridamole may not elicit maximal coronary vasodilation compared with that induced by papaverine (10,32).

Clinical implications. The data obtained indicate that many patients with chest pain and angiographically normal coronary arteries exhibit limited nutritive perfusion reserve. The limitation of perfusion reserve is detectable noninvasively. Its response to putative therapeutic intervention should facilitate objective evaluation of benefit without the need for repeated cardiac catheterization and ultimately help to clarify the nature of the fundamental derangement responsible for the syndrome.

We thank Philip A. Ludbrook, MD, Alan J. Tiefenbrunn, MD and the physicians and technical staff of the cardiac catheterization laboratory of Barnes Hospital for their assistance with the acquisition and analysis of coronary angiograms; Theron Baird and Colleen Schaab, RN for technical assistance with the positron emission tomographic studies; the staff of the Washington University Medical Cyclotron for preparation of tracers and Joyce Kalayeh for preparation of the manuscript.

References

1. Cannon RO III, Watson RM, Rosing DR, Epstein SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. J Am Coll Cardiol 1983;1:1359–73.
2. Sax FL, Cannon RO III, Hanson C, Epstein SE. Impaired forearm vasodilator reserve in patients with microvascular angina. N Engl J Med 1987;317:1366–70.
3. Greenberg MA, Grose RM, Neuburger G, Silverman R, Strain JE, Cohen MV. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia in patients with angina pectoris and normal coronary arteries. J Am Coll Cardiol 1987;9:743–51.
4. Cannon RO III, Schenke WH, Leon MB, Rosing DR, Urqhart J, Epstein SE. Limited coronary flow reserve after dipyridamole in patients with ergonovine-induced coronary vasoconstriction. Circulation 1987;75:163–74.
5. Opherk D, Zebe H, Weihe E, et al. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. Circulation 1981;63:817–25.
6. Cannon RO III, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries: role of small coronary arteries. Am J Cardiol 1985;55:50B–60B.
7. Cannon RO III, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol 1988;61:1338–43.
8. Wilson RF, Laughlin DE, Ackell PH, et al. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;72:82–92.
9. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. J Am Coll Cardiol 1989;14:639–52.
10. White CW, Wilson RF, Marcus ML. Methods of measuring myocardial blood flow in humans. Prog Cardiovasc Dis 1988;31:79–94.
11. Bergmann SR, Fox KAA, Rand AL, et al. Quantification of regional myocardial blood flow in vivo with $H_2{}^{15}O$. Circulation 1984;70:724–33.
12. Knabb RM, Fox KAA, Sobel BE, Bergmann SR. Characterization of the functional significance of subcritical coronary stenosis with $H_2{}^{15}O$ and positron-emission tomography. Circulation 1985;71:1271–8.
13. Walsh MN, Bergmann SR, Steele RL, et al. Delineation of impaired regional myocardial perfusion by positron emission tomography with $H_2{}^{15}O$. Circulation 1988;78:612–20.
14. Herrero P, Markham J, Bergmann SR. Quantitation of myocardial blood flow with $H_2{}^{15}O$ and positron emission tomography: assessment and error analysis of a mathematical approach. J Comput Assist Tomogr 1989;13:862–73.
15. Ter-Pogossian MM, Ficke DC, Yamamoto M, Hood JT. Super PETT I: a positron emission tomography utilizing photon time-of-flight information. IEEE Trans Med Imag 1982;3:179–87.
16. Welch MJ, Kilbourn MR. A remote system for the routine production of oxygen-15 radiopharmaceuticals. J Labeled Compd & Radiopharm 1985;22:1193–200.
17. Welch MJ, Ter-Pogossian MM. Preparation of short half-lived radioactive gases for medical studies. Radiat Res 1968;36:580–7.
18. Hoffman EJ, Huang S-C, Phelps ME. Quantitation in positron emission computed tomography. 1. Effect of object size. J Comput Assist Tomogr 1979;3:299–308.
19. Ter-Pogossian MM, Bergmann SR, Sobel BE. Influence of cardiac and respiratory motion on tomographic reconstructions of the heart: implication for quantitative nuclear cardiology. J Comput Assist Tomogr 1982;6:1148–55.
20. Bortone AS, Hess OM, Eberli FR. Abnormal coronary vasomotion during exercise in patients with normal coronary arteries and reduced coronary flow reserve. Circulation 1989;79:516–27.
21. Rossen JD, Simonetti I, Marcus ML, Braun P, Winniford MD. The effect of diltiazem on coronary flow reserve in humans. Circulation 1989;80:1240–6.
22. Meller J, Goldsmith SJ, Rudin A, et al. Spectrum of exercise thallium-201 myocardial perfusion imaging in patients with chest pain and normal coronary angiograms. Am J Cardiol 1979;43:717–23.
23. Kaul S, Newell JB, Chesler DA, Pohost GM, Okada RD, Boucher CA. Quantitative thallium imaging findings in patients with normal coronary angiographic findings and in clinically normal subjects. Am J Cardiol 1986;57:509–12.
24. Cannon RO III, Bonow RO, Bacharach SL, et al. Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. Circulation 1985;71:216–26.
25. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Usefulness of a high-dose dipyridamole-echocardiography test for diagnosis of syndrome X. Am J Cardiol 1987;60:508–12.
26. Dole WP. Autoregulation of the coronary circulation. Prog Cardiovasc Dis 1987;29:293–323.
27. Mosher P, Ross J Jr, McFate PA, et al. Control of coronary blood flow by an autoregulatory mechanism. Circ Res 1964;14:250–9.
28. Walsh MN, Geltman EM, Steele RL, et al. Augmented myocardial perfusion reserve after coronary angioplasty quantified by positron emission tomography with $H_2{}^{15}O$. J Am Coll Cardiol 1990;15:119–27.
29. Berland J, Cribier A, Cazor JL, Hecketsweiler B, Letac B. Angina pectoris with angiographically normal coronary arteries: a clinical, hemodynamic and metabolic study. Clin Cardiol 1984;7:485–92.
30. Schofield PM, Brooks NH, Bennett DH. Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms. Br Heart J 1986;56:327–33.
31. Hoffman EJ, Phelps ME, Wisenberg G, Schelbert HR, Kuhl DE. Electrocardiographic gating in positron emission computed tomography. J Comput Assist Tomogr 1979;3:733–9.
32. Rossen JD, Simonetti I, Marcus ML, Winniford MD. Coronary dilation with standard dose dipyridamole and dipyridamole combined with handgrip. Circulation 1989;79:566–72.