
Noninvasive Assessment of Coronary Collaterals in Man by PET Perfusion Imaging

Linda L. Demer, K. Lance Gould, Richard A. Goldstein, and Richard L. Kirkeeide

Division of Cardiology, Positron Diagnostic and Research Center, The University of Texas Medical School, Houston, Texas, and Division of Cardiology, University of California, Los Angeles, School of Medicine, Los Angeles, California

At present, coronary collateralization cannot be identified or assessed noninvasively in patients. In animal studies, coronary collaterals are associated with coronary steal, defined as a regional fall in perfusion during coronary arteriolar vasodilation. To determine the effect of coronary arteriolar vasodilation on collateral bed perfusion in man, myocardial perfusion imaging was performed before and after pharmacologic coronary vasodilation in patients with coronary artery disease (CAD). Regional myocardial activity of ^{82}Rb or ^{13}N ammonia was measured by positron emission tomography (PET) at rest and with intravenous dipyridamole/handgrip stress in 28 patients with angiographic collaterals and in 25 control patients with similar CAD severity by quantitative arteriography. Regional myocardial activity decreased after dipyridamole, indicating coronary steal, in 25 of 28 patients with angiographic collaterals and in only 4 of 25 control patients without angiographic collaterals. These findings suggest that developed collaterals are associated with myocardial steal in patients with CAD, allowing potential use of PET for non-invasive identification of coronary collateralization.

J Nucl Med 1990; 31:259-270

Identification of coronary collaterals is relevant for clinical decision-making as well as for clinical studies of the protective value of collaterals in ischemia and acute occlusion. At present, collaterals are detected by coronary angiography, requiring an invasive procedure, and providing limited information not suitable for quantitation.

The phenomenon of coronary steal, defined as decreased perfusion to a collateralized region of myocardium in response to coronary arteriolar vasodilation without change in aortic perfusion pressure or heart rate, has been observed in some animal studies (1-6) but not in others (7,8,9). The clinical occurrence and significance of steal remain uncertain, because methods for assessing coronary or collateral flow in man are

inadequate. Radioactive isotope techniques have now made it possible to assess myocardial perfusion noninvasively.

This study was undertaken to assess the effect of dipyridamole-induced coronary arteriolar vasodilation on perfusion of collateralized myocardium assessed by positron emission tomography (PET) in patients with well-developed coronary collaterals compared to those with comparable coronary disease without collaterals.

METHODS

One hundred and eleven patients underwent rest-stress PET perfusion imaging and quantitative coronary angiography at the University of Texas School of Medicine between July 1985 and October 1986. Cardiac catheterization reports were retrospectively reviewed, and cineangiograms of those patients reported to have any form of collateral circulation were evaluated by two experienced readers without knowledge of the PET scan results, prior to quantitative analysis of the perfusion images. Patients who had undergone coronary artery bypass surgery were excluded. From this group, twenty-eight patients were identified as having well-developed, intercoronary collaterals by angiography.

Of the remaining patients without reported arteriographic collaterals, those with coronary artery disease (CAD), defined as abnormal stenosis flow reserve by quantitative arteriography (flow reserve < 4.5) or documented prior myocardial infarction, constituted the control group. Absence of collaterals in these patients was verified by review of cineangiograms by the same readers without knowledge of the PET scan results. From this group, twenty-five patients were identified as having CAD without intercoronary collaterals by angiography.

Coincidentally, half of the patients in each group had a history of transmural myocardial infarction. All patients gave informed consent in accordance with the protocol approved by the Committee for Protection of Human Subjects. Results are reported as mean \pm s.d., and statistical significance are assessed by the chi-square test.

Angiography

Coronary angiography was performed using multiple, orthogonal projections within 14 wk of the PET scan with a mean interval of two weeks. Angiograms were reviewed by two investigators without knowledge of the PET scan results. Collaterals were considered present when there was: (1) dense or faint retrograde filling of the entire coronary arterial system

Received Sept. 22, 1989, revision accepted Oct. 5, 1989.
For reprints contact: Linda L. Demer, MD, PhD, Division of Cardiology, 47-123 CHS, UCLA School of Medicine, 10833 LeConte Ave., Los Angeles, CA 90024-1679.

distal to a stenosis or occlusion; or (2) dense retrograde filling of isolated segments within that region. Collaterals were considered absent if there was no or only faint retrograde filling of one isolated segment.

Quantitative Arteriographic Analysis

For nonoccluded arteries, stenosis severity on arteriograms was determined by automated quantitative analysis utilizing automated border recognition and cross-sectional densitometry techniques to determine relative percent narrowing, absolute lumen cross-sectional area, and integrated length effects. This method has been previously shown to have an accuracy within ± 0.1 mm in phantoms and a reproducibility of 2% to 3% *in vivo* (10).

Positron Imaging

Imaging was performed using the previously described University of Texas multi-slice tomograph (11). Patients were positioned in the camera after fluoroscopic determination of heart location. Patient position was monitored using laser light markers to align marks applied to the skin of the chest. Transmission images were obtained using a ^{68}Ga ring to correct for photon attenuation.

The resting perfusion image, consisting of nine simultaneous slices, encompassing the entire heart, was obtained after intravenous (i.v.) injection of either cyclotron-produced [^{13}N] ammonia (33 patients) or generator-produced rubidium-82 (^{82}Rb) (20 patients) according to availability of the rubidium generator. To avoid contamination from blood-pool activity, acquisition was started one minute after the end of ^{82}Rb infusion and three minutes after [^{13}N] ammonia infusion.

Transmission images contained 100 to 200 million counts collected for 15 to 20 min. Emission images contained 30–60 million counts after 12 to 19 mCi of [^{13}N] ammonia collected over 15 to 20 min and 15 to 20 million counts after 30 to 50 mCi of ^{82}Rb collected over 6 to 7 min. For each patient, the same tracer, tracer doses, and acquisition times were used for rest and stress scans.

After waiting five half-lives following the rest image to allow tracer decay, dipyridamole (0.56 mg/kg) was infused over four minutes. Unilateral submaximal handgrip at 25% of predetermined maximum was begun two minutes after completion of the dipyridamole infusion and held for four minutes. Two minutes after the start of the handgrip, a second i.v. injection of the same tracer in the same dose and activity was administered, and imaging was repeated. Patients who developed significant angina pectoris, as judged by the staff cardiologist supervising the procedure, were given 125 mg of aminophylline intravenously to reverse the dipyridamole effects. The mean dose of ^{82}Rb was 41 mCi per injection (range = 30 to 55). The mean dose of [^{13}N] ammonia was 17 mCi per injection (range = 11 to 19). Mean dose was the same for the collateralized and control groups.

Blood pressure and pulse were recorded every two minutes for 20 min after the dipyridamole infusion was begun. Electrocardiograms (ECGs) were obtained before, during, and after dipyridamole infusion.

Image Analysis

Positron perfusion images were displayed in isocount color format as nine simultaneous tomographic slices within an interactive graphics program to outline regions of interest

(ROIs). The mean number of counts per pixel was measured within each anatomic region of each image slice. This measure is proportional to relative regional perfusion. A histogram of the distribution and s.d. of activity within each region was obtained in order to minimize edge effects.

Each image plane of left ventricular myocardium was divided into lateral, anterior, septal, and inferoposterior regions. Due to normal oblique asymmetric image planes, not all tomographic slices contained all four regions. Each nine-slice, cardiac image was divided into a mean of 18 ± 4 regions. The divisions were the same for each pair of rest and stress images in order to avoid artifacts related to geometry. Border zones were excluded. Mean counts, counts/pixel, and s.d. were recorded for each region of each image plane or slice. Repeat analyses by the same (LLD) or a different observer (RAG) were within $\pm 3\%$.

Definition of PET Steal

Any region of the positron tomographic image having an absolute decrease in counts during dipyridamole/handgrip stress, compared to rest, was defined as having PET steal. The degree of steal was expressed as the ratio of mean tracer activity during stress relative to rest in the central-most ROI in the steal area. This ratio was compared to the corresponding ratio for a reference region of the same heart, where the reference region was supplied by a normal coronary artery or that with the least disease.

RESULTS

Regional PET steal, defined as an absolute decrease in mean counts/pixel of any image region, stress compared to rest (Fig. 1), occurred in 25 of the 28 patients with angiographic collaterals. The location of angiographic collaterals matched the regions of PET steal in all but three patients (Table 1). In these three cases, the region of PET steal extended beyond the region of angiographic collateralization, suggesting either additional collaterals not visible by angiography or endo-



FIGURE 1

Example of steal by positron imaging in a patient with an occluded LAD artery. Resting perfusion is uniform (left image). With dipyridamole handgrip stress (right image), there is not only an apparent anterior defect on the positron image but also a fall in absolute mean counts/pixel in the area of the anterior defect, indicating myocardial steal. The isocount color scheme in these images is normalized to the maximal counts in each one's respective 9-slice, total heart scan.

TABLE 1
Patients with Collaterals: Quantitative Arteriography and Clinical Characteristics Versus Qualitative Steal

Patient	Diseased artery	SFR*	Trace†		Prior MI	Location	
			Collateralized artery	Dose (mCi)		Steal	Abnormal wall motion (at rest)
1	RCA	0	RCA	N(15,15)	—	+ P-L	I
2	OM	0	OM	R(53,53)	—	+ Diffuse	I
	RCA	1.8					
	LM	3.7					
3	OM	0	OM	R(30,30)	I-P	+ L	I
4	RCA	1.1	RCA	R(40,40)	—	+ I-P	P,Ap
5	RCA	0	RCA	N(15,15)	N-Q	+ I-P	—
	Cx	0.8					
6	RCA	0	RCA	N(18,18)	—	+ I-P	—
	LAD	1.5					
7	Cx	2.1	Cx	N(18,18)	A-P	+ I-P-L	I-P-L
8	LAD	1.1	LAD	N(17,11)	—	+ A-S	—
	Cx	0	Cx				
9	Cx	0	RCA	N(18,17)	Sm I	+ Diffuse	I-P
	RCA	0					
10	RCA	0	RCA	R(40,40)	N-Q	+ I-P	A-Ap-I
	LAD	2.3					
11	LAD	0	RCA	R(45,45)	I	+ P	I-P
	RCA	0					
12	RCA	99.0%‡	RCA	R(40,40)	I	+ I-P	A-I
	LAD	2.3					
13	Cx	1.0	Cx	R(40,40)	—	+ I-P-L	—
14	LAD	2.6	LAD	N(18,18)	—	+ A-L	—
15	RCA	0	RCA	R(40,40)	A	+ P	—
	LAD	1.7					
16	LAD	0	LAD	R(40,40)	A-I-L	+ A-I-P	AAp [§] L-1
	RCA	0	RCA				
	Cx	2.0					
17	LAD	0	LAD	R(40,40)	A-I	+ A-Ap	AAp [§] S-I
	RCA	0.7					
18	RCA	0	RCA	N(18,18)	I-L	+ Sm I-P	I-P
	Cx	3.3					
19	RCA	1.9	RCA	N(17,18)	—	+ A-L-P	Ap-S-I-P
20	Cx	0	Cx	N(18,17)	—	+ I-L	—
	RCA	1.2					
21	Cx	0	Cx	N(17,18)	—	—	A-P-L
	RCA	0	RCA				
	Dx	1.8					
22	LAD	0	LAD	N(17,17)	—	+ A-S-L	A
23	Cx	0	Cx	N(16,17)	—	+ A-L	Ap-I
24	RCA	0	RCA	N(17,19)	—	—	S-P
25	RCA	0	RCA	N(18,18)	I	—	I
	LAD	3.5					
26	RCA	0	RCA [¶]	N(17,18)	I	+ I-P	I-P-L
27	RCA	0	RCA	N(18,18)	I	+ I-P-L	I
28	RCA	3.4	PDA	N(18,18)	I	+ I-P-L	—

Legend. Angiographic results of patients with coronary collaterals compared to presence and location of PET steal. LM, LAD, RCA, Cx, OM, and Dx = left main, left anterior descending, right coronary, circumflex, obtuse marginal and diagonal arteries, respectively; A, Ap, I, P, L = anterior, apical, inferior, posterior, and lateral regions, respectively; N-Q = non-Q-wave infarction; Sm = small.

* SFR = stenosis flow reserve by quantitative coronary arteriography of most severe narrowing for each artery. The value 0 refers to 100% occlusion.

† Doses of tracer (N = N-13-ammonia; R = rubidium-82) for rest, stress images.

‡ Quantitative analysis could not be performed for the RCA in patient 12 due to overlying structures. The value given is the % diameter narrowing ascertained by the angiographer without knowledge of the PET scan results.

§ Indicates dyskinesia; otherwise, wall motion abnormality refers to hypokinesia in the regions listed.

¶ Re-occlusion following balloon angioplasty.

cardial steal in adjacent myocardial vascular beds supplied by stenotic arteries.

Of 25 control patients with coronary disease of comparable severity without collaterals, four showed decreased counts indicating myocardial steal. The remainder showed no regions of steal (Table 2). This correspondence between angiographic coronary collaterals and evidence of myocardial steal by PET is significant at the $p < 0.01$ level (chi-square = 29).

Quantitative Changes in Tracer Activity

In patients with collaterals, tracer activity in regions with steal decreased to as low as 61% of resting activity, with a mean decrease to 85% (Table 3). In the same patients, tracer activity in representative regions without steal increased to as much as 189% of resting activity, with a mean increase to 127% (Table 3).

In patients without collaterals, tracer activity in regions with steal (four patients) decreased to as low as 83% of resting activity, with a mean of 87.5% (Table 4). In the same patients, tracer activity in regions without steal increased to as much as 180% of resting activity with a mean increase to 127% of resting activity (Table 4).

Exceptions

The first patient with PET steal without angiographic collaterals had diffuse coronary spasm at cardiac catheterization and a steal pattern by PET that was scattered in various parts of the heart not following the anatomic distribution of the coronary arteries.

The second patient had PET steal in the inferoposterior wall and a right coronary artery stenosis with a stenosis flow reserve of 2.0. This patient had undergone successful PTCA of a lateral circumflex branch twelve weeks earlier.

The third patient had a mild left anterior descending lesion (59% diameter reduction, stenosis flow reserve = 2.9). A severe PET defect appeared in the anterior wall myocardium, and ST depression developed during dipyridamole/handgrip stress. Since mild lesions usually do not produce ischemia with dipyridamole stress, this lesion may have had superimposed spasm which could mimic myocardial steal if it occurred only during the stress scan.

The fourth patient had a previous inferior myocardial infarction due to left circumflex occlusion. On cardiac catheterization at the time of PET scanning, the posterior wall motion had normalized despite persistent occlusion of the circumflex. During dipyridamole/handgrip stress, angina pectoris developed with sufficient severity to require aminophylline. The PET scan showed myocardial steal posteriorly. These findings suggest the presence of collaterals that could not be seen on angiography.

All three patients with collaterals who did not demonstrate PET steal had completely occluded right cor-

onary arteries (RCAs) with collateral filling from the left system. One involved the entire RCA and included bridging collaterals as well as inter-coronary collaterals; the second patient had a distal occlusion of the RCA. The third patient had circumflex occlusion in addition to RCA occlusion. Only the second patient had myocardial infarction; all three had inferior wall motion abnormalities.

Coronary Angiographic Results

The collateral vessels found on angiography in these patient groups most commonly supplied the distal right coronary artery from the left coronary arteries (15 patients). In six patients, the distal RCA provided collaterals to the left circulation. In five patients collaterals joined the left anterior descending and circumflex arteries. In one patient, the left circumflex artery provided collaterals to both the RCA and LAD. In another patient, there was diffuse collateralization involving all three major coronary arteries.

There was complete, proximal occlusion of at least one major epicardial coronary artery in 9 (32%) of 28 patients with collaterals and 5 (20%) of 25 controls. For the remaining patients without occlusions, mean percent diameter narrowing was 68% and mean stenosis flow reserve was 2.1 for collateralized patients; for control patients, mean percent diameter narrowing was 63% and stenosis flow reserve was 2.7. This difference in stenosis severity of patent arteries was not statistically significant. In the 9 out of 28 patients with complete occlusions of the major proximal/epicardial coronary arteries, who also had well-developed angiographic collaterals, mean ejection fraction was 29 ± 9 with minimal to mild decreases in regional left ventricular wall motion. Ejection fractions are given in Table 5.

Symptoms During Dipyridamole Stress

Twelve of 28 patients with angiographic collaterals reported chest pain during dipyridamole/handgrip stress. Six of these required reversal of dipyridamole effect by i.v. aminophylline. In comparison, only six of 25 control patients without angiographic collaterals reported chest pain, of whom three required aminophylline, two had ST depression on electrocardiogram, and one had PET steal. Two control patients, in addition to the above six, had ECG changes with no angina, and no PET steal. The observed difference between the two groups in frequency of dipyridamole-induced chest pain does not reach statistical significance ($0.25 > p > 0.10$). Of the 12 patients with collaterals who developed chest pain with dipyridamole, 11 had PET steal. Of the five control patients with chest pain, one had PET steal.

Of the eight control patients who had ECG changes and/or angina pectoris with dipyridamole, six had one or more significantly stenotic, but patent, coronary arteries as well as a severe PET defect without steal. For these six, the mean diastolic blood pressure increased

TABLE 2
Control Patients: Quantitative Arteriography and Clinical Characteristics vs. Qualitative Steal

Patient	Diseased artery	SFR [*]	Tracer [†] dose (mCi)	Prior MI	Location	
					Steal	Abnormal wall motion (at rest)
1C	RCA	2.8	N(18,18)	I	—	—
2C	Cx	2.8	R(30,30)	—	—	S
3C	Cx	2.6	N(18,15)	—	—	—
4C	LAD	3.4	N(17,15)	N-Q	—	—
5C	OMI	3.7	N(18,18)	I-P-L	—	Ap-I
6C	RCA	0	R(35,35)	I	—	Ap-I-P-L
7C	RCA	4.3	R(55,55)	—	—	I-P
8C	LAD	spasm	R(40,40)	—	Scattered	—
9C	Cx	0.9	N(16,16)	—	—	—
10C	RCA	2.0	R(40,40)	—	I-P	—
	LAD	2.5				
	Cx	3.1				
11C	LAD	3.0	N(19,17)	—	—	—
12C	OM	1.1	R(40,40)	—	—	—
	LAD	4.4				
13C	LAD	2.9	N(18,18)	—	A	—
	Cx	4.4				
14C	LAD	1.4	R(40,40)	—	—	—
	Cx	2.0				
15C	LAD	90% [‡]	R(40,40)	A-Ap	—	Ap [§]
16C	OM	0	R(40,40)	A-I	—	—
	RCA	4.7				
17C	LAD	3.8	R(40,40)	A	—	—
18C	LAD	1.7	N(17,17)	I	—	AAp-I
	Cx	3.5				
	RCA	2.9				
19C	LAD	2.5	N(17,17)	—	—	—
	Dx	0.9				
20C	Dx	0	N(18,18)	—	—	—
21C	RCA	1.8	N(17,17)	I	—	—
	Ramus	3.6				
22C	Dx	1.1	N(17,17)	—	—	—
	LAD	3.9				
23C	OM	4.7	N(18,17)	I	—	I
24C	Cx	0	N(18,18)	I-L	A-L	—
25C	Cx	1.6	N(18,18)	—	—	—

Legend. Angiographic results of control patients without coronary collaterals compared to presence and location of PET steal.

^{*} Abbreviations are as defined in Table 1.

[†] Doses of tracer for rest and stress images.

[‡] Quantitative analysis could not be performed for the LAD lesion in Patient 15C due to overlying structures. The value given is the % diameter narrowing ascertained by the angiographer without knowledge of the PET scan results.

[§] Dyskinetic wall motion; otherwise, wall motion abnormality refers to hypokinesis.

from 73 to 78 mmHg and the mean heart rate increased from 70 to 90 beats/min. Although ischemia due to increased demand cannot be ruled out in these patients, these changes are less than expected to cause ischemia in lesions with mean stenosis flow reserves of 2.1 ± 1.6 . These findings may be the result of subendocardial steal, which causes decreased perfusion in only one layer of the heart wall, below the resolution of the PET camera. With subendocardial steal, flow to the endocardium decreases disproportionately to transmural flow (12).

This phenomenon may permit local ischemia undetectable by PET.

The seventh patient had a total left circumflex occlusion but nearly normal posterior left ventricular wall motion and steal without angiographic collaterals as described earlier. The eighth patient had a 58% diameter narrowing of the RCA associated with spasm at cardiac catheterization and no PET defect. Thus, angina pectoris or ECG ST segment depression after dipyridamole hand-grip stress occurs in association with various

TABLE 3
Perfusion Tracer Activity in Patients with Collaterals

Patient	Steal area			Reference area		
	Rest counts ($\times 10^2$)	Stress counts ($\times 10^2$)	Ratio S/R	Rest counts ($\times 10^2$)	Stress counts ($\times 10^2$)	Ratio S/R
1	226.3	196.0	0.87	222.3	241.4	1.09
2	249.5	204.4	0.82	278.7	281.2	1.01
3	13.2	11.2	0.85	13.3	21.5	1.60
4	209.4	168.9	0.81	211.7	236.3	1.11
5	194.9	150.2	0.77	138.7	135.0	0.99
6	229.1	217.9	0.95	218.1	412.5	1.89
7	589.0	359.2	0.61	255.5	399.0	1.56
8	367.0	271.3	0.74	415.2	479.5	1.15
9	420.0	273.1	0.65	462.0	472.0	1.02
10	69.5	63.0	0.91	69.5	77.4	1.12
11	90.4	76.5	0.85	80.4	93.8	1.18
12	103.1	100.2	0.97	95.5	104.8	1.09
13	98.7	91.7	0.93	87.3	104.1	1.20
14	581.3	513.4	0.88	486.9	504.9	1.04
15	62.6	48.1	0.77	40.5	46.5	1.15
16	81.7	71.7	0.88	88.7	112.1	1.26
17	53.7	51.0	0.95	58.6	78.8	1.34
18	351.2	346.9	0.99	380.6	690.1	1.81
19	418.0	399.2	0.95	382.6	405.0	1.06
20	596.0	557.3	0.93	659.4	716.5	1.09
21				499.2	669.5	1.34
22	390.8	357.2	0.91	386.3	429.8	1.11
23	295.6	238.9	0.80	289.2	457.1	1.58
24				230.7	269.6	1.16
25				433.4	593.4	1.40
26	328.2	301.9	0.92	257.2	339.0	1.32
27	155.9	109.5	0.70	140.3	173.3	1.24
28	345.0	318.9	0.92	409.4	720.0	1.76

Mean tracer activity (counts/pixel) at rest and with stress in the steal area (when steal is present) and in a reference area supplied by a normal or the least diseased coronary artery (see Methods).

coronary abnormalities, which can usually be identified by positron imaging as CAD either with or without steal.

Hemodynamic Changes

There was little change in diastolic blood pressure during dipyridamole infusion compared to rest (Fig. 2) in all patients, with or without steal. In patients with angiographic collaterals, there was a mean increase in diastolic pressure of 2.7 ± 11.2 mmHg. In controls, diastolic pressure decreased by a mean of 0.3 ± 9.0 mmHg. Heart rate increased slightly in both groups (Fig. 3). In patients with angiographic collaterals, the mean increase was 15 ± 8 beats per minute from an average rate of 68 to 84 beats per minute. In control patients, the mean increase was 17 ± 10 beats per minute from an average of 72 to 89 beats per minute.

Tracer

The choice of positron emitting tracer did not appear to affect the results. Of the 28 patients with collaterals,

TABLE 4
Perfusion Tracer Activity in Control Patients

Patient	Steal area			Reference area		
	Rest counts ($\times 10^2$)	Stress counts ($\times 10^2$)	Ratio S/R	Rest counts ($\times 10^2$)	Stress counts ($\times 10^2$)	Ratio S/R
1				306.5	435.0	1.42
2				97.4	118.9	1.23
3				144.3	187.5	1.30
4				312.5	365.9	1.17
5				214.1	255.1	1.19
6				124.0	146.0	1.10
7				15.1	27.1	1.80
8	181.3	168.1	0.93	173.5	184.3	1.06
9				392.8	511.2	1.30
10	52.2	45.0	0.86	64.2	77.2	1.20
11				280.7	354.5	1.26
12				61.6	97.2	1.59
13	632.1	526.8	0.83	576.6	577.5	1.00
14				84.3	96.2	1.14
15				40.9	50.7	1.24
16				227.1	266.5	1.17
17				108.6	143.5	1.32
18				217.2	261.3	1.20
19				632.7	825.6	1.31
20				292.9	339.4	1.16
21				1177.8	1542.3	1.31
22				883.1	1070.4	1.21
23				299.3	410.0	1.37
24	668.0	588.2	0.88	783.9	898.7	1.15
25				720.3	1065.4	1.50

Mean tracer activity (counts/pixel) at rest and with stress in the steal area (when steal is present) and in a reference area supplied by a normal or the least diseased coronary artery (see Methods).

18 received [^{13}N]ammonia and 10 received ^{82}Rb . The three patients with collaterals who did not demonstrate PET steal all received [^{13}N]ammonia. Of the 25 control patients, 15 received [^{13}N]ammonia and 10 received ^{82}Rb . Of the four control patients who did demonstrate PET steal two received [^{13}N]ammonia and two received ^{82}Rb .

DISCUSSION

Knowledge of the protective value and effect of coronary collaterals on myocardial function in chronic and acute coronary stenosis and occlusion is necessary for appropriate medical and interventional therapy. Early clinical studies provided contradictory results that were shown to be a result of patient selection problems and the limitations of angiography for assessing collaterals (13). As proposed by Schaper in his recent review (14), new methods for measuring regional myocardial perfusion should be used in place of angiography to evaluate the clinical effects of collaterals. The present study

TABLE 5
Global Left Ventricular Ejection Fractions in Collateralized and Control Groups

Patients with Collaterals		Control Patients	
Patient	Ejection fraction	Patient	Ejection fraction
1	0.73	1c	>0.5
2	0.45	2c	0.42
3	0.54	3c	>0.5
4	0.63	4c	0.62
5	0.69	5c	>0.5
6	0.77	6c	0.38
7	0.53	7c	0.65
8	0.77	8c	0.77
9	0.61	9c	>0.5
10	0.43	10c	>0.5
11	0.66	11c	n/a
12	n/a	12c	>0.5
13	>0.5 [†]	13c	0.55
14	>0.5	14c	0.62
15	>0.5	15c	n/a
16	0.49	16c	0.62
17	0.53	17c	0.71
18	0.57	18c	0.47
19	0.46	19c	0.78
20	>0.5	20c	0.75
21	>0.5	21c	0.67
22	0.66	22c	>0.5
23	>0.5	23c	0.66
24	0.52	24c	n/a
25	0.67	25c	0.69
26	0.56		
27	0.55		
28	0.68		

Global LVEFs by contrast or radionuclide ventriculography in patients with and without coronary collaterals.

n/a = not available.

[†]>0.5 = films not available; interpreted by the angiographer as "normal."

was performed to test the feasibility of such an approach.

Prior Evidence of Coronary Steal

Previous investigators have demonstrated steal in the presence of intercoronary collaterals and single vessel disease (1-6). Others have detected steal only when the collateral supply artery is stenosed proximal to the origin of the collaterals (7,8,9). Cardiac vein flow measurements in patients failed to show evidence of steal (15). Differences in technique may account for some of the discrepancies. For example, studies of acute dogs may fail to show coronary steal because native collaterals have lower conductance than gradually-developed collaterals (16); even with well-developed collaterals, steal may be obliterated by alpha agonists such as methoxamine, used to maintain blood pressure during dipyridamole infusion in anesthetized open chest dogs (2). In addition, cardiac vein flow measurements may not detect steal when only the distal LAD is involved.

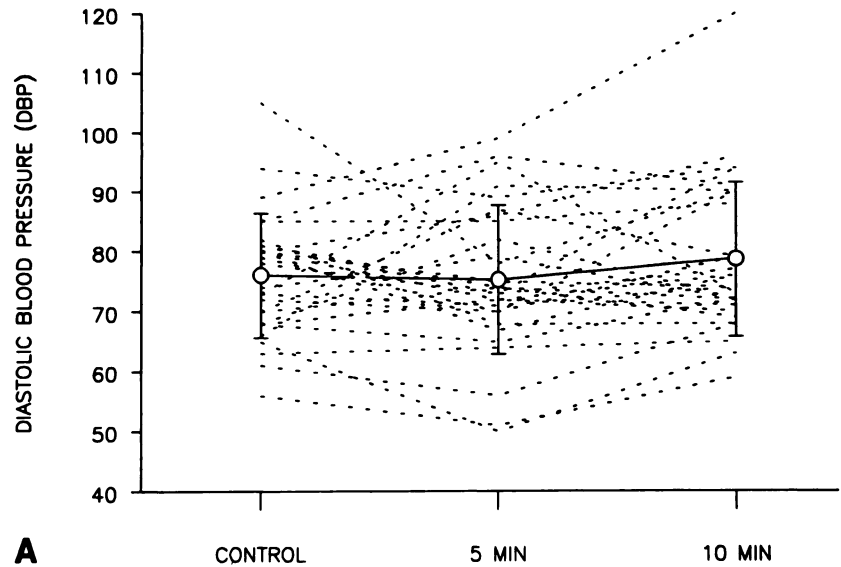
Since cardiac vein flow is equal to the combined drainage from both proximal and distal regions, the increase in flow to the normal proximal LAD may outweigh the steal in the distal bed, resulting in a net increase in venous flow despite coronary collateral steal.

Indirect evidence also is available from echocardiographic and thallium scintigraphic observations. L'Abbate and colleagues (17) showed left ventricular dysfunction by echocardiography in collateralized regions in patients after dipyridamole stress. In a series of 38 patients, Imamura et al. (18) found an increase in the size of exercise-induced thallium perfusion defects in peri-infarct zones with good collaterals and no change in those with no or poor collaterals. Similar results were reported by Nienaber et al. (19) in a series of 80 patients.

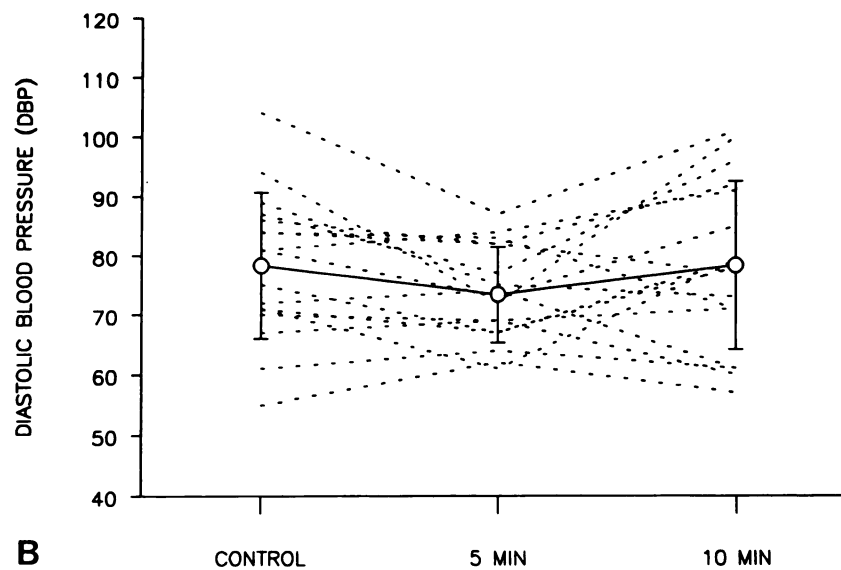
Chambers and Brown (20) found that the presence of well-developed coronary collaterals on angiography was a significant multivariate predictor of dipyridamole-induced ST segment depression in patients with CAD. In contrast, thallium redistribution was a significant predictor of dipyridamole-induced ST segment depression by logistic regression before but not after "correction" for presence of angiographic collaterals. This indirect result also is consistent with a correlation between angiographic collaterals and thallium defects.

Network Model of Myocardial Steal

In patients with collaterals, the native, recipient artery often is not completely occluded. In such circumstances, when antegrade flow remains in arteries receiving collateral flow, the occurrence of steal depends on the balance between remaining antegrade coronary flow reserve, if any, the flow reserve of the supply artery, and the collateral conductance. These relationships add substantial complexity, requiring systems analysis to predict the effect of arteriolar vasodilation on perfusion of the collateralized bed as a function of collateral conductance and stenosis severity of the native and supply arteries. Using a computer simulation with assumptions of normal coronary flow reserve of 5, and autoregulation, over the physiologic ranges, it was found that with increasing collateral conductance (i.e., with collateral flow accounting for a progressively greater proportion of resting flow), myocardial perfusion in the collateralized bed falls below resting values in a nonlinear manner after maximal coronary arteriolar vasodilation (21). This simulation incorporates both linear (viscous) resistance, and nonlinear (inertial and separation) resistance to flow in the proximal coronary arteries. It includes the assumptions that collateral resistance is not negligible and that pressure of the supply artery at the origin of collaterals falls with distal vasodilation whether or not there is a stenosis of the supply artery. This latter assumption is supported by evidence from Harrison et al. (22) who used extrapolation of the relation between collateral flow and recipient artery pressure as distal microvascular collaterals were progressively occluded



A



B

FIGURE 2

(A) Changes in diastolic blood pressure with dipyridamole/handgrip stress in patients with PET steal at baseline and at 5 and 10 min after infusion of dipyridamole. Error bars indicate mean and s.d. (B) Changes in diastolic blood pressure with dipyridamole/handgrip stress in patients without PET steal at baseline and at 5 and 10 min after infusion of dipyridamole. Error bars indicate mean and s.d.

by microspheres to show a mean value of 74 mmHg pressure at the origin of collaterals without a supply artery stenosis, 6 mmHg less than mean aortic pressure. This difference would be accentuated at higher flow rates.

Simulation results for a wide range of physiologic conditions and proximal stenosis severity showed non-linear reduction in collateralized bed perfusion with increasing collateral conductance. This phenomenon corresponds to a decrease in perfusion pressure at the origin of collateral vessels during arteriolar vasodilation with increased coronary flow through the native supply artery. Collateral perfusion pressure decreases in high flow conditions due to viscous resistance in the proximal supply artery introduced by either a stenosis or the artery itself.

According to the model, myocardial steal may theoretically occur even when the supply artery is not stenosed because normal anatomic tapering provides suffi-

cient inherent resistance to create a pressure gradient between the aorta and the collateral origin during the four- to five-fold increase in flow occurring with maximal vasodilation. The degree of resistance in a normal proximal arterial tree has been measured in dogs as 12% to 20% of total normal coronary resistance under resting conditions (6,23). However, because the viscous pressure loss in a normal artery is much less than the combined viscous and separation loss of a stenosis, the magnitude of steal is much less in the absence of a supply artery stenosis according to this model. Thus, the failure to document steal in animals without supply artery stenoses may be due to the small change in perfusion below the detection threshold of the microsphere technique.

Subendocardial Steal

Subendocardial steal is defined as a decrease in perfusion of subendocardial layers of myocardium with

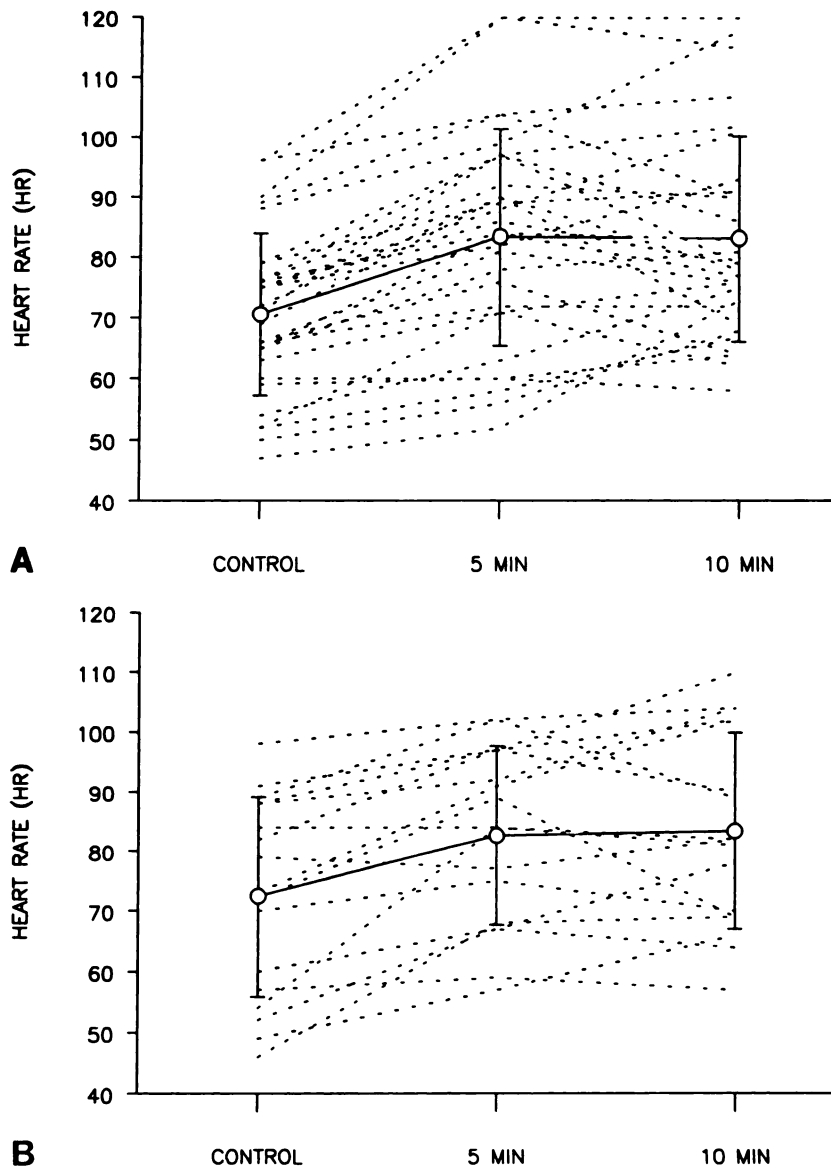


FIGURE 3

(A) Changes in heart rate with dipyridamole/handgrip stress in patients with PET steal at baseline and at 5 and 10 min after infusion of dipyridamole. (B) Changes in heart rate with dipyridamole/handgrip stress in patients with PET steal at baseline and 5 and 10 min after infusion of dipyridamole.

coronary arteriolar vasodilation, while epicardial flow increases. It has been shown to occur after potent arteriolar vasodilation in the presence of a severe proximal stenosis in the absence of collaterals (24). However, despite decreased subendocardial perfusion, epicardial perfusion increases and mean transmural perfusion remains constant or increases.

The PET camera used in this study does not resolve subendocardial-subepicardial differences. As a result, mild subendocardial steal due to severe stenoses without collaterals probably does not account for the present findings.

LIMITATIONS

Patient Groups

It has been shown (13) that, in general, when patients are classified according to presence or absence of coro-

nary collaterals, more patients with advanced coronary heart disease are found in the collateral group. This observation is a result of the association between collateralization and severe disease. In the present study, the mean severity was greater among the patients with collaterals. However, the range of stenosis severity is wide and overlaps to a large extent with the group of patients without collaterals so that the findings are not attributable to differences in stenosis severity.

Angiography

As noted by Schaper in his recent review (14), angiography is not an ideal standard against which to compare myocardial steal by perfusion imaging because of its limited resolution and limited functional information. No ideal standard is available for studies in man. Animal studies using microspheres may be useful in clarifying the accuracy of PET in identifying coro-

nary collateral circulation. Nevertheless, collateral physiology is known to vary substantially from species to species (14).

Quantitation of Steal

In this study, myocardial steal was expressed in terms of radiotracer activity rather than absolute perfusion. In general, quantitation of absolute perfusion requires correction of tracer activity for extraction, for partial volume effects, and for input function data, none of which were available in these patients. In general, tracer activity does not relate directly to perfusion because tracer extraction falls at higher flow rates, as occurs in normal myocardium during dipyridamole-induced arteriolar vasodilation. At flows from below normal to three times resting levels, however, activity and perfusion are nearly linearly related (25). In this study, changes in tracer activity in regions of steal would be expected to parallel changes in perfusion because perfusion remains near resting levels in collateralized myocardium.

Partial Volume and Spillover Effects

Direct partial volume effects were minimized by measurement of relative change in tracer activity in the same ROIs at rest and stress so that geometric factors would be constant. It also is possible that the PET steal may be enhanced indirectly by the partial volume effect in relation to wall motion. Specifically, if collateral steal is sufficiently severe to induce ischemia and new or worse wall motion abnormalities, the resultant decrease in wall thickening may cause a further reduction in tracer activity through the partial volume effect. Future efforts to quantify steal by PET would need to take this into account.

Another theoretical consideration is the possible effect of dipyridamole on blood-pool clearance of these tracers. If the tracer clearance rate is increased by dipyridamole, less spillover may occur in the dipyridamole image, creating apparent steal in regions of rest defects. The effect of dipyridamole on clearance of ^{82}Rb and [^{13}N]ammonia has not been established, and such an effect should be small given the small fraction of tracer in the recirculating blood pool (26) and the short imaging time for these tracers. In addition, such an effect would be equally likely to occur in subjects in the collateral and control groups where myocardial infarctions were nearly equally prevalent (53% vs. 44%, respectively).

Serial arterial blood samples were not obtained in these patients. However, the input functions for rest and dipyridamole stress were reproduced as closely as possible by administration of the same radionuclide and the same dose under both conditions. For rubidium-82 studies, the injections were automated providing nearly identical bolus administration. Since cardiac

output changes minimally compared to the increase in coronary flow (27) the total radionuclide dose delivered to the myocardium is higher during dipyridamole/handgrip stress than at rest, except in regional areas of decreased perfusion due to myocardial steal.

Physiologic Variables

A decrease in blood pressure during the dipyridamole PET scan may create PET steal without myocardial steal (false-positive) by causing decreased flow. Similarly, an increase in blood pressure may prevent PET steal in the presence of myocardial steal (false-negative). For this reason, vital signs were closely monitored in these subjects in recognition that dipyridamole may produce mild systemic vasodilation resulting in lower blood pressure. Handgrip was used to counteract this effect. Results showed that pressure and heart rate changed minimally from baseline in these patients (Figs. 2 and 3). In addition, lack of PET steal among almost all control patients suggests that effects of dipyridamole on blood pressure do not account for the findings of PET steal in patients with collaterals.

Bridging Collaterals

It is important to note that the present study relates to intercoronary collaterals rather than bridging collaterals. Intracoronary, bridging collaterals connect proximal and distal portions of the same artery and behave as flow-limiting stenoses rather than steal-inducing collaterals, because the supply and recipient portions of the artery share the same arteriolar bed and flow reserve. It is necessary to have imbalance in distal flow reserve to induce steal.

Exercise Stress

The arteriolar vasodilation occurring with exercise stress may also cause similar directional changes in perfusion and possibly steal. Exercise stress may not be as potent as dipyridamole in simulating arteriolar vasodilation, and the effect may be blunted by increased arterial pressure, heart rate, and the catecholamine effects associated with exercise stress.

Clinical Significance

Identification of collaterals is important for clinical decision-making (28,29) and for clinical research addressing the physiologic importance of collaterals in protecting against resting ischemia and infarction. These results are preliminary evidence that myocardial steal occurs regularly after potent coronary arteriolar vasodilation in patients with collaterals. In many instances, no electrocardiographic evidence of ischemia occurred, suggesting that the degree of steal was not physiologically severe. In other cases, angina pectoris or ECG changes clearly indicated ischemia, suggesting more significant myocardial steal. Analysis by our

model indicates that the severity of steal is closely related to the amount of collateral flow at rest. If a large portion of resting perfusion is provided by collaterals, coronary vasodilation causes a fall in perfusion pressure at the origin of the collaterals, a corresponding fall in collateral flow, and proportionally severe steal and myocardial ischemia. Ultimately, with accurate quantitation of myocardial perfusion by PET, the degree of steal may be used to assess the collateral conductance and functional importance of collateral flow at rest.

CONCLUSIONS

These findings indicate a correspondence between angiographically evident coronary collaterals and regional reduction in perfusion tracer uptake during pharmacologic coronary arteriolar vasodilation. These preliminary data suggest that noninvasive perfusion imaging may be useful for studying the clinical importance of collaterals and, ultimately, for enhancing clinical decision making. This method may contribute to our understanding of the natural history of collaterals, their protective value, factors influencing their growth, and methods of promoting their development in patients.

ACKNOWLEDGMENTS

The authors thank Robert Ekas, PhD, Stephen Adler, BA, Barry Elson, RT, Richard Holmes, RT, Patricia Felli, and Jonathan McLean for technical assistance.

Supported in part by Grants R01HL26862, R01HL26885, and 5T32HL07591 from the National Institutes of Health; DE-FG05-84ER60210 from the Department of Energy, and a joint collaborative research project with the Clayton Foundation for Research.

Presented in part at the Society for Nuclear Medicine meetings in Washington, DC, June 1986.

REFERENCES

1. Flameng W, Wusten B, Winkler B, et al. Influence of perfusion pressure and heart rate on local myocardial flow in the collateralized heart with chronic coronary occlusion. *Am Heart* 1975; 89:51-59.
2. Chiariello M, Ribeiro LGT, Davis MA, et al. "Reverse coronary steal" induced by coronary vasoconstriction following coronary artery occlusion in dogs. *Circulation* 1975; 52:809-815.
3. Cohen MV, Sonnenblick EH, Kirk ES. Coronary steal: Its role in detrimental effect of isoproterenol after acute coronary occlusion in dogs. *Am J Cardiol* 1976; 38:880-888.
4. Schaper W, Lewi P, Flameng W, et al. Myocardial steal produced by coronary vasodilation in chronic coronary artery occlusion. *Basic Res Cardiol* 1973; 68:3-20.
5. Gross GJ, Warltier DC. Coronary steal in four models of single or multiple vessel obstruction in dogs. *Am J Cardiol* 1981; 48:84-92.
6. Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one-vessel occlusion and other arteries normal. *Circulation* 1983; 67:1009-1015.
7. Becker LC. Effect of nitroglycerin and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. *J Clin Invest* 1976; 58:1287-96.
8. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. *Circulation* 1978; 57:1103-1110.
9. Hellman DB, Pitt B. Effect of ethyl adenosine on myocardial flow after coronary artery occlusion. *Am J Physiol* 1976; 231:1495-9.
10. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VII. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. *J Am Coll Cardiol* 1986; 7:103-113.
11. Gould KL, Goldstein RA, Mullani M, et al. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VIII. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. *J Am Coll Cardiol* 1986; 7:775-789.
12. Neill WA, Oxendine J, Phelps N, Anderson RP. Subendocardial ischemia provoked by tachycardia in conscious dogs with coronary stenosis. *Am J Cardiol* 1975; 35:30-36.
13. Levin DC. Pathways and functional significance of the coronary collateral circulation. *Circulation* 1974; 50:831-837.
14. Schaper W, Gunter G, Winkler B, Schaper J. The collateral circulation of the heart. *Prog Cardiovasc Dis* 1988; 31:57-77.
15. Marchant E, Pichard AD, Casanegra P, et al. Effect of intravenous dipyridamole on regional coronary blood flow with 1-vessel coronary artery disease: evidence against coronary steal. *Am J Cardiol* 1984; 53:718-721.
16. Schaper W, Flameng W, Winkler B, et al. Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. *Circ Res* 1976; 39:371-377.
17. Picano E, Simonetti I, Masini M, et al. Transient myocardial dysfunction during pharmacologic vasodilation as an index of reduced coronary reserve: a coronary hemodynamic and echocardiography study. *J Am Coll Cardiol* 1986; 8:84-90.
18. Imamura I, Araki H, Fukuyama T, et al. Significance of collateral circulation on peri-infarct zone: assessment with stress thallium-201 scintigraphy. *Clin Cardiol* 1986; 9:137-144.
19. Nienaber CA, Spielmann RP, Salge D, et al. Nichtinvasive identifizierung von kollateralisiertem Myokard durch 201-Thallium-Tomographie in Vasodilatation und Redistribution. *Z Kardiol* 1987; 76:612-620.
20. Chambers CE, Brown KA. Dipyridamole-induced ST segment depression during thallium-201 imaging in patients with coronary artery disease: angiographic and hemodynamic determinants. *J Am Coll Cardiol* 1988; 12:37-41.
21. Demer L, Gould KL, Kirkeeide R. Assessing stenosis severity: coronary flow reserve, collateral function, quantitative coronary arteriography, positron imaging, and digital subtraction angiography: a review and analysis. *Prog Cardiovasc Dis* 1988; 30:307-322.
22. Harrison DG, Chapman MP, Christy JP, Marcus ML. Studies of functional site of origin of native coronary collaterals. *Am J Physiol* 1986; 251:H1217-1224.
23. Wyatt D, Lee J, Downey J. Determination of coronary collateral flow by a load line analysis. *Circ Res* 1982; 50:663-670.
24. Nakamura M, Nakagaki O, Nose Y, Fukuyama T, Kikuchi Y. Effects of nitroglycerin and dipyridamole on regional

- myocardial blood flow. *Basic Res Cardiol* 1978; 73:482-496.
25. Goldstein RA, Mullani NA, Marani SK, et al. Myocardial perfusion with rubidium-82. II. Effects of metabolic and pharmacologic interventions. *J Nucl Med* 1983; 24:907-915.
 26. Mullani N, Gould KL. First-pass measurements of regional blood flow with external detectors. *J Nucl Med* 1983; 24:577-581.
 27. Brown AG, Josephson MA, Peterson RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. *Am J Cardiol* 1981; 48:1077-1085.
 28. Gregg DE, Patterson RE. Functional importance of the coronary collaterals. *N Engl J Med* 1980; 303(2):1404-1406.
 29. Fuster V, Frye RL, Kennedy MA, Connolly DC, Mankin HT. The role of the collateral circulation in the various coronary syndromes. *Circulation* 1979; 59(6):1137-1144.