Abnormal Coronary Flow Reserve and Abnormal Radionuclide Exercise Test Results in Patients With Normal Coronary Angiograms

VICTOR LEGRAND, MD, JOHN McB. HODGSON, MD, ERIC R. BATES, MD, FRED M. AUERON, MD, G.B. JOHN MANCINI, MD, FRCP(C), FACC, JOSEPH S. SMITH, MD, MILTON D. GROSS, MD, ROBERT A. VOGEL, MD, FACC

Ann Arbor, Michigan

Coronary flow reserve, exercise thallium-201 scintigraphy and exercise radionuclide ventriculography were compared in 18 patients with chest pain and angiographically normal coronary arteries. Regional exercise thallium-201 perfusion was abnormal in three patients, regional exercise wall motion was abnormal in three other patients and results of both tests were abnormal in one additional patient. Left ventricular ejection fraction responses were abnormal in five of these seven patients. The coronary flow reserve of arterial distributions with abnormal perfusion or regional dysfunction was significantly lower than that of distributions associated with normal radionuclide results (1.42 ± 0.23 versus 2.58 ± 0.83, $p < 0.001$).

All patients with abnormal scintigraphic results had low coronary flow reserve (<1.95) in at least one distribution. Perfusion abnormalities appeared to be more localized in the arterial distributions with the lowest flow reserve. Only two patients had low flow reserve (<1.95) with normal scintigraphic results; both were hypertensive. These data suggest that abnormal exercise scintigraphic findings in patients with angiographically normal coronary arteries and chest pain are indicative of true blood flow or perfusion abnormalities.

(J Am Coll Cardiol 1985;6:1245–53)

Several investigators (1–4) have reported abnormal results on radionuclide exercise tests in patients with angiographically normal coronary arteries. Some of these results can be explained on the basis of coronary spasm (5), cardiomyopathy (6) or superimposition of extracardiac structures (7). In the majority of cases, however, the reason for these abnormalities is not clear. As coronary angiography has long been considered the standard for the evaluation of noninvasive exercise tests, these abnormal results were considered to be false.

Coronary flow reserve is a physiologic variable that assesses the ability of coronary flow to increase under hyperemic stimulation. Studies in patients with left ventricular hypertrophy (8–11), hypertension (11–13) and syndrome X (14,15) have revealed abnormal hyperemic blood flow responses in the absence of coronary stenoses. Additionally, evaluation of patients with coronary artery disease has shown significant discrepancies between anatomically defined lesion severity and functional significance (16). Discrepancies between coronary anatomy and physiology are thus well recognized.

Recently, Vogel et al. (17) developed a method for measuring regional coronary reactive hyperemia, induced by intracoronary contrast medium injection, at the time of cardiac catheterization. This technique was used in the current study to assess regional coronary flow reserve in patients referred to cardiac catheterization whose angiogram revealed normal coronary arteries. Radionuclide exercise tests were obtained for all of these patients. In this study we compared the results of exercise scintigraphy on a regional basis with coronary flow reserve in patients with normal coronary arteries and a chest pain syndrome, so as to clarify any discrepancies between coronary anatomy and physiology.

From the Cardiology and Nuclear Medicine Sections, Department of Internal Medicine, Veterans Administration Medical Center, Ann Arbor, Michigan. This work was supported in part by research funds of the Michigan Heart Association, Lathrup Village, Michigan and the Veterans Administration. Dr. Legrand is a recipient of a NATO Scientific Research Grant (Brussels, Belgium). Manuscript received March 8, 1985; revised manuscript received July 8, 1985, accepted July 16, 1985.

Address for reprints: Robert A. Vogel, MD, Cardiology Section, Veterans Administration Medical Center, 2215 Fuller Road, Ann Arbor, Michigan 48105.

Methods

Study patients. From January to June 1984, 64 male patients with chest pain participated in a prospective protocol that compared coronary arteriography, coronary flow

0735-1097/85/$3.30

reserve and exercise scintigraphic test results. Patients were informed of the risks of cardiac catheterization and exercise scintigraphy and gave consent to participation in this study, which was approved by our Institutional Committee on Human Research on January 9, 1984. Patients received an additional 0.72 total body rads associated with their scintigraphic studies. Of these 64 patients, 18 were found to have angiographically normal coronary arteries. Their mean age was 53 years (range 35 to 64). No patient had valvular heart disease, cardiomyopathy or a history of electrocardiographic evidence of myocardial infarction. Hypertension (blood pressure > 160/100 mm Hg) or a history of hypertension controlled by medications was noted in 11 cases. All 18 patients had exercise thallium-201 scintigraphy and exercise radionuclide ventriculography within 2 days of cardiac catheterization. All medications were discontinued at least 12 hours before both the exercise tests and catheterization.

Radionuclide Techniques

Exercise electrocardiography with thallium-201. Symptom-limited treadmill exercise was performed using the standard Bruce protocol with 12 lead electrocardiographic monitoring. Ischemic electrocardiographic changes were defined as horizontal or downsloping ST segment depression of 1 mm or greater 80 ms after the J point.

Thallium-201 (2.5 mCi) was injected intravenously 1 minute before discontinuation of exercise. Three myocardial scintigrams (40° left anterior oblique, anterior, 70° left anterior oblique) were obtained beginning approximately 8 minutes after cessation of exercise. Redistribution images were obtained 3 hours later using constant time of acquisition. Images were recorded on conventional transparency film and stored in a computer for subsequent processing and quantitative analysis (MDS A^2). Quantitative analysis of thallium-201 uptake and washout was performed using a circumferential profile method (18). Images were interpreted by consensus of three experienced observers without knowledge of the patients' clinical status. Both unprocessed images and quantitative data were analyzed to provide the final interpretation. Regions with defects on postexercise imaging were interpreted as persistent, improved (abnormal washout) or normal on the redistribution image.

Quantitative data were also used to examine the relation between segmental thallium uptake during exercise and regional coronary flow reserve. On the thallium scintigrams taken in the 45° left anterior oblique projection, the ratio of mean circumferential profile counts from the anteroseptal region (30 to 150°) to those from the posterolateral region (210 to 330°) was calculated. This regional thallium activity ratio was compared with the corresponding ratio of left anterior oblique to circumflex artery flow reserve obtained in a similar left anterior oblique projection (in patients with abnormal scintigraphic results or low flow reserve, or both).

Radionuclide ventriculography. After in vivo labeling of red blood cells by technetium-99m (25 mCi), radionuclide ventriculography was performed at supine rest in the right anterior oblique, left lateral and left anterior oblique views. With the camera in the left anterior oblique position, multistage bicycle exercise was begun at a work load of 200 kilopond-meters (kpm)/min and increased by 200 kpm/min every 3 minutes up to the symptom-limited maximal work load. Scintigraphy was performed during the last 2 minutes of each stage. Data were stored and analyzed using a general nuclear medicine computer (MDS A^2). Ejection fraction was calculated by dividing stroke counts by end-diastolic counts. Relative volume changes were assessed from end-diastolic and end-systolic counts. All counts were first corrected for heart rate by dividing the raw counts by the product of the number of cycles processed and frame duration. To compensate for radioactive decay during the acquisition period, a blood sample was drawn from a peripheral vein at the end of the study. The activity contained in the sample (S) was determined, and blood activity (Bl) at the time of acquisition was back calculated:

$$\text{Bl (counts/s)} = \text{S (counts/s)}\ e^{0.00192t},$$

where t = elapsed time. Finally, a ratio of heart rate-corrected ventricular activity to blood activity was determined that was proportional to ventricular volume.

After image enhancement by space-time smoothing, left ventricular wall motion was assessed by viewing the scintigraphic data in a closed loop format on the computer's video display. Corresponding rest and exercise images were evaluated by three experienced observers who were unaware of the patient's clinical status. Regional exercise-induced dysfunction was defined as any worsening of segmental regional wall motion during exercise as compared with the rest state, and a global abnormality was defined as a less than 5% rise in ejection fraction associated with a relative increase in end-systolic volume.

Angiographic Techniques

Coronary arteriography. Selective coronary angiography, using the Judkins technique, was performed in multiple views. All epicardial coronary arteries were completely normal and free of luminal irregularities. In nine patients with chest pain at rest that suggested coronary artery spasm, up to 0.25 mg of ergonovine maleate was injected intravenously, and selective right and left coronary angiograms were repeated 3 to 4 minutes later.

Coronary flow reserve measurement. Coronary flow reserve was determined using digital subtraction angiography and a technique described by Hodgson et al. (19). Selective coronary angiography for subsequent processing was performed in the view that best separated the myocardial perfusion bed to be studied from other structures (aorta, diaphragm, coronary sinus) and neighboring perfusion beds. Usually a left anterior oblique or left posterior oblique view was chosen for the left coronary artery, and a left anterior oblique or right anterior oblique view for the right coronary. Coronary angiograms were acquired using a digital angiographic computer (DPS-4100C, ADAC Labs) interfaced to a standard cineangiographic system (Philips Optimus M200). The radiographic input signal was kept constant (fixed kV, mA and pulse width X-ray exposure). Video output signals were directly converted into digital images by logarithmic analog to digital conversion. One digital image per cardiac cycle was obtained. It was recorded in a 512 × 512 eight bit mode matrix. This frame was electrocardiographically gated and was obtained during cardiac diastasis just before atrial contraction. The patient was instructed to maintain held inspiration for 10 to 15 seconds during image acquisition. Sodium-meglumine diatrizoate (Renografin-76) was injected at a flow rate of 4 ml/s for both coronary arteries with a total of 7 ml for the left and 5 ml for the right by means of an electrocardiographically triggered power injector (Mark IV, Medrad). The heart rate was kept constant during image acquisition by atrial pacing at a rate 5 beats/min higher than the basal heart rate.

To determine the regional coronary flow reserve, two sets of images per coronary artery were obtained. First, the passage of a single bolus of contrast medium was recorded at rest, at least 3 minutes after contrast injection. Images during contrast-induced hyperemic flow were then separately obtained by recording the passage of a bolus of contrast medium 10 seconds after 5 to 7 ml of the medium was injected. The doses of contrast agent used to induce hyperemia were identical to the doses used to image the coronary artery.

Image processing was performed using standard mask-mode subtraction. The last single frame obtained before contrast administration was selected as the mask. Five to seven consecutive end-diastasis frames obtained after contrast administration were selected as the image subset. A single contrast intensity and appearance time-modulated functional image was then generated from each set of enhanced frames. On this functional image, the intensity value of each pixel corresponds to the cumulative contrast density reached during image acquisition. The appearance time of contrast was color coded, with a different color assigned to each postcontrast injection cardiac cycle. Only pixels with an intensity above a preset threshold appeared on the final picture. This threshold was set at a level that excluded most of the background noise and was between 12 and 17% (mean 13.5%) of the maximal intensity. Acquisition and processing variables were identical for each pair of images (baseline and hyperemia) so that each set was technically comparable.

Regional myocardial contrast appearance time and density (time from onset of injection to its regional appearance within the myocardium and regional density achieved at the end of the series, respectively) were obtained using an automatic histographic analysis of a region of interest defined by the operator on the functional image. As contrast density is directly related to the volume of distribution in the myocardium and flow is inversely related to myocardial contrast appearance time, digital estimate of coronary flow was calculated as

$$Q = \frac{\text{Volume}}{\text{Time}} = k\ CD/AT,$$

where Q = mean regional coronary flow; CD = mean cumulative contrast density; AT = mean contrast appearance time; and k = a constant related to the technical characteristics of the radiographic equipment, the anatomic characteristics of the patient, the location of the myocardial region of interest and the injection characteristics. As each pair was technically identical, the coronary flow reserve, or ratio between hyperemic (h) and basal (b) coronary flows, was given by

$$\text{Coronary flow reserve} = \frac{Q_h}{Q_b} = \frac{CD_h}{AT_h} \div \frac{CD_b}{AT_b}.$$

Animal studies have demonstrated a close relation between flow ratios measured by an electromagnetic flow probe and CD/AT ratios measured by digital subtraction angiography (r = 0.92).

Reproducibility of sequential measures was calculated as ± 13% and inter- and intraobserver variability values were excellent (19). To minimize vagaries due to the technique, baseline and hyperemic studies were acquired with the patient in the same position relative to the camera and X-ray tube and with identical contrast injection characteristics. Studies with motion artifacts or arrhythmias were repeated. In addition, hyperemia was induced in the standard manner described, heart rate was kept constant by pacing and mean blood pressure did not differ by more than 5% between comparative studies.

Data analysis. Angiographically assessed regional coronary flow reserve was obtained for 49 arterial distributions (left anterior descending, 18; left circumflex, 17; right coronary or left posterior descending, 14) and compared with thallium-201 perfusion and radionuclide ventriculographic wall motion in the same distribution. Comparisons between groups were made with an unpaired *t* test. Differences were considered significant when confidence limits exceeded 95% ($p < 0.05$). The results are expressed as mean ± SD.

Results

Clinical and electrocardiographic characteristics. The characteristics of 11 patients with normal radionuclide test results were compared with those obtained in 7 patients with abnormal test results (Table 1). Only the average age of patients was different between the two groups.

JACC Vol. 6, No. 6
December 1985:1245–53

Table 1. Characteristics of the 11 Patients Without and 7 Patients With Abnormal Radionuclide Test Results

	Normal Test Results (n = 11)	Abnormal Test Results (n = 7)
Age (yr)	50 ± 7.9*	57.7 ± 4.7
Angina pectoris	3	5
Hypertension		
Uncontrolled	3	3
Controlled	3	2
Medications		
Diuretics	2	3
Nitrates	7	5
Beta-adrenergic blocking agents	4	4
Ca^{2+} antagonists	3	1
Exercise		
Duration (s)	481 ± 108	426 ± 122
Level (m)	8.74 ± 1.72	8.26 ± 2.03
Rate-pressure product (× 10^2)	293 ± 62	245 ± 65

*$p < 0.05$.

Seven patients had abnormal radionuclide test results (Table 2). Five had anginal pain (exertional pain relieved by rest and nitrates) and two had atypical chest pain. Three were hypertensive at the time of the study, and two had a history of hypertension controlled by medication. Two patients had abnormalities on the electrocardiogram at rest; one had left ventricular hypertrophy by voltage criteria and another had diffuse nonspecific T wave abnormalities. The treadmill exercise test was terminated because of severe shortness of breath in five patients, general fatigue in one patient and hip pain in one patient. Two patients (Cases 1 and 3) complained of chest pain during and after exercise, and the exercise electrocardiogram demonstrated an ischemic response in two other patients.

Radionuclide results. Exercise thallium-201 scintigraphy revealed segmental abnormalities in four patients. Patient 1 had a reversible inferoposterior defect and abnormal washout in the anterior region. Patient 4 had a persistent inferoposterior defect. Patient 8 had apical and inferoseptal defects with redistribution. Patient 11 had abnormal anterior and anteroseptal washout.

Exercise radionuclide ventriculography revealed segmental abnormalities in four patients. In these patients, relative left ventricular end-systolic volume increased from 3 to 38% (mean 17.5%), relative end-diastolic volume increased from 9 to 42% (mean 22%) and ejection fraction ranged from a 3% decrease to a 4% increase (mean 1.5% increase). Regional wall motion study revealed global hypokinesia in three patients (Cases 3,6 and 17), and inferoapical and posterolateral hypokinesia in one patient (Case 4). One additional patient (Case 11) with an abnormal thallium-201 scintigram had an abnormal exercise ejection fraction response, but no segmental wall motion abnormality. Five of the seven patients with regional scintigraphic abnormalities had an abnormal exercise ejection fraction response, whereas all of the 11 patients without segmental scintigraphic abnormalities had a normal ejection fraction response.

Angiographic results. Contrast ventriculographic findings were normal for all patients. One patient (Case 9) had mitral valve prolapse. Coronary vessels were completely normal in all subjects, without luminal irregularities. Ergonovine challenge was performed in 9 patients and was positive in only one patient (Case 11), producing focal, subtotal occlusion of the proximal left anterior descending coronary artery.

Coronary flow reserve. The coronary flow reserve of at least two major arterial distributions was determined in all patients. In five instances, the flow reserve of only two arterial distributions was assessed because of left coronary

Table 2. Clinical and Electrocardiographic Characteristics of Seven Patients With Abnormal Functional Test Results and Normal Coronary Angiograms

Patient No.	Chest Pain	HTN	Medications*	Rest ECG	Exercise-Limiting Symptoms	RPP	Exercise ECG
1	AP	+	Nitrates, atenolol	LVH	Hip pain	144	–
3	AP	–	Nitrates	nl	Fatigue	228	–
4	Atyp	+	HCTZ, propranolol	STTW	Dyspnea	206	–
6	Atyp	+(c)	HCTZ, atenolol	nl	Dyspnea	254	–
8	AP	–	Nitrates	nl	Dyspnea	293	+
11	AP	+(c)	HCTZ/amiloride, nitrates, propranolol	nl	Dyspnea	224	+
17	AP	+	Nitrates, nifedipine	nl	Dyspnea	366	–

*Discontinued before exercise test. AP = angina pectoris; Atyp = atypical chest pain; (c) = controlled by medication; ECG = electrocardiogram; HCTZ = hydrochlorothiazide; HTN = hypertension; LVH = left ventricular hypertrophy; nl = normal; RPP = rate pressure product; STTW = ST and T wave abnormalities.

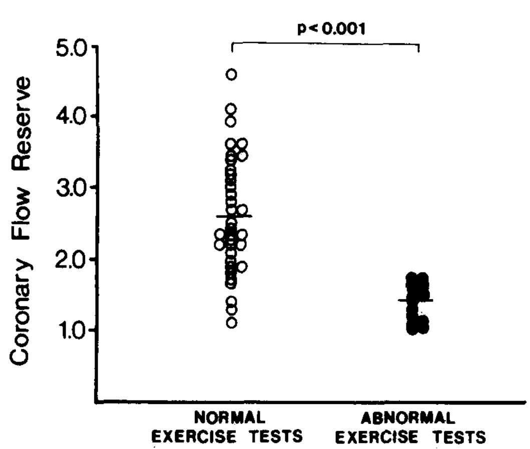
artery dominance, excessive motion, poor inspiration or catheter wedging in the coronary ostium.

All arterial distributions with abnormal thallium-201 perfusion or regional dysfunction during exercise had low coronary flow reserve values (< 1.95 for our laboratory), ranging between 1.00 and 1.74 (mean 1.42 ± 0.23). By comparison, coronary flow reserve of arterial distributions associated with normal regional radionuclide test results ranged from 1.12 to 4.60 (mean 2.58 ± 0.83; $p < 0.001$) (Fig. 1). Mean coronary flow reserve was similar for each major coronary artery and was always significantly higher ($p < 0.001$) for arterial distributions not associated with scintigraphic abnormalities (Fig. 2).

Individual coronary flow reserve determinations are shown in Figure 3. The flow reserve of six patients with abnormal radionuclide tests was reduced in all arterial distributions; in three patients, radionuclide angiography showed regional left ventricular dysfunction during exercise. In three others thallium-201 perfusion manifested regional abnormalities. In one patient (Case 4), the flow reserve of the left anterior descending coronary artery was normal (4.10), whereas the flow reserve of the left circumflex and left posterior descending coronary arteries were reduced (1.20 and 1.23). This patient demonstrated hypokinesia and thallium-201 perfusion defects in the inferior and posterolateral areas.

The coronary flow reserve of patients with normal radionuclide test results was above 1.95 in all but two cases (Cases 15 and 18). These two patients with low regional flow reserves (1.12 and 1.39 in Case 15; 1.71, 1.81 and 3.08 in Case 18) also had hypertension that was not controlled by medication. Another hypertensive patient (Case 16), however, and three patients (Cases 5,7 and 10) with a history of prior hypertension had normal results on radionuclide tests and normal flow reserve.

Figure 1. Coronary flow reserve for arterial distributions without (**open circles**) and with (**closed circles**) radionuclide abnormalities (exercise thallium-201 scintigraphy or radionuclide ventriculography, or both).



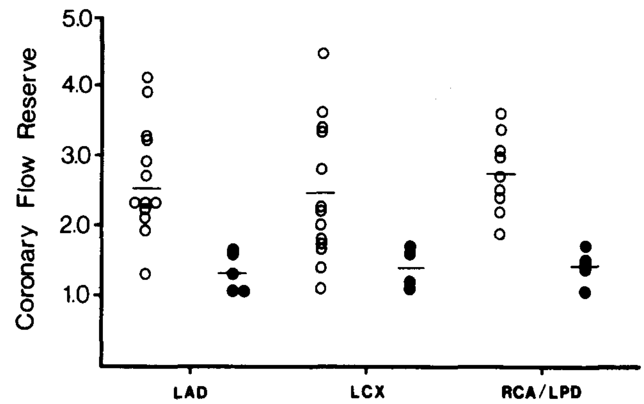


Figure 2. Coronary flow reserve for each major arterial distribution. Arterial distributions with normal radionuclide results (**open circles**) and those with abnormal results (**closed circles**) are represented. Flow reserve differences between vascular distributions with normal and abnormal radionuclide results are significant ($p < 0.001$) within each major arterial distribution. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA/LPD = right coronary artery or left posterior descending coronary artery.

Relation between relative thallium distribution and coronary flow reserve. The relative perfusion provided by the left anterior descending (LAD) and circumflex (LCX) arteries was analyzed in the left anterior oblique projection for patients with a low flow reserve. In this projection, perfusion beds of these arteries are not overlapping and can be adequately compared by both techniques. Regional LAD/LCX ratios of mean stress thallium activity and regional LAD/LCX ratios of flow reserve for the patients are given in Table 3. Flow reserve ratios were, respectively, 0.60 and 0.55 for Cases 1 and 11, the two patients with the lowest LAD/LCX stress thallium uptake ratios. The flow reserve ratio was 3.33 for the patient in Case 4, who had a defect in the circumflex distribution. It approached unity for the five patients without thallium perfusion abnormalities and for the patient in Case 8, who had an inferoapical defect. The 4 hour thallium ratios increased in Cases 1 and 11 with an abnormal clearance rate of thallium in the anterior and anteroseptal regions.

Relation between exercise limitation and coronary flow reserve. Maximal metabolic demand during exercise was estimated by the rate-pressure product achieved during exercise thallium scintigraphy and by the triple index (heart rate × blood pressure × exercise/baseline ratios of end-diastolic volume) achieved during exercise radionuclide ventriculography. These indexes were compared with coronary flow reserve for all but two patients (Cases 2 and 16) who stopped exercise at a submaximal level because of musculoskeletal problems without signs of ischemia. No correlation was found between these indexes and the lowest coronary flow reserve in each patient. However, a fair, but significant, correlation was observed between the triple in-

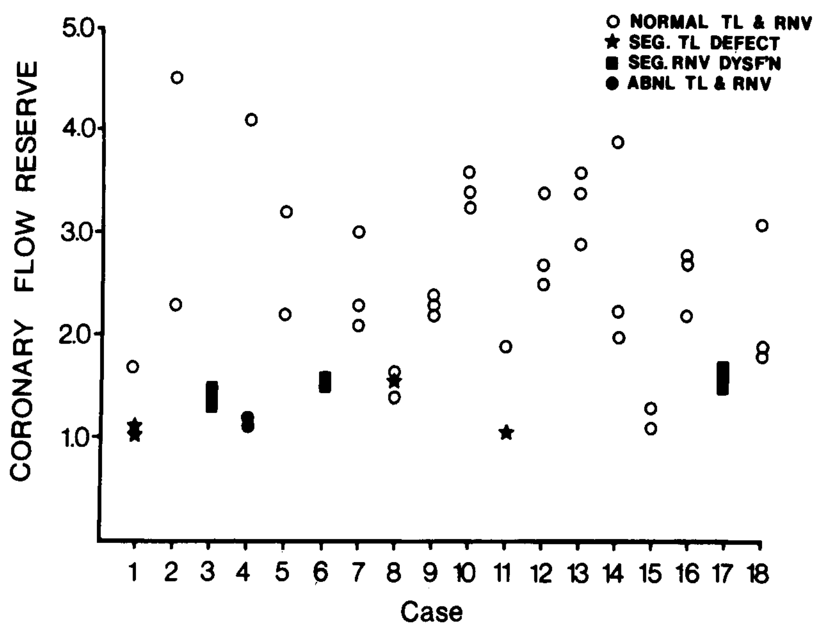


Figure 3. Individual patient results for coronary flow reserve determinations. At least two determinations were made in each of the 18 patients. Scintigraphic results for the corresponding arterial distribution are indicated. ABNL = abnormal; DYSF'N = dysfunction; RNV = radionuclide ventriculography; SEG. = segmental; TL = thallium-201.

dex and the mean coronary flow reserve: $y = 0.56x + 1.74$; $r = 0.52$; $p < 0.05$ (Fig. 4).

Discussion

The accuracy of functional testing has always been determined by results from coronary angiography. Although a close relation exists between scintigraphic abnormalities and the presence of coronary disease, numerous studies (1–4) have shown abnormal exercise test results in the absence of any epicardial coronary artery disease. Although our study confirms that radionuclide stress test results can be abnormal in the absence of angiographically visible coronary stenoses, the major observation is that all abnormal exercise thallium-201 and radionuclide ventriculographic test results were associated with abnormal flow reserve values. Inversely, seven of nine patients with low flow reserve values had abnormal exercise scintigraphic test results.

Abnormal flow reserve and normal coronary arteries. Two of the seven patients with abnormal exercise test results were found to have abnormalities that have been shown previously to be associated with abnormal scintigraphy and normal coronary arteries. One factor observed in patients with normal arteries and abnormal exercise tests is coronary spasm (5). Patient 11 had resting and exertional angina and demonstrated spasm of the left anterior descending coronary artery after injection of ergonovine. Interestingly, the flow reserve was markedly reduced in the left anterior descending artery distribution (1.01), whereas this artery was known not to be in spasm. Ergonovine challenge was negative in three other patients with low flow reserve. Despite the absence of electrocardiographic Q waves or history of prolonged chest pain, Patient 4 had a persistent inferoposterior thallium-201 defect and abnormal wall motion both at rest and during exercise. He is likely, thus, to have had a silent myocardial infarction. Myocardial infarction can be asymptomatic (20) and can occur in the absence of angiographic coronary stenoses (21,22). Coronary spasm has been proposed as a precipitating factor (23,24), but ergonovine challenge was negative in this case. Experimental studies have shown that coronary flow reserve is reduced after repeated episodes of ischemia (25), but chronic flow reserve after myocardial infarction has not been extensively studied. The etiology of the five other abnormal exercise test results is not known.

Table 3. Comparison Between Relative Thallium Distribution and Coronary Flow Reserve in Nine Patients With Abnormal Flow Reserve

Patient No.	Regional Thallium Activity Ratio: Exercise LAD/LCX	Regional Thallium Activity Ratio: 4 hour LAD/LCX	Regional Flow Reserve Ratio LAD/LCX
1	0.82	1.01	0.60
3	0.93	0.97	1.00
4	1.38	1.40	3.33
6	0.89	0.87	1.00
8	0.91	0.86	0.85
11	0.75	1.00	0.55
15	0.86	0.95	0.81
17	0.96	0.96	0.92
18	0.98	1.04	1.10

Correlation between exercise LAD/LCX ratio and LAD/LCX coronary flow reserve ratio: $y = 0.21x + 0.71$; $r = 0.974$. LAD = left anterior descending; LCX = circumflex artery.

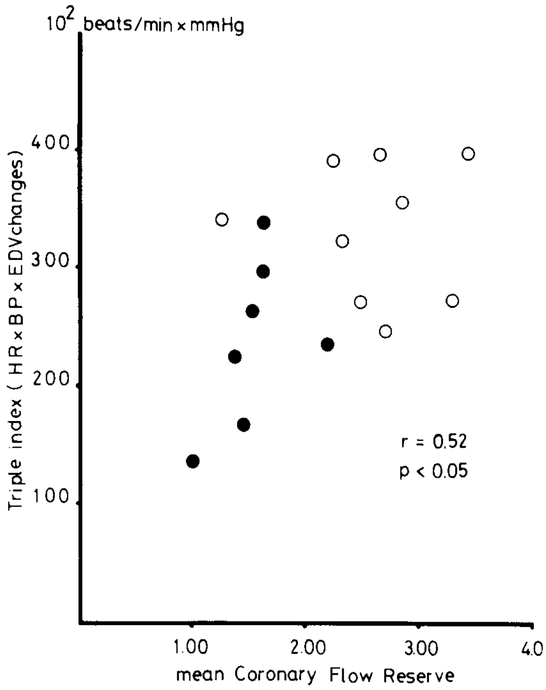


Figure 4. Relation between maximal metabolic requirements achieved during symptom-limited exercise (expressed by the triple index) and mean coronary flow reserve. The **closed circles** represent patients with abnormal scintigraphic results. The **open circles** represent those with normal functional tests. Two of the 18 patients who stopped exercise because of musculoskeletal problems are not included. A positive correlation was found between the two variables: $y = 0.56x + 1.74$; $r = 0.52$; $p < 0.05$. BP = blood pressure; EDV = end-diastolic volume; HR = heart rate.

Using other techniques, abnormal coronary flow reserve has been observed in patients with hypertension (11–13) or left ventricular hypertrophy, or both (8–11). Although uncontrolled hypertension or a history of hypertension was noted in 11 patients in this study, only two patients had electrocardiographic criteria for left ventricular hypertrophy, of whom one had abnormal flow reserve. No echocardiographic studies, however, were performed to assess the presence or severity of left ventricular hypertrophy in these subjects. Angiographic quantitation of left ventricular hypertrophy remains crude and therefore was not performed as part of this study. It is not clear whether decreased hyperemic flow (13,26–28) or increased basal flow (9,10,29), or both (12), are responsible for the abnormal flow reserve in the presence of hypertension or left ventricular hypertrophy. Moreover, subtle differences in muscle mass may have substantial implications for flow distribution. Knowledge of perfusion per gram at baseline and during maximal hyperemia would help clarify this issue. The current investigation cannot address this problem because the angiographic technique allows determination of only relative flow changes to an arterial distribution for which myocardial mass is not known.

Scintigraphic abnormalities, exercise limitation and coronary flow reserve. A false positive thallium-201 scintigram is sometimes due to soft tissue attenuation (7) or apical thinning (30). In this study, decreased thallium activity thought to be due to valve planes, soft tissue superimposition or apical thinning was not interpreted as abnormal. Moreover, we used quantitative analysis in conjunction with visual interpretation to improve diagnostic accuracy (18,31). The defects detected appeared in the vessel distribution with the lowest flow reserve in three patients and was inferoseptal and apical in a fourth patient who had similarly low flow reserve values in all arterial distributions (Fig. 3, Table 3). Because thallium-201 recognizes relative perfusion abnormalities, it is understandable that the scintigrams were abnormal in the vascular distributions with the lowest coronary flow reserve. Although five of the seven patients with segmental scintigraphic abnormalities had abnormal exercise ejection fraction responses, the results of thallium-201 and radionuclide ventriculography did not agree consistently. This may represent a different pathophysiologic mechanism in these patients as compared with those having significant arterial stenoses.

The mean coronary flow reserve at rest in patients with normal coronary arteries appears to be an indicator of exercise limitation. Although weak, the correlation between an index of metabolic requirement during exercise (triple index) and flow reserve indicates that higher flow demands are met by higher vascular reserves. However, the comparison between these two variables may be of limited value if exercise is interrupted because of extracardiac reasons or if metabolic and flow requirement determinations are inaccurate. This can explain in large part the dispersion observed between flow reserve and triple index, as well as the lack of correlation with rate-pressure product.

Study limitations. This study has several limitations. *First,* contrast medium does not stimulate maximal coronary blood flow. Adenosine triphosphate, papaverine or dipyridamole are more potent vasodilators (32–34). However, multiple coronary flow reserve determinations would be more difficult to perform because of the prolonged vasodilator effects of these drugs (33,34). This point is critical when digital radiographic techniques are used to measure flow reserve; repeated determinations are sometimes required because of technical difficulties and the risks involved with catheterization are known to increase with the duration of the procedure. Thus, the coronary flow reserve determined in this study by contrast induced hyperemia may be somewhat underestimated. Nevertheless, significant differences in flow reserve between patient groups with normal and abnormal functional tests were found.

Second, determination of coronary flow reserve by digital subtraction angiography requires precisely timed contrast medium injection and data acquisition, as well as patient cooperation. Despite these technical limitations, interpretable studies were obtained for 18 of 19 patients referred for catheterization who were found to have normal coronary arteries.

Third, it is well known that coronary flow is altered by intracoronary contrast medium injection. Hodgson et al. (35) reported that when using an ionic contrast agent (Renografin-76), these alterations are predictable and occur in parallel during the first few seconds of both baseline and hyperemic flow. It is for this reason that this technique assesses relative blood flow from the "washin" portion of the time-density curve. Nonionic contrast agents were not used because they produce less hyperemia but similar initial blood flow alterations. Animal studies have demonstrated a good correlation between coronary flow reserve determinations made by electromagnetic flow meter and this digital subtraction angiographic technique with the use of an ionic contrast agent (19). Using this method to measure flow reserve in human subjects has advantages compared with other techniques: measurements can be made in all major coronary distributions, and information is readily available at the time of catheterization.

Fourth, although the medications were stopped for 12 hours or longer before the exercise tests, we cannot exclude the persistence of some pharmacologic effects that would have tended to make some of the results negative. Thus, it is possible that the results would have been even more striking if the patients had not been receiving any medications for a longer period.

Conclusion. From this study, which provides the first correlation of regional blood flow and exercise scintigraphic data in human subjects, we conclude that patients with angiographically normal coronary arteries and abnormal radionuclide test results have abnormal coronary flow reserve in arterial distributions corresponding to scintigraphic abnormalities. Although it is appropriate that exercise scintigraphy be used as a noninvasive method for predicting coronary anatomy, abnormal scintigraphic results in patients with normal arteriograms likely depict true physiologic blood flow or myocardial perfusion abnormalities.

We are indebted to Glenn Beauman, Michael LeFree and Sandy Simon for technical assistance; and to Diane Bauer for assistance in preparing the manuscript.

References

1. 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.
2. Berger BC, Abramowitz R, Park CH, et al. Abnormal thallium 201 scans in patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1983;52:365–70.
3. Berger HJ, Sands MJ, Davies RA, et al. Exercise left ventricular performance in patients with chest pain, ischemic-appearing exercise electrocardiograms, and angiographically normal coronary arteries. Ann Intern Med 1981;94:186–91.
4. Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJC. The declining specificity of exercise radionuclide ventriculography. N Engl J Med 1983;309:518–22.
5. Fuller CM, Raizner AE, Chahine RA, et al. Exercise-induced coronary arterial spasm: angiographic demonstration, documentation of ischemia by myocardial scintigraphy and results of pharmacologic intervention. Am J Cardiol 1980;46:500–6.
6. Bulkley BH, Hutchins GM, Bailey I, Strauss HW, Pitt B. Thallium-201 imaging and gated cardiac blood pool scans in patients with ischemic and idiopathic cardiomyopathy: a clinical and pathologic study. Circulation 1977;55:753–60.
7. Dunn RF, Wolff L, Wagner S, Botvinick EH. The inconsistent pattern of thallium defects: a clue to the false positive perfusion scintigram. Am J Cardiol 1981;48:224–32.
8. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med 1982;307;1362–6.
9. Pichard AD, Smith H, Holt J, Meller J, Gorlin R. Coronary vascular reserve in left ventricular hypertrophy secondary to chronic aortic regurgitation. Am J Cardiol 1983;51:315–20.
10. Pichard AD, Gorlin R, Smith H, Ambrose J, Meller J. Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type: evidence for an impaired coronary vascular reserve. Am J Cardiol 1981;47:547–54.
11. Nichols AB, Sciacca RR, Weiss MB, Blood DK, Brennan DL, Cannon PJ. Effect of left ventricular hypertrophy on myocardial blood flow and ventricular performance in systemic hypertension. Circulation 1980;52:329–49.
12. Strauer BE. Ventricular function and coronary hemodynamics in hypertensive heart disease. Am J Cardiol 1979;44:999–1006.
13. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation 1984;69:1–7.
14. 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.
15. 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.
16. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819–24.
17. Vogel R, LeFree M, Bates E, et al. Application of digital techniques to selective coronary arteriography: use of myocardial contrast appearance time to measure coronary flow reserve. Am Heart J 1984;107;153–64.
18. Garcia E, Maddahi J, Berman D, Waxman A. Space/time quantitation of thallium-201 myocardial scintigraphy. J Nucl Med 1981;22:309–17.
19. Hodgson JMcB, Legrand V, Bates E, et al. Validation in dogs of a rapid angiographic technique to measure relative coronary blood flow during routine catheterization. Am J Cardiol 1985;55:188–94.
20. Margolis JR, Kannel WB, Feinleib M, Dawber TR, McNamara PM. Clinical features of unrecognized myocardial infarction—silent and symptomatic. Eighteen year follow up: the Framingham study. Am J Cardiol 1973;32:1–7.
21. Rosenblatt A, Selzer A. The nature and clinical features of myocardial infarction with normal coronary arteriogram. Circulation 1977; 55:578–80.
22. Cheitlin MD, McAllister HA, de Castro CM. Myocardial infarction without atherosclerosis. JAMA 1975;231:951–9.
23. Braunwald E. Coronary spasm and acute myocardial infarction—new possibility for treatment and prevention. New Engl J Med 1978;299:1301–3.
24. Legrand V, Deliege M, Henrard L, Boland J, Kulbertus H. Patients

with myocardial infarction and normal coronary arteriogram. Chest 1982;82:678–85.

25. Nicklas JM, Sanford G, Van Heyningen CA. Decreased flow reserve following transient myocardial ischemia (abstr). J Am Coll Cardiol 1984;3:546.

26. Mueller TM, Marcus ML, Kerber RE, Young JA, Barnes RW, Abboud FM. Effect of renal hypertension and left ventricular hypertrophy on the coronary circulation in dogs. Circ Res 1978;42:543–9.

27. Holtz J, Restorff WV, Bard P, Bassenge E. Transmural distribution of myocardial blood flow and of coronary reserve in canine left ventricular hypertrophy. Basic Res Cardiol 1977;72:286–92.

28. Kobayashi K, Tarazi RC, Lovenberg, Rakusan K. Coronary blood flow in genetic cardiac hypertrophy. Am J Cardiol 1984;53:1360–4.

29. Bache RJ, Vrobel TR, Ring WS, Emery RW, Andersen RW. Regional myocardial blood flow during exercise in dogs with chronic left ventricular hypertrophy. Circ Res 1981;48:76–87.

30. Cook DJ, Bailey I, Strauss HW, Rouleau J, Wagner HN, Pitt B. Thallium-201 for myocardial imaging: appearance of the normal heart. J Nucl Med 1976;17:583–9.

31. Berger BC, Watson DD, Taylor GJ, et al. Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. J Nucl Med 1981;22:585–93.

32. Bookstein JJ, Higgins CB. Comparative efficacy of coronary vasodilatory methods. Invest Radiol 1977;12:121–7.

33. Marcus ML. Pharmacologic agents. In: The Coronary Circulation in Health and Disease. New York: McGraw-Hill, 1983:416–52.

34. Barner HB, Kaiser GC, Willman VL. Effect of nitroglycerine and papaverine on coronary flow in man. Am Heart J 1974;88:13–7.

35. Hodgson JMcB, Mancini GBJ, Vogel RA. Characterization of changes in coronary blood flow during the first six seconds after contrast injection (abstr). J Am Coll Cardiol 1984;3:589.