Early Detection of Abnormal Coronary Flow Reserve in Asymptomatic Men at High Risk for Coronary Artery Disease Using Positron Emission Tomography

Firat Dayanikli, MD; David Grambow, MD; Otto Muzik, PhD; Lori Mosca, MD; Melyvn Rubenfire, MD; Markus Schwaiger, MD

Background The objective of this study was to compare coronary flow reserve (CFR) as a measure of vascular integrity in asymptomatic middle-aged men with family history of coronary artery disease (CAD) and a high-risk lipid profile with men without risk factors for CAD using positron emission tomography (PET). Previous studies suggested that the assessment of CFR is a sensitive means to detect vascular abnormalities before angiographic appearance of CAD. N-13 ammonia PET scanning allows noninvasive evaluation of regional and global myocardial blood flow and thereby quantification of CFR.

Methods and Results We used dynamic N-13 ammonia PET imaging in conjunction with intravenous adenosine to assess regional and global CFR in asymptomatic middle-aged men with high risk (group 1, n=16) and men without any known risk factors (group 2, n=11) for CAD. Group 1 patients were selected based on positive family history of CAD, one or more lipid abnormalities, and a normal stress test. No patient had history of diabetes or hypertension. A three-compartment tracer kinetic model developed and validated in our institution was used to calculate myocardial blood flow. Absolute myocardial blood flow (mL/100 g per minute) was calculated in five territories for each patient. CFR was defined as the ratio of blood flow during maximum pharmacological vasodilatation to blood flow at rest. Comparisons of CFR between the two groups of patients were performed. The mean age was similar between groups (group 1, 49.3±0.5 years; group 2, 48.1±8.7 years; P=NS). Group 1 had higher total cholesterol (mg/dL) (241.4±34 versus 173.4±34, P<.001), total cholesterol to high-density lipoprotein cholesterol ratio (6.4±1.6 versus 4.1±1.4, P<.001), and low-density lipoprotein cholesterol (mg/dL) (167±33 versus 107±32). No group 1 patient had evidence of ischemia by exercise ECG or exercise or pharmacological radionuclide perfusion studies. The mean global absolute myocardial blood flow at rest was not significantly different among groups (group 1, 76±18; group 2, 66±8; P=NS, in mL/100 g per minute). However, blood flow after adenosine infusion was higher for group 2 (group 1, 217±56; group 2, 264±39; P<.001), which resulted in a larger CFR for group 2 (group 1, 2.93±0.86; group 2, 4.27±0.52; P<.001). Univariate linear regression analysis revealed significant negative correlation of CFR to total cholesterol (P<.05, r=−.41), low-density lipoprotein (P<.05, r=−.38), and total cholesterol to high-density lipoprotein cholesterol ratio (P<.05, r=−.47).

Conclusions Noninvasive quantification of absolute myocardial blood flow by N-13 ammonia PET allows the detection of abnormal vasodilatory response to intravenous adenosine in male patients with family history of CAD and high-risk lipid profiles. Early assessment of alterations of vascular reactivity to adenosine in relation to high-risk lipid profiles in asymptomatic men may allow early detection of preclinical atherosclerosis and may initiate modification and/or elimination of risk factors that may slow, retard, or even reverse the progression of CAD. (Circulation. 1994;90:808-817.)

Key Words • coronary disease • tomography • blood flow

In the past decade, we witnessed an increased understanding about the pathophysiology of coronary artery disease (CAD). The dynamic nature of this disease is defined by the atherosclerotic plaque, endothelial function, and an interaction of cellular elements with the vessel wall. In addition, the modification of disease process by altering risk factors such as lipid abnormalities is well appreciated.

The evaluations of treatment strategies for primary and secondary prevention of CAD are costly and require a large study population. Clinical end points usually include death, cardiac event rate, and need for revascularization.1-7

The benefit of lowering serum cholesterol has been measured by clinical end points in combination with the rate of progression and regression by serial coronary arteriography.1-8 However, angiographically defined coronary lesions reflect advanced disease states with structural alterations resulting from a longstanding atherosclerotic process. This anatomic end point therefore may not be a sensitive marker for the short-term effect of, for example, lipid-lowering therapy.

The evaluation of lipid lowering or other measures for primary prevention of CAD in asymptomatic patients should concentrate on measurements that provide a sensitive detection of the early disease process and include functional characterization of vascular integrity. Carotid artery wall thickness and brachial arterial flow reserve are two such examples.8 These techniques have

Received December 8, 1993; revision accepted April 15, 1994.
From the Divisions of Nuclear Medicine (F.D., O.M., M.S.) and Cardiology (D.G., L.M., M.R.), Department of Internal Medicine, the University of Michigan Hospitals, Ann Arbor.
Correspondence to Markus Schwaiger, MD, Nuklearmedizinische Klinik und Poliklinik, der Technische Universität München, Klinikum rechts der Isar, Ismaninger Strasse 22, 8000 München 80, FRG.
© 1994 American Heart Association, Inc.
promise, but the large carotid artery and the muscular brachial artery differ significantly from the coronary arteries in several respects, including relation to classic lipid risk factors.

The earliest abnormality associated with CAD is the demonstration of abnormal coronary flow reserve (CFR), an integrating parameter of endothelial function and vascular smooth muscle relaxation. Quantitative analysis of CFR with positron emission tomography (PET) is accurate and reproducible. Abnormal CFR by PET has been demonstrated in patients with syndrome X, cardiac transplantation, hypertrophic cardiomyopathy, and hypertension in the absence of abnormalities on coronary arteriography. If abnormalities in CFR can be detected by quantitative PET in asymptomatic persons, this tool could be very useful for evaluating the effects of various primary and secondary prevention strategies.

Methods

To test the hypothesis that CFR is a sensitive means to detect early CAD, we measured CFR by quantitative PET scan using N-13 ammonia before and after intravenous adenosine infusion in asymptomatic middle-aged men with no clinical evidence of CAD but with a high likelihood of early CAD.

Study Design and Criteria

Two groups of asymptomatic men were recruited for a baseline N-13 ammonia PET coronary blood flow study followed by determination of coronary flow reserve by pharmacologic stress with intravenous adenosine.

To determine the usefulness of rest/adenosine N-13 ammonia PET in detecting preclinical abnormalities, we recruited 16 persons without clinical evidence of CAD based on stress testing who had a high risk for developing premature CAD. The study group was recruited from a group of men from outpatient clinics and a primary prevention screening program of the University of Michigan. All patients fulfilled the following criteria: a family history of premature cardiovascular disease in a first-degree relative (<5 years in men and <60 years in women); low-density lipoprotein-cholesterol (LDL-C) >190 mg/dL, high-density lipoprotein-cholesterol (HDL-C) <35 mg/dL, or both; and a negative stress test for ischemia within the preceding 90 days. Eleven asymptomatic men of comparable age (range, 32 to 63 years; 48±3±8.3) with no risk factors for CAD and normal lipids were recruited as persons with a very low probability of CAD. The probability of significant disease in this population was <1%. The normal men were recruited from institutional personnel. Exclusion criteria for all persons included any of the following: cerebral vascular disease; carotid artery bruit; peripheral bruit or abnormal pulse; history of anginal pain or a myocardial infarction; hypertension requiring treatment; ECG evidence of myocardial infarction or left ventricular hypertrophy; diabetes mellitus; use of vasodilating drugs; alcohol intake >10 oz per week; and conditions associated with secondary hypercholesterolemia.

Sixteen high-risk men with an age range of 29 to 61 years (48.8±7.7, P=NS compared with control) agreed to participate in the study (group 1, Table 1). Three of the 16 patients in group 1 and none of the normal volunteers were current smokers (>10 cigarettes per day).

All group 1 patients were on diet therapy for at least 6 months before the study. Patients on cholesterol-lowering agents for <1 year were accepted pending fulfillment of lipid entry criteria. Twelve patients were receiving lipid-lowering agents at the time of the study. Six were prescribed a statin, four bile resins, and two a fibric acid derivative.

All participants were fasting for at least 8 hours, and caffeine intake and all antithrombotic mixtures were stopped 24 hours before PET studies. Blood samples for repeat verification of lipid values were obtained after an overnight fast just before the PET scan.

Lipid analysis was performed in the University of Michigan Medical Center Hospital Laboratory using standard techniques (Kodak Ektachem 700 analyzer).

The study protocol was approved by the institutional review board and radiation safety committee of the University of Michigan. Informed consent was obtained before enrolling each subject into the study.

PET Imaging Protocol

Dynamic PET measurements were performed using our whole-body PET scanners, which allow simultaneous acquisition of 15 contiguous transaxial images (model CTI 931 and Siemens/ECAT 931). After placement in the PET scanner, a "sprint scan" of the thorax was obtained to align the heart within the field of view of the scanner using 0.5 mCi of N-13 ammonia. The patient's position with respect to the camera was checked by a cross-shaped, low-power laser beam and pen markers on the patient's skin. A transmission scan then was obtained for 15 minutes for attenuation correction using retractive germanium-68 ring sources. After completion of the transmission scan, 25 mCi N-13 ammonia (physical half-life, 9.9 minutes) diluted in 20 mL of normal saline was administered as a slow bolus into a peripheral arm vein over 30 seconds using a Harvard pump (Gould, Inc.). The dynamic PET data acquisition consisted of varying frame duration (12×10 seconds, 6×30 seconds, 2×300 seconds), with a total of 90 frames. At least 90 minutes was allowed between the rest and pharmacologic stress study, during which the N-13 activity within the gantry decayed to 3%.

For the stress study, adenosine was infused at a dose of 0.14 mg/kg per minute over 6 minutes, as previously reported. Twenty-five microliters of N-13 ammonia was administered in a similar fashion as the baseline study during the third minute of the adenosine infusion. ECG was continuously monitored. Systolic and diastolic arm blood pressures were obtained at 1-minute intervals during the first 10 minutes of adenosine infusion and thereafter at the conclusion of the scanning. Pressure-rate product (PRP) was calculated as heart rate times systolic blood pressure and expressed as divided by 100.

Image Processing

The images were reconstructed using a Hann filter with a cutoff frequency of 0.35. All reconstructed images consisted of 15 transaxial images (oriented perpendicular to the sagittal and coronal planes of the body) with a slice thickness of 6.75
mm, resulting in an in-plane resolution of 8.5±0.35 mm at full width at half maximum (FWHM) and 6.6±0.49 mm FWHM in the axial orientation.

Twelve transaxial images were created in the short-axis view of the heart using a SUN workstation (SUN Microsystems, Inc). The vertical and horizontal cardiac long-axis angles were defined using the last frame of the N-13 ammonia dynamic sequence with the best tissue to blood ratio and were later used for the reorientation of all 20 frames.

**Myocardial Tissue and Blood Pool Regions**

A previously described method for automated region definition was used for kinetic analysis of the acquired dynamic data set. The algorithm automatically defines myocardial regions of interest based on radial activity profiles with a blood volume fraction of about 60%. The definition allows us to incorporate correction for partial volume effects and blood to tissue cross-contamination into the model equation.

Twelve myocardial regions per plane were defined in the six to eight planes in the last time frame of the dynamic study sequence, with a marked contrast between blood and tissue. These regions were copied to other time frames of the dynamic sequence. The dynamic image sequence was corrected for patient motion as previously described by Muzik et al before time-activity curves were generated. The dynamic image set was sampled, and 96 (8 planes times 12 regions) time-activity curves were stored for further analysis.

To determine the arterial input function of radioactivity, a circular region was placed on two most basal planes in the resliced images. As previously shown, these planes with the largest ventricular diameter allow the placement of a sufficient large blood region in the center of left ventricle and are free of resolution distortions.

**Myocardial Blood Flow and Vascular Resistance Calculation**

The tracer kinetic model for N-13 ammonia developed by Hutchins et al was validated at our institution was used to calculate myocardial blood flow. In brief, we have previously demonstrated that a three-compartment model allows separation of the N-13 ammonia initial extraction from retention.

Based on experimental data by Schelbert et al, the initial extraction fraction has been shown to be >90%, even for flow values up to 500 mL/100 g per minute. Therefore, myocardial blood flow (MBF(NH3)) can be expressed as

\[(1) \text{MBF}_{\text{NH3}}(\text{mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}) = K_i(\text{mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1})\]

The unidirectional clearance rate, K_i, is estimated by fitting the following equation to the regional time-activity curves.

\[(2) C_u(t) = \frac{1}{(t_s-t_i)} \frac{t_s}{t_i} \int_{t_i}^{t_s} (1-TBV)p_{\text{true}} \left[ \frac{K_i k_1}{k_2 + k_3} \int_0^T C_u(u) du + \frac{T}{k_3} \left( C_u(u) \cdot e^{-(k_2+k_3)(T-t)} \right) du \right] + \]

\[TBV \cdot C_u(T) dT\]

C_u is the measured concentration by the tomograph averaged over the acquisition period and is fitted to the averaged tissue concentration predicted by the model. K_i represents tracer delivery and extraction into the myocardium and carries the dimension (mL·g⁻¹·min⁻¹), k_2 and k_3 are true rate constants (L/min); C_u represents the arterial blood pool concentration. The time t_i is the midscan time of the ith scan, and the time points t_s, t_i mark the beginning and the end of the ith data acquisition period. p_{true} represents myocardial tissue density in units of (g tissue/mL tissue). The parameter TBV defines the total blood volume fraction (vascular and spillover contribution) in the studied region.

As described by Hutchins et al, the factors (1-TBV) and TBV correct for resolution distortions caused by the finite resolution of the tomograph. Five territories were defined on the polar map, and myocardial blood flow was calculated for each of these territories (anterior, lateral, septal, inferior, and apex).

Myocardial vascular resistance was calculated by dividing the mean blood pressure [(SBP+DBP*2)/3] by blood flow.

To provide objective definition of regional scintigraphic abnormalities, semiquantitative analysis and circumferential profile analysis also were used as previously described. All polar maps were compared with a normal database.

**Radionuclide Studies**

Stress and pharmacologic thallium-201 studies were performed according to previously described methods. Bruce protocol was used for exercise stress tests. Adenosine was the agent of choice for pharmacologic stress. The reinjection technique using a stress dose of 3 mCi and rest dose of 1 mCi of thallium-201 was used. In the case of Tc-99m sestamibi, same-day protocol was used, with 8 mCi and 25 mCi during rest and stress, respectively. All polar map displays were compared with a normal database.

**Statistical Analysis**

Mean and standard deviations were calculated for all continuous variables. A two-sample Student’s t test was used in the case of continuous variables and Fisher’s exact test in the case of discrete variables to analyze for statistical significance. ANOVA was used for comparison of more than three groups. Univariate analysis of the effects of each continuous variable (age, lipid variables, change in blood pressure, and heart rate) was performed with linear regression. All tests of significance were two-tailed, and a value of P<.05 was considered statistically significant.

**Results**

A total of 27 patients underwent dynamic PET study at rest and in conjunction with adenosine. Group 1 consisted of 16 asymptomatic men between the ages of 29 and 61 years (48.8±7.7) with high risk for CAD as defined by the inclusion criteria. Group 2 included 11 men with no risk factors for CAD with an age range of 32 to 63 years (48.3±8.3).

**Lipid Profiles**

A comparison of age and lipid profile in the high-risk patients (group 1) and low-risk volunteers (group 2) is shown in Table 1. TC, LDL-C, triglycerides (TG), TC/HDL-C ratio, and LDL-C/HDL-C ratio were significantly higher in group 1 compared with group 2. Although HDL-C was lower in group 1 patients, this was not statistically significant (P=NS). There was no significant correlation between age and coronary flow reserve in either group or groups combined together. Body mass index (kg/m²) was not different between groups.

**Stress Testing**

None of the normal volunteers underwent conventional stress testing because of the very low probability of CAD. All group 1 patients underwent stress testing within 3 months of the study. Fourteen of the 16 underwent radionuclide stress imaging to ensure that
there was no evidence of regional flow abnormalities due to significant occlusive epicardial coronary disease. Two patients underwent a symptom-limited exercise treadmill without imaging. All exercise stress ECGs were normal by standard criteria for ischemia. Thirteen of 14 exercise tests were performed to a good or excellent workload by energy output (as predicted for age and sex) and PRP. None of the 14 patients had scintigraphic evidence of ischemia or impaired reserve by visual and quantitative interpretation of the scans. The hemodynamic variables associated with the stress and description of the study are summarized in Table 2.

### Response to Adenosine

All patients underwent N-13 ammonia PET scanning at rest and with adenosine. The hemodynamic data during these studies are presented in Table 3. Rest and stress heart rate, systolic blood pressures, and rest and stress PRPs were not different between groups. Both groups showed a similar increase in PRP (group 1, 15±15%; group 2, 17±16%) in response to adenosine infusion, which was not statistically different (P=NS). Similarly, the side effects experienced during adenosine infusion were similar for both groups and included flushing, shortness of breath, headache, and chest heaviness. None of the group 1 or group 2 patients had any ECG changes during adenosine infusion.

### Visual and Semiquantitative Analyses

With the exception of one patient (No. 3), none had evidence for regional perfusion abnormalities by visual and semiquantitative analysis of PET images. Patient 3 had a reversible inferoposterior perfusion abnormality in the PET scan. Tc-99m sestamibi single-photon emission computed tomography imaging in this patient revealed a subtle fixed inferoposterior defect that was attributed to diaphragmatic attenuation.

### Quantitative Baseline Myocardial Blood Flow

Baseline flow values for group 1 ranged from 70.5 to 82.7 mL/100 g per minute (mean±SD, 76.4±18.8; Table 4). Baseline myocardial blood flow (MBF) was slightly lower for group 2, ranging from 61.4 to 70.6 (mean±SD, 66.2±8.7). Comparison of mean MBF did not reveal significant differences (P=NS). The resting blood flow was more heterogeneous in five segments of group 1 patients. The coefficient of variance (COV) for five different regions was significantly higher in group 1 patients (0.20±0.13 versus 0.09±.05, P<.01).

### Table 2. Study Description and Hemodynamic Variables Associated With Stress Tests

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of Stress</th>
<th>Stage*</th>
<th>Duration, min</th>
<th>Max HR</th>
<th>Max BP</th>
<th>Max PRP</th>
<th>Symptoms†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ExMIBI</td>
<td>4</td>
<td>13.5</td>
<td>157</td>
<td>197/88</td>
<td>309</td>
<td>Fatigue</td>
</tr>
<tr>
<td>2</td>
<td>ExThal</td>
<td>6</td>
<td>16.0</td>
<td>185</td>
<td>190/76</td>
<td>333</td>
<td>Fatigue</td>
</tr>
<tr>
<td>3</td>
<td>AdMIBI</td>
<td>NA</td>
<td>NA</td>
<td>86</td>
<td>145/79</td>
<td>124</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>ExThal</td>
<td>5</td>
<td>13.5</td>
<td>166</td>
<td>179/77</td>
<td>297</td>
<td>Fatigue</td>
</tr>
<tr>
<td>5</td>
<td>ExThal</td>
<td>6</td>
<td>15.2</td>
<td>164</td>
<td>220/88</td>
<td>360</td>
<td>Fatigue</td>
</tr>
<tr>
<td>6</td>
<td>ExThal</td>
<td>5</td>
<td>14.0</td>
<td>192</td>
<td>170/71</td>
<td>326</td>
<td>Fatigue</td>
</tr>
<tr>
<td>7</td>
<td>ExMIBI</td>
<td>5</td>
<td>13.1</td>
<td>165</td>
<td>206/81</td>
<td>340</td>
<td>Fatigue</td>
</tr>
<tr>
<td>8</td>
<td>ExThal</td>
<td>5</td>
<td>13.0</td>
<td>185</td>
<td>199/73</td>
<td>368</td>
<td>Fatigue</td>
</tr>
<tr>
<td>9</td>
<td>ExThal</td>
<td>3</td>
<td>6.2</td>
<td>126</td>
<td>157/84</td>
<td>198</td>
<td>Fatigue</td>
</tr>
<tr>
<td>10</td>
<td>ExThal</td>
<td>6</td>
<td>16.0</td>
<td>174</td>
<td>206/100</td>
<td>358</td>
<td>Fatigue</td>
</tr>
<tr>
<td>11</td>
<td>ExThal</td>
<td>4</td>
<td>10.3</td>
<td>150</td>
<td>168/80</td>
<td>252</td>
<td>Fatigue</td>
</tr>
<tr>
<td>12</td>
<td>ExThal</td>
<td>6</td>
<td>16.5</td>
<td>185</td>
<td>193/75</td>
<td>357</td>
<td>Fatigue</td>
</tr>
<tr>
<td>13</td>
<td>ExThal</td>
<td>5</td>
<td>15.0</td>
<td>169</td>
<td>216/78</td>
<td>370</td>
<td>Fatigue</td>
</tr>
<tr>
<td>14</td>
<td>ExTest</td>
<td>5</td>
<td>13.0</td>
<td>183</td>
<td>263/93</td>
<td>481</td>
<td>Fatigue</td>
</tr>
<tr>
<td>15</td>
<td>ExTest</td>
<td>5</td>
<td>13.3</td>
<td>176</td>
<td>189/72</td>
<td>332</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

HR indicates heart rate; BP, blood pressure; PRP, pressure-rate product; ExMIBI, exercise Tc-99m sestamibi; ExThal, exercise thallium-201; AdMIBI, adenosine Tc-99m sestamibi; and ExTest, exercise test.

†Reason for discontinuation of the test.

### Table 3. Hemodynamic Data During PET Scan

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Rest</th>
<th>Stress</th>
<th>Rest</th>
<th>Stress</th>
<th>Rest</th>
<th>Stress</th>
<th>Change in PRP, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>69±11</td>
<td>81±17</td>
<td>133±14</td>
<td>131±14</td>
<td>9309±2071</td>
<td>10 811±2793</td>
<td>16±15</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>69±13</td>
<td>82±14</td>
<td>124±15</td>
<td>121±15</td>
<td>8552±1790</td>
<td>10 013±2317</td>
<td>17±16</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR indicates heart rate; BP, blood pressure; PRP, pressure-rate product. PRP is defined as product of SBP in mm Hg and HR.
Myocardial Blood Flow During Vasodilatation

The MBF to whole left ventricular myocardium was significantly higher during adenosine infusion in group 2 patients (264.5±39.2 versus 217.5±56.1 mL/100 g per minute, P<.05). The largest flow differences during stress between group 1 and group 2 were in the septum and apex (Table 4). The regional analysis of maximal blood flow did not reveal significant differences in the heterogeneity of flow among groups during adenosine infusion (COV for group 1, 0.14±0.08 versus group 2, 0.12±0.05, P=NS for COV).

Global and Regional Coronary Flow Reserves

Global CFR (mean left ventricular flow after adenosine divided by mean flow at baseline) was significantly lower in group 1 (2.93±0.87 versus 4.28±0.53, P<.001; Table 5). Regional analysis of flow reserve revealed all segments to have significant differences among groups; however, lateral wall and apex revealed the largest differences of CFR (Table 4). The variability of CFR was statistically higher for group 1 patients (COV: 0.23±0.14 for group 1, 0.11±0.03 for group 2; P<.05).

Myocardial Vascular Resistance

Mean blood pressures were 98±11 mm Hg and 95±10 mm Hg at rest and during stress for high-risk patients, respectively, and 93±9 mm Hg, 89±12 mm Hg for normal volunteers. There was no statistical difference between mean blood pressures and heart rate of either group. Group 1 had a slightly lower myocardial vascular resistance (MVR) at rest (group 1, 137.2±50.2; group 2, 144.3±22.6; P=NS) but higher MVR during maximal vasodilatation, which did not reach statistical significance (group 1, 488±27.1; group 2, 356.8±11; P=1.3). However, the ratio of MVR stress/rest was significantly higher for high-risk men (group 1, 0.35±0.11; group 2, 0.24±0.04; P<.010).

Segmental Analysis of Coronary Flow Reserve

Segmental analysis of CFR values for five different regions (anterior, lateral, inferior, septal, and apex) of the left ventricle revealed a total of 135 segments (80 for group 1 and 55 for group 2). The mean CFR and the standard deviation (4.27±0.52) of our volunteers were taken as a reference point. Values below 1, 2, and 3 SD were calculated. Table 6 shows the number of segments below each cutoff value. A cutoff threshold of CFR of 3.75 (1 SD below mean) revealed an incidence of 75% of segments as abnormal for group 1. At a cutoff threshold value of 3.22 (2 SD below the mean), 66% of segments in group 1 fell below this value. Thirteen of the 16 high-risk patients had at least one segment below a CFR of 3.22 (2 SD below the mean). Among these 13 patients, 12 had a CFR of <3.22 in at least three or more segments. At 3 SD below the mean (cutoff, 2.69), 11 group 1 patients had at least one segment below this threshold value.

Comparison of Lipids Versus Coronary Flow Reserve and Myocardial Vascular Resistance

Univariate analysis of CFR when both groups were combined revealed significant negative correlation between TC (r = −.41, P<.05), LDL-C (r = −.38, P<.05), TC/HDL-C ratio (r = −.47, P<.01), LDL-C/HDL-C ratio (r = −.45, P<.05), and TG (r = −.33, P=.08) versus CFR (Fig 1). The most significant negative correlation was between TC/HDL-C ratio and CFR. In addition, there was a positive correlation of HDL-C versus CFR, which was not statistically significant (r = .28, P=.18).

When lipid variables were categorized into tertiles, similar trends were identified. Categorical analysis of lipid variables revealed significant differences among groups of TC/HDL-C ratios (P<.05) (Fig 2). The trend, namely, decreasing CFR values with increasing levels of TC, LDL-C, TG, and TC/HDL-C ratio, was noted. In addition, increase in CFR values with higher HDL was observed.

In addition, MVR showed significant correlation to TC (r = −.51, P<.05) and LDL (r = −.50, P<.05) in high-risk patients. The correlation to HDL (r = .38) and TG (r = .28) did not achieve statistical significance. When

---

### Table 4. Regional Coronary Blood Flow Values

<table>
<thead>
<tr>
<th>Region</th>
<th>Group 1 (n=16)</th>
<th>Group 2 (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>73.0±17.8</td>
<td>61.4±12.0</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral</td>
<td>79.7±35.2</td>
<td>67.7±8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Septum</td>
<td>75.1±22.1</td>
<td>67.6±10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior</td>
<td>76.9±26.3</td>
<td>70.6±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior</td>
<td>77.2±22.5</td>
<td>66.0±10.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 5. Global Myocardial Blood Flow and Flow Reserve

<table>
<thead>
<tr>
<th>Group</th>
<th>Rest Flow, mL/100 g per minute</th>
<th>Stress Flow, mL/100 g per minute</th>
<th>Stress/Rest Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76.4±18.8</td>
<td>217.5±56.1</td>
<td>2.93±0.87*</td>
</tr>
<tr>
<td>2</td>
<td>66.2±8.7</td>
<td>264.5±39.2</td>
<td>4.28±0.53</td>
</tr>
</tbody>
</table>

*P<.001; †P<.05.

### Table 6. Segmental Analysis

<table>
<thead>
<tr>
<th>Coronary Flow Reserve</th>
<th>Group 1 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 SD (CFR=3.75)</td>
<td>60 /80 (75%)</td>
</tr>
<tr>
<td>&lt;2 SD (CFR=3.22)</td>
<td>53 /80 (66%)</td>
</tr>
<tr>
<td>&lt;3 SD (CFR=2.69)</td>
<td>37 /80 (46%)</td>
</tr>
</tbody>
</table>

Coronary flow reserve (CFR) values depict cutoff values calculated 1, 2, and 3 SD below the mean CFR of normal volunteers.
TC/HDL ratio was analyzed in tertiles, there was an increasing myocardial vascular resistance with increasing TC/HDL ratios (ie, TC/HDL<4.5, MVR=35.8±8.9; 4.5<TC/HDL<6.0, MVR=41.1±14.4; TC/HDL>6.0, MVR=51.1±32.3) when both groups were pooled together.

Discussion

We have demonstrated that high-risk asymptomatic men with no clinical evidence for CAD have impaired CFR. Using PET before and after adenosine infusion, men at risk for CAD based on family history and high-risk lipid profile have a more heterogeneous and lower coronary vasodilator response by flow and vascular resistance measurements than normal volunteers. Moreover, there is a significant negative correlation between CFR and vascular resistance to the level of TC, LDL-C, and the ratio of TC/HDL-C.

To our knowledge, this is the first noninvasive study using PET as a noninvasive means to describe the relation between plasma cholesterol levels and coronary flow measurements based on PET perfusion imaging.

The data suggest that PET may be a useful noninvasive tool to monitor vascular reactivity and regression/progression of coronary atherosclerosis after pharmacologic interventions in primary or secondary prevention trials.

Regional Myocardial Blood Flow and Coronary Flow Reserve

Determination of CFR has been commonly used to assess functional responses to physiological or pharmacologic stimuli in patients with and without coronary atherosclerotic disease. Multiple studies demonstrated diminished flow reserve in patients with severe left ventricular hypertrophy,24 essential hypertension,16 dilated cardiomyopathy,25 and diabetes mellitus.26 Therefore, we specifically excluded patients with conditions that are known to be associated with impaired flow reserve.

In our control population of normal volunteers, the average and range of CFR (mean±SD, 4.27±0.53; range, 3.46 to 5.2) was similar to that reported in other studies.9,18,27-29 Our major finding was that the global CFR values were lower for high-risk men compared with normal volunteers.

The mean resting MBF was higher in high-risk patients, which, however, did not reach statistical significance. There was also a trend toward higher PRP in high-risk patients at rest, which was not statistically significant. No patient was on any medications that might affect vascular tone and thus increase resting flow. The higher resting MBF levels in group 1 most likely reflect higher energy demand of the myocardium due to heart rate and blood pressure. However, we
cannot exclude entirely hormonal or metabolic effects increasing myocardial oxygen demand and subsequently resting MBF.

Based on visual and semiquantitative analysis of the PET images, only one patient displayed a reversible inferoposterior perfusion abnormality that may be associated with regional CAD. This patient had a mild fixed inferior defect by Tc-99m sestamibi imaging that was attributed to diaphragmatic attenuation. This discrepancy between results suggests an increased sensitivity of PET imaging in detecting mild flow reserve abnormalities. The absence of regional perfusion abnormalities in all other patients suggests a global reduction of maximal blood flow, which reflects global changes in vascular reactivity or balanced atherosclerotic involvement of coronary arteries.

The regional variation in maximal blood flow of the group 1 patients was not statistically larger than in the control group, which indicates the global reduction of CFR. However the heterogeneity of resting MBF was greater in high-risk men than in volunteers. The reasons for these observations are not clear at the present time.

Technical factors are unlikely to account for this difference, since both groups were studied during the same period. Physiological factors affecting regional vascular tone may differ among both groups.

**Relation Between Lipid Parameters, Coronary Flow Reserve, and Myocardial Vascular Resistance**

Since various lipid values have been shown to be independent predictors of primary coronary events in hyperlipidemic subjects, we analyzed the relation of all lipid variables to measured CFR and vascular resistance. TC/HDL-C ratio was identified as having the strongest correlation to CFR. This finding is of interest considering that an elevated TC/HDL-C ratio (or low HDL-C) is highly predictive of initial cardiovascular events in middle-aged adults and highly prevalent among angiographically documented CAD. Recently Seiler et al described similar correlations between TC, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, and vasomotor relaxation of coronary arteries evaluated by angiography during exercise. Significant correlations also were present between myocardial vascular resis-
tance to TC and LDL in our high-risk patients, confirming the hypothesis of the interaction of blood cholesterol levels and vascular reactivity. Future studies assessing the effects of lipid-lowering therapy on CFR and MVR are needed to define the reversibility of the impaired flow response.

Factors That May Impair Coronary Flow Reserve in Patients With Family History of CAD and an Undesirable Lipid Profile

Previous animal studies have suggested abnormalities of relaxation of rabbit and porcine vascular rings exposed to hypercholesterolemic conditions despite the absence of atherosclerosis. Abnormal endothelium-derived relaxing factor (EDRF) release was believed to be responsible for impaired relaxation in the conduit vessels from rabbits, monkeys, and high-cholesterol-fed swine. The possibility of intimal thickening of the arterial wall due to infiltration of foam cells and lipid-laden smooth muscle cells preventing the interaction of EDRF and smooth muscle cells also was suggested. However, morphological changes alone could not account for the endothelium-dependent alterations, since abnormalities in the microcirculation of rabbits (which do not develop atheromatous lesions) with diet-induced atherosclerosis also were described.

Intracoronary Doppler flow measurements in conscious patients showed that angiographically normal epicardial coronary arteries respond to increases in blood flow with vasodilatation and that this reaction is impaired in the presence of mild atherosclerosis. It has been postulated that increases in shear forces associated with high arterial flow will trigger the release of a vasodilating substance from endothelial cells that has characteristics similar to endothelium-derived relaxing factor (EDRF). Thus, the shear stresses on the endothelium of epicardial vessels caused by vasodilatation of coronary resistance vessels may elicit more pronounced vasodilatation in normal vessels, whereas vessels with early atherosclerosis may reveal impaired relaxation.

Similar mechanisms of vasodilatation were held responsible for sodium nitroprusside (an endothelium-independent vasodilator) and EDRF (which is related or identical to nitric oxide). EDRF is hypothesized to cause an increase in cyclic GMP levels within the vascular smooth muscle, mediating an action similar to nitrates. This action is mediated by an enzyme, guanylate cyclase, which might be inactivated by the oxidation of the hememoyetin in the enzyme. Furthermore, it is hypothesized that hypercholesterolemia may reduce the responsiveness to endogenous and exogenous nitrates by altering the redox state of the smooth muscle, causing alterations in the lipid bilayer and affecting ionic fluxes as well as enhancing responsiveness of vascular smooth muscles to endogenous vasoconstrictors.

Conceivably, multiple alterations at the vascular smooth muscle and the endothelial cell level might have contributed to the decreased responsiveness of coronary vessels to adenosine in our patients. However, the observed reduction of CFR may not only be a consequence of endothelial or vascular smooth muscle dysfunction. Global reduction of maximal blood flow may reflect balanced atherosclerotic involvement of coronary arteries. Intervention studies with lipid-lowering drugs are necessary to identify the reversibility of impaired flow response in this patient population in order to prove the hypothesis of endothelial dysfunction.

Our results are in agreement with previous work in humans that have shown that hypercholesterolemia and other risk factors cause abnormal vasodilator responses not only in individuals with angiographically defined atherosclerosis but also in individuals without occlusive coronary vessel disease. Recently, Creager et al have shown blunted response to endothelium-dependent and independent vasodilators in the forearm vessels of hypercholesterolemic asymptomatic patients using venous occlusion plethysmography. More recently, Seiler et al demonstrated impaired vasodilatory response of normal epicardial coronary arteries during exercise in patients with hypercholesterolemia and described significant correlations between lipid parameters and exercise-induced vasomotion, all of which agree with our findings.

Limitations of the Study

The presence of mild coronary stenosis not sufficient to cause ischemia and clinical symptoms and not detected by routine TI-201 or Tc-99m sestamibi imaging cannot be totally excluded in our patients because no patient underwent coronary angiography. However, it would be difficult to justify ethically and on clinical grounds the performance of an invasive test with potential morbidity and mortality in an asymptomatic patient population.

This first study was done on a male population only. It is unclear whether the same results can be extrapolated to female patients. A similar study with inclusion of female subjects is warranted.

Most of group 1 patients were on diet therapy or lipid-lowering medical therapy, which probably underestimates the effect of risk factors on CFR. To define the relation of plasma cholesterol levels and CFR, patients should be investigated before and during lipid-lowering therapy. Such a study is currently under way in our institution to investigate whether the altered coronary response observed in group 1 patients is only a consequence of high lipid values or reflects early structural alterations of vessel wall. However, this study was not designed to answer this question.

Conclusions

Noninvasive quantification of MBF by dynamic N-13 ammonia PET imaging allows quantitative determination of CFR. Our study revealed a decrease in adenosine-induced CFR in asymptomatic men with positive family history of CAD and lipid abnormalities. There was a significant correlation between the impairment of CFR and severity of lipid abnormalities.

This study demonstrates that PET provides a noninvasive tool for identifying patients with altered functional vascular reactivity. Future studies must define the prognostic value of these early changes in asymptomatic patient populations. It is expected that such an imaging approach may be useful in the evaluation of dietary or pharmacologic interventions for primary or secondary prevention of CAD.
Acknowledgments

This work was performed during the tenure of an established investigatorship of Dr Schwaiger and was supported in part by the National Institutes of Health, Bethesda, Md (RO1-HL41047). The authors thank members of the Cyclotron Unit for preparation of tracer and technical assistance of the technologists in the PET suite (Jill Rothery, Andrew Weeden, Paul Kison, Edward McKenna) during PET studies. They also appreciate the statistical advice provided by Dr Anthony Schork of the School of Public Health, University of Michigan. Adenosine was provided by Medco Labs.

References


Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography.
F Dayanikli, D Grambow, O Muzik, L Mosca, M Rubenfire and M Schwaiger

_Circulation_. 1994;90:808-817
doi: 10.1161/01.CIR.90.2.808

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/2/808

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/