Relation Among Stenosis Severity, Myocardial Blood Flow, and Flow Reserve in Patients With Coronary Artery Disease

Marcelo Di Carli, Johannes Czernin, Carl K. Hoh, Victor H. Gerbaudo, Richard C. Brunken, Sung-Chen Huang, Michael E. Phelps and Heinrich R. Schelbert

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Abstract

Background Coronary arteriography is considered the "gold standard" for evaluating the severity of a coronary stenosis. Because the resistance to blood flow through a stenotic lesion depends on a number of lesion characteristics, the physiological significance of coronary lesions of intermediate severity is often difficult to determine from angiography alone. This study of patients with coronary artery disease seeks to determine the relation between myocardial blood flow and flow reserve measured by positron emission tomography (PET) and the percent area stenosis on quantitative coronary arteriography.

Methods and Results We studied 28 subjects: 18 patients with coronary artery disease (66±8 years) and 10 age-matched healthy volunteers (64±13 years) with dynamic N-13 ammonia PET imaging at rest and after dipyridamole (0.56 mg/kg). The percent cross-sectional area stenosis was quantified on the coronary arteriograms as described by Brown et al. In the 18 patients, a total of 41 non–infarct-related coronary vessels were analyzed. Myocardial blood flows in normal regions of patients with coronary artery disease were not different than those in healthy volunteers, both at rest and after dipyridamole. As a result, the myocardial flow reserve was also similar in both groups (2.4±0.4 versus 2.6±0.7, respectively; P=NS). Quantitative PET estimates of hyperemic blood flow (r=.81, P<.00001), flow reserve (r=.78, P<.00001), and an index of the "minimal coronary resistance" (r=.78, P<.00001) were inversely and nonlinearly correlated with the percent area stenosis on angiography. Of note, PET estimates of myocardial flow reserve successfully differentiated coronary lesions of intermediate severity (50% to 70% and 70% to 90%; 2.4±0.4 versus 1.8±0.5, respectively; P=.04).

Conclusions In patients with coronary artery disease, noninvasive measurements of myocardial blood flow and flow reserve by PET are inversely and nonlinearly related to stenosis severity as defined by quantitative angiography. Importantly, coronary lesions of intermediate severity have a differential flow reserve that decreases as stenosis increases that can be detected noninvasively by PET, thus allowing better definition of the functional importance of known coronary stenosis.
Coronary arteriography is the current “gold standard” for evaluating the severity of a coronary stenosis. Angiographic stenosis severity is usually expressed in percent diameter stenosis. However, this approach is limited because it does not include other lesion characteristics such as length, shape, and eccentricity that may also affect the impedance to blood flow. Accordingly, Gould, Kirkeeide, and colleagues proposed and validated the use of a single measure of coronary flow reserve on quantitative arteriography as a parameter that reflects all the various anatomic factors influencing stenosis severity. Similarly, other investigators also reported a close correlation between coronary flow reserve measured with intracoronary Doppler probes and luminal stenosis by quantitative arteriography.

The evaluation of the physiological significance of coronary lesions may also be assessed noninvasively with myocardial perfusion imaging during pharmacologically induced coronary vasodilation. Most previous reports comparing myocardial perfusion imaging and angiographic findings, however, examined both imaging and angiographic results in terms of sensitivity and specificity rather than as a continuous spectrum of severity. Quantification of myocardial blood flow and flow reserve with N-13 ammonia and positron emission tomography (PET) has been validated extensively in animals and humans. Furthermore, this technique has been used successfully for diagnosis of coronary artery disease, for assessing the significance of coronary stenosis, and for evaluating the results of interventions such as coronary revascularization.

We hypothesized that myocardial flow reserve based on quantitative measurements derived from N-13 ammonia PET imaging is related to luminal area stenosis on coronary angiography. Accordingly, this study of patients with coronary artery disease seeks to determine the relation between myocardial blood flow and flow reserve measured by N-13 ammonia and PET and percent area stenosis on quantitative coronary arteriography.

Methods

Study Group

The study group consisted of 28 subjects: 18 patients with chronic coronary artery disease undergoing coronary angiography for evaluation of chest pain and 10 age-matched healthy volunteers (7 men and 3 women; mean±SD, 64±13 years of age) with a low probability (<5%) of coronary artery disease based on the absence of symptoms and coronary risk factors, a normal resting ECG, and a normal submaximal treadmill test. In the healthy control volunteers, no regional flow defects were noted both at rest and during hyperemia by visual inspection and by polar mapping after comparison to a database of healthy individuals as described previously. The homogeneous N-13 ammonia uptake argues further that these healthy volunteers were indeed free of significant coronary artery disease. The patients with coronary artery disease (14 men and 4 women; mean age, 66±8 years) had a mean left ventricular ejection fraction of 45±14%. None had a history of hypertension, aortic stenosis, or hypertrophic cardiomyopathy. Six patients had a history of previous myocardial infarction based on clinical history, the presence of pathologic Q waves on the resting ECG, and the presence of regional wall motion abnormalities on contrast left ventriculography. Infarct-related coronary arteries were excluded from analysis. In addition, 7 vessels were excluded from analysis owing to the lack of adequate visualization on coronary angiography. The mean time interval between the PET study and coronary angiography was 3.7 months (range, 2 days to 5 months). All patients were clinically stable between the PET study and the angiographic procedure. Of the 18 patients with coronary artery disease, 10 had three-vessel disease, 6 had two-vessel disease, and 2 had single-vessel disease. These 18 patients had 41 diseased
coronary arteries that were unrelated to prior infarction. If a vessel was affected by several stenoses in series, only the most severe stenosis was considered for analysis. Each subject signed an informed consent form approved by the Human Subject Protection Committee of the University of California, Los Angeles.

**Positron Emission Tomography**

All subjects refrained from caffeine-containing beverages or theophylline-containing medications for 24 hours before the PET study. Myocardial blood flow at rest and after administration of 0.56 mg/kg dipyridamole IV infused over 4 minutes was quantified noninvasively with N-13 ammonia and dynamic PET imaging.

The whole-body tomograph (Model 931/8, CTI/Siemens) used in this study acquires 15 transaxial planes with an in-plane spatial resolution of 6.5-mm full-width half-maximum (FWHM), has an interplane spacing of 6.75 mm, and covers a 10-cm axial field of view. The images were reconstructed with a Shepp filter with a cutoff frequency of three cycles per pixel, resulting in an effective in-plane resolution of 11-mm FWHM.

A 20-minute transmission scan was acquired for correction of photon attenuation. Beginning with the IV bolus administration of N-13 ammonia (15 to 20 mCi), serial images were acquired for 19 minutes (12 frames of 10 seconds each, 2 frames of 30 seconds, 1 frame of 60 seconds, and 1 frame of 900 seconds). Forty-five minutes after physical decay of N-13 ammonia, 0.56 mg/kg dipyridamole IV was infused over 4 minutes. A second dose of N-13 ammonia (15 to 20 mCi) was injected 4 minutes after dipyridamole infusion, and images were recorded in the same acquisition sequence. Patient motion was minimized by fastening a Velcro strap across the patient's chest. Arterial blood pressure and ECGs were recorded continuously throughout the study.

**Quantification of Blood Flow**

Transaxial images were reoriented on a Macintosh IIci personal workstation (Apple Computer Inc) into six contiguous short-axis slices of the left ventricle, progressing from the apex to the base. To quantify regional myocardial blood flows at rest and during hyperemia, three short-axis slices of the rest and the hyperemic studies were selected in each patient. With the first of the serially acquired images that clearly visualized the left ventricular myocardium, sectorial regions of interest encompassing the myocardial segments supplied by each non–infarct-related coronary artery were assigned to each of the three midventricular short-axis slices. Within each vascular territory, the regions of interest were placed to the area that on visual inspection had the lowest N-13 ammonia concentration on the dipyridamole-stress images. The size of each sectorial region of interest was adjusted to the individual coronary anatomy, eg, the size of the stenosed vessel, the anatomic location of the stenosis, and the dominance as defined on the coronary angiograms. In coronary artery territories with normal N-13 ammonia activity on the stress images, the region of interest was assigned to the entire vascular territory. In each territory of stenosed arteries, an attempt was made to assign rather large regions of interest (typically encompassing >36° of the myocardial circumference of a given short axis cross section) to minimize statistical noise. The regions of interest were then copied to the first 2 minutes of serially acquired N-13 ammonia images, and regional myocardial tissue time-activity curves were obtained. In each vascular territory, a single time-activity curve was then obtained by averaging of the corresponding N-13 ammonia data in adjacent ventricular planes. A 25-mm² region of interest (10 pixels) was placed in the left ventricular blood pool and copied to the first 12 frames of the serially acquired images to obtain the arterial input function.

Partial volume effects were corrected with a recovery coefficient that assumed a homogenous myocardial wall thickness of 1 cm. The myocardial N-13 activity curves also were corrected for spillover of activity from the blood pool to the myocardium and for physical decay of N-13. The time-activity curves were then fitted with a previously validated two-compartment tracer kinetic model. The arterial input function was not corrected for N-13 metabolites because the degree of metabolite contamination in humans during the initial 2 minutes after
tracer administration is rather small. Because myocardial blood flow at rest is related to the rate-pressure product, an index of cardiac work, resting flow values were normalized to the corresponding rate-pressure product in each patient by dividing the resting flow value by the rate-pressure product multiplied by a linear factor of 10,000 in each individual patient.

The approach yields reproducible measurements of blood flow as demonstrated previously in 20 healthy volunteers studied at an average time interval of 3 to 7 days. Flow values at rest and during hyperemia in each major vascular territory differed randomly between the two measurements by an average of 10% to 15%.

Quantitative Coronary Arteriography

The stenosis severity was quantified on the coronary arteriograms as described by Brown et al.

Cineangiographic frames of orthogonal views were digitized as an interlaced television image (512×512 pixels, 256 shades of gray) and stored in a Gould-DeAnza IP-8500 image processor, interfaced to a Digital Equipment Corp VAX 11/780 computer. A range of coronary stenoses (from 18% to 97% luminal narrowing) involving major coronary arteries was outlined with an automated edge detection algorithm using a two-dimensional (2D) search. All traced lesions were corrected for pin-cushion and magnification distortion. Lesion cross-sectional area was estimated with a geometric method using biplane orthogonal views of each lesion. In this study, quantitative measurements of luminal stenosis are reported in terms of percent reduction in cross-sectional area rather than absolute values of percent diameter to minimize errors in the evaluation of eccentric lesions.

Statistical Analysis

Data are presented as mean±SD. A one-way ANOVA was used to compare estimates of myocardial blood flow, flow reserve, and "minimal coronary resistance" between groups with different degrees of luminal stenosis (ie, <50%, 50% to 70%, 70% to 90%, and >90%). Hemodynamic and myocardial blood flow results before and after dipyridamole in patients and volunteers were compared with Student's t test for paired or unpaired data as appropriate. Regression analysis used a Loess smoothed fit of the data. A probability value of <.05 was used to define statistical significance.

Results

In the 18 patients, a total of 41 non–infarct-related coronary vessels were analyzed. Eleven coronary arteries had <50% stenosis, 9 arteries had 50% to 69% stenosis, 10 arteries had 70% to 90% stenosis, and 11 arteries had >90% stenosis. Of the 41 coronary stenoses analyzed, there were 16 left anterior descending coronary arteries (10 proximal and 6 middle), 7 left circumflex coronary arteries (5 proximal and 2 middle), 5 proximal obtuse marginal coronary arteries, 1 proximal first diagonal coronary artery, and 12 right coronary arteries (3 proximal, 7 middle, and 2 distal). Five coronary arteries had 2 stenoses in series and 1 coronary artery had 3 stenoses in series.

Hemodynamics Findings

None of the patients had a history of hypertension. Two patients had a basal blood pressure of 160/85 mm Hg but no evidence of ventricular hypertrophy on ECG or 2D echocardiography. In the remaining 16 patients, blood pressure was <140/80 mm Hg. Table 1 summarizes the hemodynamic findings at rest and after dipyridamole in the patients with coronary artery disease and in the age-matched healthy volunteers. After dipyridamole, both groups of subjects demonstrated a significant increase in heart rate and rate-pressure product, whereas no significant change was observed in systolic, diastolic, or mean aortic blood pressure. No significant difference was observed in any hemodynamic parameter between the patients and the healthy volunteers.
Table 1.

Hemodynamic Findings

<table>
<thead>
<tr>
<th></th>
<th>Patients, n=18</th>
<th>Volunteers, n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Dip</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±11</td>
<td>85±16</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>134±18</td>
<td>134±23</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79±11</td>
<td>80±11</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>8649±2021</td>
<td>11 607±3975¹</td>
</tr>
<tr>
<td>Mean aortic BP</td>
<td>97±12</td>
<td>98±13</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; Dip, dipyridamole.

¹ P<.01 vs rest.

Changes in Myocardial Blood Flows and Stenosis Severity

At rest, myocardial blood flows in regions supplied by vessels with ≥70% area stenosis were lower than in those regions supplied by vessels with <50% area stenosis (0.7±0.2 versus 0.9±0.2 mL · g⁻¹ · min⁻¹, P<.01; Table 2). However, resting blood flows were similar in all groups of coronary stenoses when they were normalized to the rate-pressure product (Table 2).

Table 2.

Myocardial Blood Flow Grouped according to Percent Area Stenosis

<table>
<thead>
<tr>
<th>Percent Area Stenosis</th>
<th>&lt;50%, n=11</th>
<th>50% to 70%, n=9</th>
<th>70% to 90%, n=10</th>
<th>&gt;90%, n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial blood flow, mL · g⁻¹ · min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.9±0.2</td>
<td>0.8±0.2</td>
<td>0.7 ±0.2¹</td>
<td>0.7±0.2¹</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>2.3±0.6</td>
<td>2.0±0.4</td>
<td>1.2±0.4¹²</td>
<td>1.0±0.2¹²</td>
</tr>
</tbody>
</table>
Myocardial blood flows in regions supplied by minimally stenosed coronary arteries (<50% area stenosis) in patients with coronary artery disease were similar to those of the age-matched healthy volunteers, both at rest and after dipyridamole (0.9±0.2 versus 0.9±0.2 mL·g⁻¹·min⁻¹, P=NS, and 2.3±0.6 versus 2.3±0.5 mL·g⁻¹·min⁻¹, P=NS, respectively; Table 3⇓). As a result, the mean myocardial blood flow reserve was similar in both groups (2.4±0.4 versus 2.6±0.7, P=NS; Table 3⇓).

<table>
<thead>
<tr>
<th></th>
<th>Patients, n=18</th>
<th>Volunteers, n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Dip</td>
</tr>
<tr>
<td>Myocardial blood</td>
<td>0.9±0.2</td>
<td>2.3±0.6¹</td>
</tr>
<tr>
<td>flow, mL·g⁻¹·min⁻¹</td>
<td></td>
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</tr>
<tr>
<td>Myocardial flow</td>
<td>2.4±0.4</td>
<td>2.6±0.7</td>
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<tr>
<td>reserve</td>
<td></td>
<td></td>
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<tr>
<td>Minimal coronary</td>
<td>106±23</td>
<td>45±9</td>
</tr>
<tr>
<td>resistance, mmHg·mL⁻¹·g⁻¹·min⁻¹</td>
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</tbody>
</table>

Dip indicates dipyridamole.

Corrected indicates basal flow normalized to the rate-pressure product.

1 P<.05 vs <50%.

2 P<.01 vs 50% to 70%.
After dipyridamole, myocardial blood flows in regions supplied by arteries with <50% area stenosis increased significantly by an average of 2.4 (0.9±0.2 to 2.3±0.6 mL · g⁻¹ · min⁻¹, *P*<.001; Fig 1↓). Blood flows in regions supplied by vessels with 50% to 70% area stenosis showed a similar response to coronary vasodilatation, increasing by an average of 2.3 (0.9±0.2 to 2.0±0.4 mL · g⁻¹ · min⁻¹, *P*<.001; Fig 1↓). In contrast, reductions in hyperemic flows were observed in regions supplied by vessels with 70% to 90% area stenosis, which on average increased by 1.8 (0.7±0.2 to 1.2±0.4 mL · g⁻¹ · min⁻¹, *P*<.001; Fig 1↓). Blood flows in regions supplied by arteries with >90% area stenosis showed an attenuated response to dipyridamole, achieving an average ratio of hyperemic to rest blood flow of only 1.4 (0.7±0.2 to 1.0±0.3 mL · g⁻¹ · min⁻¹, *P*<.05; Fig 1↓).

Figure 1.

Plot of changes in myocardial blood flow after dipyridamole in each coronary territory grouped by cross-sectional area stenosis (ie, <50%, 50% to 70%, 70% to 90%, >90%). *P*<.001, **P*<.05 vs baseline myocardial blood flows.

Correlation Between Myocardial Blood Flow and Coronary Stenosis Severity

Myocardial Blood Flow
Hyperemic blood flows were inversely and nonlinearly related to the percent cross-sectional area stenosis on coronary arteriography ($r=.81$, $P<.00001$; Fig 2⇑). Importantly, despite the relatively large variability, these measurements distinguished between 50% to 70% and 70% to 90% luminal stenoses (2.0±0.4 versus 1.2±0.4 mL·g$^{-1}$·min$^{-1}$, $P<.01$; Table 2⇑). Moreover, hyperemic blood flows were significantly lower in regions supplied by vessels with lesions $>90\%$ than in those supplied by vessels with lesions $<50\%$ (1.0±0.3 versus 2.3±0.6 mL·g$^{-1}$·min$^{-1}$, $P<.001$; Table 1⇑).

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**Myocardial Flow Reserve**

Estimates of myocardial flow reserve were significantly correlated with the cross-sectional area stenosis ($r=.78$, $P<.00001$; Fig 3⇑) and with the percent diameter stenosis ($r=.77$, $P<.00001$; Fig 4⇓). Importantly, coronary lesions with 50% to 70% area stenosis had a significantly higher myocardial flow reserve than those with 70% to 90% area stenosis (2.4±0.4 versus 1.8±0.5, $P<.05$; Table 2⇑), suggesting a different vasodilator reserve among coronary lesions with a moderate degree of luminal obstruction (Fig 4⇓). Furthermore, measurements of myocardial flow reserve were significantly lower in myocardium supplied by arteries with $>90\%$ area stenosis than those supplied by vessels with $<50\%$ area stenosis (1.4±0.4 versus 2.4±0.4, $P<.001$; Table 2⇑).
Figure 3.

Scatterplot of relation between myocardial flow reserve and quantitative coronary angiographic measurements of percent area stenosis \( r=.78, \) root mean square error=0.61, \( P<.00001 \).
Minimal Coronary Resistance

To relate the hyperemic blood flow to one of its major determinants, the coronary driving pressure, the mean aortic blood pressure was divided by the hyperemic blood flow, and an index of the minimal coronary resistance was obtained. A significant correlation was observed between the estimated coronary resistances and the percent area stenosis on angiography ($r=.78$, $P<.00001$; Fig 5).
As expected, minimal hyperemic coronary resistances increased significantly with increasing stenosis severity. Estimates of minimal coronary resistances were equally as effective as hyperemic blood flows and flow reserve measurements for distinguishing mild to moderate degrees of stenosis severity (Table 2⇑). In addition, these estimates also discriminated between lesions with 70% to 90% area stenosis from those with >90% area stenosis (84±28 versus 125±52 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹, P<.05; Table 2⇑).

Discussion

The present study demonstrates that in patients with coronary artery disease, noninvasive estimates of myocardial blood flow and flow reserve made with N-13 ammonia and PET imaging are correlated closely with quantitative measurements of luminal stenosis severity on coronary arteriography. Importantly, our results indicate that noninvasive measurements of myocardial flow reserve by N-13 ammonia and PET imaging can differentiate coronary lesions of 50% to 70% stenosis from lesions of 70% to 90% on coronary arteriography.

Comparison With Previous Studies

Our results demonstrate that hyperemic blood flows and flow reserve measurements are inversely and nonlinearly related to stenosis severity on quantitative coronary arteriography. A progressive loss in vasodilator capacity, resulting in reductions in hyperemic blood flows and flow reserve with increasing stenosis severity, has been demonstrated in the animal model.23 24 Of note, the plots in Figs 2 through 4⇑⇑⇑ are virtually
identical to previously published data in animal models,\textsuperscript{23} confirming the universality of these relations using different species and different methodologies for assessment of blood flow and arteriographic measurements. Despite the considerable scatter in these relations, hyperemic blood flows and estimates of flow reserve discriminated between mild, moderate, and severe stenosis severity on coronary arteriography (Table 2\textsuperscript{f}). In humans, Wilson et al\textsuperscript{9} reported significant correlations between coronary flow reserve as measured by intracoronary Doppler techniques and stenosis severity on coronary angiography. In the same study, coronary flow reserve was estimated from flow velocities rather than from myocardial blood flows as determined in the present study by N-13 ammonia and PET imaging. Our results are in agreement with those of Uren et al\textsuperscript{25} using O-15 water and PET. They reported that resting blood flow remains unchanged regardless of the severity of coronary stenosis and that myocardial flow reserve declines with increasing angiographic stenosis.

The observed variability in hyperemic blood flows and flow reserve measurements for any given degree of luminal area stenosis may be related to physiological and angiographic variables and to limitations in some of the methodologies applied in this study. The effect of some of these factors on hyperemic blood flows and flow reserve was addressed by Czernin et al,\textsuperscript{19} including the effect of heart rate,\textsuperscript{26 27 28} resting blood flows (ie, the denominator of the myocardial flow reserve calculation), left ventricular end-diastolic pressure,\textsuperscript{29} contractility,\textsuperscript{30} and the magnitude of dipyridamole-induced hyperemia.\textsuperscript{31}

The magnitude of the blood flow response to dipyridamole-induced vasodilatation depends to a large extent on the coronary perfusion pressure.\textsuperscript{32} In this study, we estimated the minimal coronary resistance to normalize the hyperemic blood flows to the coronary perfusion pressure. Fig 4\textsuperscript{f} demonstrates that this normalization resulted in a significant reduction in data scatter, at least between 20\% and 80\% area stenosis, suggesting that the coronary driving pressure was an important determinant of these relations. The reason for the larger variability in the minimal coronary resistances observed for lesions with >80\% area stenosis is unknown but may relate to geometric factors not accounted for in this study such as shape, eccentricity, and entrance and exit angles, all of which are known to modulate vascular resistances. Nevertheless, these observations are consistent with the results of Wilson and colleagues\textsuperscript{3} using a minimal coronary vascular resistance index.

In this study, we observed that myocardial regions supplied by coronary arteries with minimal obstruction (<50\% area stenosis) had an average flow reserve of 2.4, which was not statistically different from the estimates of flow reserve in our age-matched control population (Table 3\textsuperscript{f}). These findings contrast with those of Uren et al.\textsuperscript{33} They suggested that in patients with coronary artery disease, normal myocardial regions indeed have an abnormal perfusion reserve. Previous studies\textsuperscript{34} showed that a diffuse atherosclerotic process affecting the endothelium-dependent vasodilator capability may result in a decreased myocardial flow reserve in apparently normal vessels on the arteriogram. However, our measurements of flow reserve in patients with coronary artery disease were similar to those of our age-matched control population. Moreover, our findings are further supported by previously published reports demonstrating that myocardial perfusion reserve declines with age.\textsuperscript{19 35} The apparent discrepancy between our findings and those of Uren et al might be explained by the fact that in Uren et al’s study, the flow values of patients with coronary artery disease were compared with those obtained in significantly younger volunteers. Thus, these apparently incongruent results may reflect methodological differences rather than contradictory findings.

Arteriographic factors also may have contributed to the variability in the correlation between myocardial flow reserve and the anatomic severity of individual stenosis. Fedele et al\textsuperscript{36} showed in experimental animals that maximal coronary blood flows in luminal stenoses with similar cross-sectional areas were significantly lower in “complex” (multilumen) as opposed to “simple” coronary stenosis. Although the prevalence of such complex lesions in humans is unknown, it may be relatively high in the setting of acute coronary syndromes where the prevalence of thrombus is high.\textsuperscript{37} Because patients with unstable angina or recent myocardial infarction were not included in this study, this is unlikely to account for the interindividual variability in hyperemic blood flows and flow reserve. An additional potential factor to consider is the presence of vasospasm, which is known to
exist in coronary lesions. Indeed, small, dynamic changes in stenosis severity during hyperemia may occasionally affect the resistance to blood flow and result in a variable flow reserve at any level of luminal stenosis. Although theoretically possible, it is unknown to what extent the presence of vasospasm might have affected our results. Important angiographic geometric considerations not evaluated in this study such as shape, stenoses in series, or eccentricity may also affect flow resistance and might account for some of the variability in myocardial flow reserve measurements for a given degree of luminal stenosis.

Study Limitations

Several potential methodological limitations might have influenced the results of this study. First, to correct for the partial volume-related underestimation of true myocardial N-13 ammonia concentrations, the left ventricular wall thickness was assumed to be uniform and 1 cm in all subjects. Of note, although two patients had a baseline blood pressure of 160/85 mm Hg, none of the subjects included in this study had a history of hypertension, aortic valve stenosis, or hypertrophic cardiomyopathy. Moreover, the data analysis was restricted to the non–infarct-related coronary arteries with normal regional wall motion. Therefore, we do not anticipate a significant difference in myocardial wall thickness among the myocardial regions analyzed in this study. Three patients developed chest pain during dipyridamole infusion; however, this was not associated with an actual decline in myocardial blood flow.

Second, important angiographic geometric considerations not evaluated in this study such as shape, stenoses in series, or eccentricity may also affect flow resistance and might account for some of the variability in myocardial flow reserve measured at a given degree of stenosis severity. Nevertheless, our results showed a significant correlation between hyperemic blood flows, flow reserve, and area stenosis, a major determinant of lesion resistance. Furthermore, the methods used in this study to quantify the angiographic coronary lesions have been shown to reflect stenosis severity accurately. Previous studies suggested that relative rather than absolute estimates of myocardial perfusion reserve might be a more sensitive descriptor of the physiological consequences of angiographic stenosis severity. Indeed, in the 8 patients with one- and two-vessel disease in this study, there was a significant correlation between the relative flow reserve (flow reserve in the diseased coronary vessel/flow reserve in the normal coronary vessel) and the degree of angiographic coronary stenosis ($r=.89$, root mean square error=0.13, $P<.00001$). However, this quantitative technique was not feasible in all our study patients because it assumes the presence of at least one myocardial region supplied by a normal vessel in each patient; in this study, 10 patients had three-vessel disease. The resistance to blood flow in the five vessels with stenoses in series may have not been accurately assessed. Because stenoses in series do not necessarily behave as additive resistances and because criteria for quantitative analysis of such lesions have not been established, only the most severe stenosis in each coronary artery was used for analysis. Nevertheless, the exclusion of the vessels with serial stenoses from analysis resulted in similar correlations between stenosis severity and measurements of myocardial blood flow and flow reserve, making it unlikely to account for the observed variability in hyperemic blood flows.

Clinical Implications

In patients with coronary artery disease, noninvasive measurements of myocardial blood flow and flow reserve by N-13 ammonia PET imaging are inversely and nonlinearly related to stenosis severity as defined by quantitative coronary arteriography. Importantly, coronary lesions of intermediate severity have a differential myocardial flow reserve that decreases with increasing stenosis severity. These differences can be detected noninvasively by N-13 ammonia PET imaging, thus allowing better definition of the functional importance of known coronary stenoses. Additionally, measurements of regional myocardial blood flow can define functional consequences of an anatomically characterized coronary stenosis. Thus, the scatter of the data about the regression line between stenosis severity and flow reserve or hyperemic flows may indeed be attributable to a possible discrepancy between structure and function.
Accurate assessment of the physiological severity of coronary stenoses may have an important role as an aid for more objective determination of medical versus mechanical treatment of coronary artery stenosis and for assessment of the results of such treatments, especially because more readily available clinical tools such as chest pain are poorly related to stenosis severity. Although relative rather than absolute measurements of flow reserve may be equally accurate in defining stenosis severity, the validity of such relative measurements hinges on the presence of normally perfused myocardium. However, such normal myocardium may not always be available for comparison in patients with three-vessel coronary artery disease, as was the case in this study. In addition, these measurements may be clinically useful in patients with silent coronary artery disease as the only basis for choosing medical or mechanical intervention to prevent sudden death and myocardial infarction and for monitoring progression or regression of coronary artery disease.

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