Prediction of the physiologic significance of coronary arterial lesions by quantitative lesion geometry in patients with limited coronary artery disease

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ABSTRACT  Studies in animals with normal coronary arteries have shown that coronary flow reserve can be predicted by angiographic measurements of arterial stenosis. Studies in man, however, suggest that even quantitative analysis of coronary angiograms cannot predict the physiologic significance of individual coronary lesions. These studies, however, were carried out in patients with either widespread, diffuse coronary artery disease or by measurement techniques that tend to underestimate maximal coronary flow reserve. To determine the relationship between coronary arterial stenosis and coronary flow reserve (CFR) in patients with discrete limited coronary atherosclerosis, we studied 50 patients with a single discrete coronary stenosis in only one or two vessels. The minimum coronary arterial cross-sectional area (mCSA), percent area stenosis (%AS), and percent diameter stenosis in the left and right anterior oblique projections were determined by the Brown/Dodge method of quantitative coronary angiography. A No. 3F coronary Doppler catheter was placed immediately proximal to the lesion. Measurements of CFR were obtained by intracoronary administration of papaverine in doses sufficient to provide maximal arteriolar vasodilation. In 25 patients, a translesional pressure gradient was obtained with an angioplasty catheter. CFR measured in patients with coronary artery disease was compared with that in 13 patients with normal coronary vessels. In normal patients, CFR averaged 5.0 ± 0.6 (peak/resting velocity ratio; mean ± SEM, range 3.7 to 8.2). In patients with limited coronary artery disease, CFR was closely correlated with %AS (r = .85), mCSA (r = .79), and the translesional pressure gradient (r = .83). Additionally, the most severe percent diameter stenosis in either the left or right anterior oblique view was also highly correlated with CFR (r = .82). Importantly, all arteries with lesions producing less than 70% area stenosis and less than 50% diameter stenosis, or with greater than 2.5 mm² mCSA had CFR of over 3.5. These results suggest that, in contrast to the poor correlation of percent area and percent diameter stenosis to CFR measured in patients with multivessel coronary artery disease, CFR measured at angiography in patients with discrete, limited coronary artery disease correlates closely with luminal stenosis determined precisely with quantitative coronary angiography. Differences in the extent of diffuse arterial narrowing may account for these discrepancies.


IN NORMAL CORONARY ARTERIES, myocardial blood flow is primarily regulated by the resistance of the arteriolar vessels; the epicardial coronary arteries provide little resistance to coronary blood flow under physiologic circumstances.1-3 As a stenosis develops in an epicardial coronary vessel, a transtenotic pressure gradient develops leading to arteriolar vasodilation and maintenance of normal resting blood flow to the myocardium.1-3 Although studies in animals have shown that resting coronary blood flow can be maintained at normal levels until more than 90% of the arterial cross-sectional area is obstructed, the inability of the distal arteriolar bed to vasodilate further limits the amount that coronary blood flow can increase in response to increasing myocardial metabolic demands. Coronary stenoses that limit myocardial blood flow during maximal arteriolar vasodilation can be termed physiologically significant.
Studies in normal animals with coronary stenoses produced by external vascular constriction have shown that the stenoses become physiologically significant when 60% to 75% of the luminal cross-sectional area is obstructed.1-3 At that level of obstruction, the ratio between maximal hyperemic blood flow and resting blood flow (i.e., coronary flow reserve) falls and continues to decline in a predictable, exponential fashion as the stenosis becomes more severe. Although many factors other than the maximal extent of arterial obstruction also affect the resistance to blood flow produced by an individual coronary lesion (e.g., length, eccentricity, exit and entrance angles), the flow reserve capacity of normal animal vessels containing an artificial stenosis can still be predicted accurately by hydraulic equations.4-8

Studies in man, however, suggest that the relationship between coronary luminal stenosis and flow reserve might be significantly different when coronary obstruction is produced by atherosclerosis rather than experimental constriction of a normal vessel. In a previous study, we examined the relationship between coronary luminal obstruction and flow reserve in patients with two- and three-vessel coronary artery disease undergoing open heart surgery.9,10 In these patients both visual and precise quantitative angiographic measurement of luminal diameter or area stenosis correlated poorly with the direct measurements of the physiologic impact of the lesion, coronary flow reserve. These studies, performed in patients with widespread coronary artery disease, suggest that measurements of the degree of luminal obstruction that compare the dimensions of focal obstructive lesions to the dimensions of "angiographically normal" portions of the vessel (e.g., percent stenosis) do not predict the physiologic significance of individual obstructive coronary lesions. Since histologic, echocardiographic, and angiographic studies have shown that most patients with widespread coronary artery disease have diffuse thickening of the arterial wall in angiographically "normal" portions of the vessel, measurements of percent stenosis may not adequately reflect the extent of luminal obstruction in this subgroup of patients with advanced coronary atherosclerosis.11-13

Until recently, measurement of the flow reserve in coronary vessels of patients with less severe coronary artery disease has been hampered by methodologic limitations in measuring coronary blood flow in conscious humans and by the lack of a technique for making multiple measurements of maximal coronary flow reserve during a single catheterization. The recent development and validation of a small subselective coronary Doppler catheter and characterization of the dose-response kinetics of intracoronary papaverine have made possible repeat measurements of coronary flow reserve in individual vessels of patients undergoing cardiac catheterization.14,15 The purpose of this study was to determine the relationship between coronary flow reserve and luminal obstruction produced by individual coronary lesions in patients with discrete coronary artery stenoses and limited coronary disease.

Methods

Patient selection. Fifty patients who underwent diagnostic coronary angiography and were found to have only one discrete lesion in the vessel under study and no more than two coronary vessels with obstructive lesions (visual inspection, diameter stenosis > 50%) were selected for study. Before measurement of coronary flow reserve, each patient underwent M mode and cross-sectional echocardiography to exclude ventricular hypertrophy and valvular heart disease. Left ventricular function was shown to be normal by contrast or equilibrium radionuclide ventriculography (left ventricular ejection fraction > 50% with normal regional wall motion). Twenty-three patients were studied before coronary angioplasty. In these patients, a prior angiogram was available and was used to establish eligibility into the study.

Patients with abnormalities that might affect the vasodilator capacity of the arteriolar vasculature were excluded from the study. These included (1) Patients with historical or electrocardiographic evidence of myocardial infarction. Myocardial infarction was defined by either (a) a clinical history of infarction with an elevation of total serum creatine kinase, increased creatine kinase MB fraction, and classic evolutionary electrocardiographic changes (with or without development of Q waves), or (b) an electrocardiogram showing pathologic Q waves of greater than 0.04 sec in duration and a focal wall motion abnormality demonstrated by contrast or equilibrium radionuclide ventriculography. (2) Left ventricular hypertrophy (septal or posterior wall thickness > 1.1 cm by echocardiography or left ventricular mass > 130 g/m2 by cine computed tomography [Imatron]). (3) Left ventricular dysfunction (left ventricular ejection fraction < 50% or focal wall motion abnormalities). (4) Presence of valvular heart disease. (5) Angiographic suggestion of intraluminal thrombus or filling defect. (6) Presence of left main coronary stenosis or severe proximal lesions precluding safe coronary cannulation. (7) Presence of angiographically apparent collateral circulation from the vessel under study to an adjacent perfusion field. (8) Lesions in the distal vasculature not accessible to Doppler catheter cannulation (usually the right coronary beyond posterior descending origin and the left anterior descending beyond the second diagonal branch). Additionally, vessels in which a branch vessel with greater than 12% of the cross-sectional area of the parent vessel arose proximal to the coronary lesion were not studied. In some patients, small vessels with a cross-sectional area less than 12% that of the parent vessel arose between the coronary Doppler catheter transducer and the lesion.

Measurements obtained from patients with coronary arterial stenoses were compared to flow reserve measurements obtained from 13 patients with normal coronary arteries meeting the criteria described above. Data from these patients have been previously reported.15

All studies were approved by the Institutional Review Board of the University of Iowa, and informed consent was obtained from each patient studied.
Catheterization protocol. Patients were brought to the cardiac catheterization laboratory in a fasting state. A variety of premedications were given, but no patient received atropine. Nitroglycerin (sublingual, intracoronary, or intravenous) was administered before diagnostic angiography. Angiograms of each lesion were obtained in orthogonal projections (i.e., 60 degree left anterior oblique and 30 degree right anterior oblique). A No. 3F 20 MHz coronary Doppler catheter (Cardiovascular Bioengineering, University of Iowa) was advanced through a No. 5F coronary guiding catheter (USCI Bard, Inc.) into the coronary vessel and positioned immediately proximal to the coronary lesion (16 left anterior descending, 14 circumflex, and 20 right coronary lesions). The catheter position and the Doppler range gate were adjusted to obtain an adequate tracing of phasic coronary blood flow velocity within the vessel. Care was taken to minimize the distance between the Doppler crystal and the coronary lesion.

Mean and phasic signals of coronary blood flow velocity (kHz shift), arterial pressure obtained via the guiding catheter, heart rate, and electrocardiogram were recorded continuously on a multichannel Gould recorder. The arterial pressure waveform obtained from the guiding catheter was damped by the presence of the coronary Doppler catheter; consequently, only mean arterial blood pressure could be monitored accurately.

After measurements of resting coronary blood flow velocity, 6 to 12 mg of papaverine hydrochloride (2 mg/ml 0.9% saline) were injected through the guiding catheter into the coronary ostium and the resultant increase in coronary blood flow velocity was recorded. To confirm that any dose of papaverine produced maximal hyperemia, an additional larger dose (2 to 4 mg larger than the prior dose) was administered and the resultant hyperemic response was recorded. Flow velocity was allowed to return to baseline levels between doses of papaverine. We have previously shown that intracoronary papaverine administered in this manner produces maximal coronary hyperemia equal in magnitude to that produced by intravenous dipyridamole.15

Translesional pressure gradient. In 25 coronary vessels, the translesional pressure gradient was measured with a coronary angioplasty catheter (USCI Bard, Inc.; I.4 mm outer diameter, 1.5 mm² cross-sectional area). The pressure gradient was determined as the difference between the mean arterial pressure measured via the guiding catheter and the mean pressure distal to the lesion measured with the angioplasty catheter (computerized waveform analysis, SIECOR, Siemens). To partially correct for the influence of mean aortic pressure, we also determined an index of the pressure gradient, the quotient of the translesional pressure gradient, and the mean arterial pressure.

Coronary flow reserve. Coronary flow reserve was calculated as the quotient of the peak blood flow velocity (maximal kHz shift after administration of papaverine) and resting blood flow velocity. To characterize the change in coronary vascular resistance at maximal hyperemia, a minimal coronary vascular resistance index was calculated as the quotient of [mean aortic blood pressure with peak flow velocity (mmHg)/peak blood flow velocity (kHz shift)] and [mean aortic blood pressure at resting flow velocity/resting blood flow velocity].

Angiographic analysis. Angiograms of each lesion were analyzed by the Brown/Dodge method of quantitative coronary angiography. This technique has been described in detail elsewhere.16 Briefly, each angiogram was projected onto a rectilinear grid at 5 x magnification. The outline of each coronary lesion was traced in two orthogonal projections during three portions of the cardiac cycle. The traced lesion was outlined, digitized, and computer-corrected for radiographic pin cushion and magnification distortion. The minimal cross-sectional area, maximal percent area stenosis, percent diameter stenosis in each projection, and length of each lesion were then calculated by averaging the values obtained from each portion of the cardiac cycle.

Statistical analysis. Differences between group means were analyzed by analysis of variance (Newman-Keuls method). Linear correlation coefficients were obtained by the least-squares method. Curvilinear correlation coefficients were obtained by the quadratic regression model (SAS, Cary, NC). A p value < .05 was used to define statistical significance. Except where noted, all values are expressed as mean ± SEM.

Results
Coronary flow reserve in normal vessels. Coronary flow reserve in 13 normal coronary arteries ranged from 3.7 to 8.3 (peak/resting velocity ratio) and averaged 5.0 ± 0.6. The minimal coronary vascular resistance index after intracoronary administration of papaverine was 0.21 ± 0.02 (range 0.11 to 0.26).

Relationship of coronary lesion geometry to coronary flow reserve. Coronary flow reserve was below the lower limit of normal (< 3.5) in 30 stenotic coronary vessels but normal (> 3.5) in the remaining 20 stenotic arteries. Importantly, two major determinants of resting coronary blood flow and maximal hyperemic coronary blood flow (heart rate and arterial pressure) were not significantly different in patients with normal and abnormal coronary flow reserve (table 1).

Percent area stenosis. Quantitative measurements of luminal area stenosis ranged from 51% to 99% and were closely correlated with measurements of coronary flow reserve (n = 50, r = .85; table 2, figures 1 and 2). Moreover, the flow reserve capacity of coronary arteries with less than 70% area stenosis was uniformly greater than 3.5, suggesting that lesions producing less than 70% area stenosis did not result in a physiologic impairment in coronary blood flow without superimposed dynamic changes in stenosis geometry.

Measurements of percent area stenosis were also highly correlated with the minimal coronary vascular resistance index of the vessel under study (n = 50, r = .79; figure 3). The minimal coronary vascular resis-

<table>
<thead>
<tr>
<th>MAP (mm Hg)</th>
<th>HR (bpm)</th>
<th>Proximal cross-sectional area (mm²)</th>
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<tr>
<td>CFR &gt; 3.5</td>
<td>86 ± 3</td>
<td>64 ± 2</td>
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<td>(n = 20)</td>
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<tr>
<td>CFR &lt; 3.5</td>
<td>87 ± 2</td>
<td>66 ± 2</td>
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<td>(n = 30)</td>
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CFR = coronary flow reserve.
TABLE 2
Relationship of arterial stenosis and translesional pressure gradient to coronary flow reserve

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Correlation coefficient</th>
<th>Regression equation ( ^{a} )</th>
<th>p value</th>
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<tbody>
<tr>
<td>Percent area stenosis (%AS)</td>
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<td></td>
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<tr>
<td>All vessels</td>
<td>50</td>
<td>.85</td>
<td>CFR = 5.1 + 0.04 %AS - 0.008 %AS(^2)</td>
<td>&lt;.0001</td>
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<td>LAD only</td>
<td>16</td>
<td>.86</td>
<td>CFR = 4.24 + 0.087 %AS - 0.0013 %AS(^2)</td>
<td>&lt;.0001</td>
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<td>Most severe diameter stenosis (%DS)</td>
<td>50</td>
<td>.82</td>
<td>CFR = 6.04 - 0.018 %DS - 0.00046 %DS(^2)</td>
<td>&lt;.0001</td>
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<td>Minimum cross-sectional area (mCSA)</td>
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<tr>
<td>All vessels</td>
<td>50</td>
<td>.79</td>
<td>CFR = 0.85 + 2.1 mCSA - 0.27 mCSA(^2)</td>
<td>&lt;.0001</td>
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<tr>
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<td>.64</td>
<td>CFR = 0.45 + 2.6 mCSA - 0.44 mCSA(^2)</td>
<td>.03</td>
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<tr>
<td>Cross-sectional area of proximal vessel (CSA)</td>
<td></td>
<td>.35</td>
<td></td>
<td>.50</td>
</tr>
<tr>
<td>Pressure gradient (PG)</td>
<td>25</td>
<td>.83</td>
<td>CFR = 5.3 - 0.13 PG + 0.0012 PG(^2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pressure gradient/mean arterial pressure (PG/MAP)</td>
<td>25</td>
<td>.91</td>
<td>CFR = 5.2 - 10.9 PG/MAP + 8.8 (PG/MAP)(^2)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

CFR = coronary flow reserve; LAD = left anterior descending coronary artery
\(^{a}\)Quadratic regression formula.

tance index measured in vessels with less than 70% area stenosis was always less than 0.27 \( \times \) resting resistance. When lesions in the proximal left anterior descending coronary artery were considered separately (n = 16), percent area stenosis was similarly related to coronary flow reserve (r = .86).

*Most severe diameter stenosis.* Quantitative measurements of the greatest diameter stenosis in the left or right projection ranged from 24% to 99%. This single measurement of luminal stenosis was closely correlated with coronary flow reserve (n = 50, r = .82; figures 4 and 5) and the minimal coronary vascular resistance index (r = .80, p < .0001). All vessels with lesions resulting in more than 60% diameter stenosis in at least one angiographic projection (n = 26) had depressed flow reserve (< 3.5) and a minimal coronary vascular resistance index of more than 0.35 \( \times \) resting coronary vascular resistance.

**FIGURE 1.** Relationship between the maximal change in coronary blood flow velocity after intracoronary administration of papaverine (\( \Delta \text{CBFV} \)) to quantitative angiographic measurements of percent area stenosis. The open bar represents the range of coronary flow reserve measured in 13 patients with normal coronary vessels. The shaded area along the regression line represents 1 SD above and below the mean.

**FIGURE 2.** The percent area stenosis of lesions associated with normal (> 3.5) and abnormal (< 3.5) coronary flow reserve. Arteries with lesions causing less than 70% area stenosis uniformly had normal coronary flow reserve.
Minimum arterial cross-sectional area. Minimum luminal cross-sectional area ranged from 0.1 to 5.0 mm². Measurements of minimum cross-sectional area were also highly correlated with coronary flow reserve \((n = 50, r = .79); \) figures 6 and 7). Lesions with a cross-sectional area of greater than 2.5 mm² uniformly had coronary flow reserve in excess of 3.5, suggesting that they did not produce physiologically significant obstruction to coronary blood flow. Thirty-one of 41 arteries with lesions of less than 2.5 mm² minimum cross-sectional area had diminished flow reserve. Hence, not all lesions with a minimum area of under 2.5 mm² had diminished flow reserve.

The minimum luminal cross-sectional area was also correlated with the minimal coronary vascular resistance index \((n = 50, r = .72)\). All arteries with lesions with a minimum cross-sectional area more than 2.5 mm² had a minimal coronary vascular resistance index of less than \(0.25 \times \) control resistance. The correlation between minimum cross-sectional area and coronary flow reserve of lesions in the proximal left anterior descending coronary artery was not significantly different from the correlation achieved when all lesions were considered \((n = 16, r = .64)\).

Cross-sectional area of the “normal” proximal coronary vessel. The mean cross-sectional area of the adjacent normal portion of the vessel immediately proximal to the arterial stenosis was \(7.5 \pm 0.4 \text{ mm}²\) in vessels with abnormal coronary flow reserve \((< 3.5)\) and \(7.9 \pm 0.8\) in vessels with normal flow reserve \((p = NS; \text{ tables 1 and 2})\). The cross-sectional area of the normal portion of the vessel was significantly larger in this series of patients with limited coronary artery disease \((7.8 \pm 0.4)\) than in a previous study from our laboratory performed in patients with widespread coronary artery disease \((6.7 \pm 0.7 \text{ mm}²; p < .05)\), suggesting that the current series of patients had significantly less diffuse coronary narrowing. Additionally, in contrast to the

FIGURE 6. Relationship between minimum arterial cross-sectional area and the change in coronary blood flow velocity after intracoronary administration of papaverine \((\Delta \text{CBFV})\). The open bar at right represents the range of normal coronary flow reserve measured in 13 patients with normal coronary arteries. The shaded area represents 1 SD above and below the mean.
FIGURE 7. Minimum cross-sectional area of coronary lesions in arteries with normal and abnormal coronary flow reserve. Lesions with > 2.5 mm² cross-sectional area uniformly had coronary flow reserve in excess of 3.5.

previous series, there was no relationship between the cross-sectional area of the adjacent “normal” vessel and coronary flow reserve (r = .35, p = .50).

Lesion length. Lesion length ranged from 4 to 26 mm and was not significantly correlated with measurements of coronary flow reserve or minimal coronary vascular resistance (r = .24). We also examined the relationship between lesion length, percent arterial stenosis, and predicted flow reserve (based on the quadratic model shown in figure 1) to determine whether lesions with lower than predicted flow reserve might have a greater length than lesions with higher than predicted flow reserve.

The length of lesions in arteries with coronary flow reserve of more than 0.5 SD above the predicted value was 14 ± 2 mm (range 5.2 to 26) and was significantly different from lesions in arteries with a flow reserve capacity 0.5 SD below that predicted (10 ± 2 mm, range 8.8 to 22; p < .05). Hence, lesions in vessels with a lower than predicted flow reserve capacity tended to be shorter than lesions in vessels with a flow reserve capacity higher than predicted.

Relationship of translesional pressure gradient to coronary flow reserve. A translesional pressure gradient was obtained in 25 patients and ranged from 0 to 79 mm Hg. The translesional pressure gradient was closely correlated with measurements of coronary flow reserve (n = 25, r = .83). All lesions with a translesional pressure gradient of more than 20 mm Hg had diminished coronary flow reserve (n = 20), whereas lesions with pressure gradients of less than 15 mm Hg had normal flow reserve (n = 5).

When the translesional pressure gradient (PG) was corrected for mean arterial pressure (by obtaining the quotient of the PG and mean arterial pressure [MAP]), there remained a significant relationship to flow reserve (n = 25, r = .91). Lesions with PG/MAP less than 0.15 (n = 5) had a flow reserve of more than 3.7:1, whereas lesions with PG/MAP more than 0.20 had depressed flow reserve (< 3.5:1).

Discussion

In this study of patients with limited coronary atherosclerosis, we have shown that precise angiographic measurements of luminal stenosis correlated closely with a physiologic measurement of coronary obstruction, coronary flow reserve. Importantly, lesions in major coronary vessels with less than 70% area stenosis or minimum arterial cross-sectional area of over 2.5 mm² did not functionally impair coronary blood flow or result in a significant resting translesional pressure gradient (i.e., > 15 mm Hg).

Potential methodologic limitations. There are several potential problems inherent in the measurement of coronary flow reserve with the coronary Doppler catheter and intracoronary papaverine. First, the presence of the catheter within the vessel under study might itself result in physiologically significant obstruction to maximal coronary blood flow. Prior studies in animals have demonstrated that the catheter (cross-sectional area 0.8 mm²) does not result in a reduction in coronary flow reserve in the proximal or mid left anterior descending artery of the calf.14 Other studies have shown that coronary flow reserve in normal animal vessels remained unchanged until 50% to 70% of the arterial area is obstructed.12 Since the average luminal area of the coronary vessel immediately proximal to the coronary stenosis in this study was 7.7 ± 0.5 mm² (range 3.9 to 16.0), it is unlikely that the catheter itself produced physiologically significant obstruction. Measurement of the translesional pressure gradient, however, might have been altered by obstruction produced by the angioplasty catheter (cross-sectional area 1.5 mm²). Translesional pressure gradients in vessels of less than 3.0 mm² minimal cross-sectional area, consequently, may have been exaggerated. Nonetheless, our finding of a curvilinear relationship between coronary flow reserve and the translesional pressure gradient is similar to that found by Wijns et al.13 using a 0.65 mm² catheter. They found that lesions causing less than 80% area stenosis have a translesional pressure gradient of less than 30% of the mean arterial pressure. The same was true of the patients in our study. Additionally, however, our regression equation predicts that lesions with a pressure gradient of 30% that of the mean aortic pressure will have a moderately reduced coronary flow reserve (2.7).

A second potential problem is that intracoronary
administration of papaverine could have altered luminal dimensions by causing transient vasodilation of the coronary lesion. We have previously shown, however, that intracoronary administration of papaverine does not alter the dimensions of coronary arteries previously vasodilated with nitroglycerin.\textsuperscript{15} Conversely, we have observed in two patients with severe stenoses that intracoronary administration of papaverine results in a transient decrease in coronary blood flow velocity, suggesting that transient collapse of the lesion (as reported by Gould\textsuperscript{18} and others\textsuperscript{19}) may occur after administration of a potent vasodilator in patients with severe coronary stenosis (figure 8).

Comparison with previous studies. These results confirm prior studies performed in animals, which showed that coronary flow reserve is not significantly impaired until more than 50\% to 70\% of the vascular cross-sectional area is obstructed.\textsuperscript{1,2,4} These data also demonstrate that the extent of luminal stenosis is the dominant factor accounting for obstruction to blood flow in a stenosed vessel. Hydraulic equations presented by Young and Gould and their colleagues\textsuperscript{1,4-8} have shown that the energy loss across a stenosis results from a combination of frictional losses, flow separation losses, and inertial losses (resulting from pulsatile flow). Frictional losses, primarily related to stenosis geometry, rise linearly with blood flow across the stenosis. Separation losses are a function of the percent area stenosis and other geometric features and rise exponentially with flow velocity. In this study, we determined only lesion length and the fraction of the vessel area that was obstructed. Although these studies confirm that flow reserve can be predicted by the major determinant of lesion resistance (area stenosis), other factors not measured in this study (e.g., entrance and exit angles, eccentricity) may also affect resistance and might account for some of the variability in flow reserve measured at a given degree of stenosis. We found, however, that one determinant of resistance, lesion length, is from a practical standpoint a minor determinant of resistance at hyperemic flow rates. In fact, our data suggest that shorter lesions may impair flow reserve to a greater extent than longer lesions. Differences in exit angles or other geometric factors between shorter and longer atherosclerotic lesions might account for these findings. Longer lesions, however, might be found more often in patients with widespread diffuse coronary artery disease, leading to the clinical impression that long lesions result in more severe hemodynamic compromise.

Our findings contrast with those of two previous studies from our laboratory demonstrating a poor relationship between both visual and quantitative estimates of coronary luminal stenosis and intraoperative measurements of coronary flow reserve obtained in patients with more widespread coronary artery disease.\textsuperscript{9,10} Several factors might account for the disparity in the results. First and most importantly, the patients in this study had significantly less advanced coronary atherosclerosis compared with the population we reported previously. In our previous intraoperative study, 74\% and 26\% of patients had three- and two-vessel coronary artery disease, respectively.\textsuperscript{9} In the current study, 84\% of patients had single-vessel disease, and 16\% had disease involving two coronary arteries. None had three-vessel involvement. Importantly, the dimensions of the normal portions of the coronary vessels studied were significantly greater in the present study than in the previous one (figure 9). This suggests that the extent of diffuse coronary narrowing was significantly greater in the patients studied in the operating room than in the current group of patients studied in the catheterization laboratory.\textsuperscript{10} Importantly, the relationship between minimal arterial cross-sectional area (the numerator of percent stenosis) and flow reserve was strikingly similar in both studies.

\textbf{FIGURE 8.} Recording obtained from a right coronary artery containing a severe coronary stenosis (93\% area stenosis, 0.4 mm\textsuperscript{2} minimum cross-sectional area, 9 mm in length). The top panel displays phasic blood flow velocity, the next panel mean blood flow velocity, and the bottom two panels the arterial pressure and the electrocardiogram. After intracoronary injection of papaverine, mean blood flow velocity fell to 0.47 \times resting velocity and rose to control velocity 50 sec later. The duration of the fall in flow velocity and the lack of attendant changes in aortic pressure suggest that papaverine induced an increase in stenosis resistance.
This suggests that the essential difference between the studies was in the size of the proximal vessel (the denominator in percent stenosis). Additionally, in patients studied intraoperatively, the cross-sectional area of the normal portion of the proximal left anterior descending artery was significantly correlated with measurements of flow reserve ($r = .68$, $p < .0001$), whereas in the current study no such correlation existed ($r = .35$, $p = .50$).

Additional factors such as the effects of anesthesia on resting coronary blood flow and vascular smooth muscle tone might also have altered the relationship between lesion geometry and flow reserve in patients studied intraoperatively. The range of flow reserve measured in normal coronary vessels in the operating room, however, did not vary from the normal population studied in the catheterization laboratory, suggesting that anesthesia and thoracotomy did not significantly alter arteriolar vasomotor tone or vasodilator capacity.

This study also conflicts with studies from other laboratories suggesting that coronary flow reserve measured in the catheterization laboratory cannot be predicted by angiographic measurements of luminal stenosis. Two factors probably account for this disparity. The first is methodologic. In prior studies, measurements of coronary flow reserve were obtained with digital subtraction angiographic techniques or with a coronary sinus thermodilution catheter. Both techniques tend to underestimate maximal hyperemic flow and consequently may not accurately discriminate moderate reductions in coronary flow reserve from normal. Additionally, the technique used to produce maximal vasodilation in one study was submaximal (i.e., intracoronary injection of iodinated contrast material) and the coronary sinus catheter cannot accurately relate blood flow to an individual coronary vessel. In the current study, we used a dose of intracoronary papaverine that we have previously shown to cause maximal coronary vasodilation (equivalent to intravenous dipyridamole).

Another methodologic limitation of previous studies is that the degree of luminal stenosis was not measured with quantitative angiographic techniques. Many prior investigators have demonstrated that visual interpretation of the coronary angiogram is fraught with interobserver variability. Additionally, measurements of minimal cross-sectional area are not available with nonquantitative techniques.

In prior studies, patients may not have been rigorously screened for evidence of ventricular hypertrophy, prolonged hypertension, or prior myocardial infarction. If diminished coronary flow reserve is to be attributed to epicardial coronary arterial stenosis, the arteriolar bed must be capable of normal vasodilation. In our experience, recent myocardial infarction within the perfusion field of the coronary vessel under study frequently results in a marked decrease in coronary flow reserve even when contraction of the affected myocardial wall is relatively preserved. Additionally, since many techniques measure flow reserve as a peak/resting velocity (or flow) ratio, factors altering resting blood flow (e.g., anemia, hypoxemia, excessive heart rate or arterial pressure) should be excluded. In the current study, we have made every attempt to exclude patients who might have had reduced arteriolar vasodilator capacity or resting arteriolar vasodilation.

**Physiologic considerations.** Three important physiologic considerations emerge from careful analysis of the results of this study. First, coronary lesions with more than 90% luminal area stenosis were associated with a wide range of coronary flow reserves (1.0 to 2.8 peak/resting velocity ratio). Two factors may account for the relative preservation of flow reserve in severely stenosed vessels. Resting blood flow to the subendocardium could have been reduced by severe luminal obstruction resulting in a fall in resting coronary blood flow and a subsequent increase in the peak hyperemic/resting velocity ratio. Several studies have shown that coronary lesions with more than 90% area stenosis have reduced blood flow at rest. Additionally, studies in animals suggest that, despite a reduction in subendocardial resting blood flow distal to a severe stenosis, the subepicardial muscle may maintain normal resting blood flow without complete exhaustion of vasodilator reserve. Both of these factors may have
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resulted in the diversity of flow reserve ratios obtained in patients with a severe coronary stenosis.

Second, it cannot be assumed that all lesions producing less than 70% area stenosis or with greater than 2.5 mm² cross-sectional area never result in myocardial ischemia. These studies were performed after coronary vasodilation with nitroglycerin. Coronary lesions are known to be dynamic. Lesions that do not result in functional obstruction when vasodilated might restrict increases in coronary blood flow if smooth muscle tone is augmented. However, in such patients, treatment with vasodilating agents might be more appropriate than anatomic correction of the coronary stenosis (e.g., coronary angioplasty or coronary bypass surgery). Additionally, the normal dimensions of coronary arteries may be influenced by a variety of factors (e.g., sex, body size, coronary dominance, left ventricular mass), 29 and total reliance of absolute measurements of coronary dimensions should be tempered by these factors.

Finally, although this study has shown that maximal hyperemic coronary blood flow is usually blunted by coronary stenoses producing more than 70% luminal area obstruction, the reduction of flow reserve is often modest (i.e., flow reserve > 3.0:1) in lesions with 70% to 80% area obstruction. Since coronary blood flow in animals rises less than threefold with all but heavy exertion, the clinical importance of lesions resulting in a small reduction in flow reserve may be minimal without superimposed vasospasm. 30, 31

In summary, we have shown that precisely measured angiographic variables of coronary arterial obstruction (percent area stenosis, minimum cross-sectional area) predict the coronary flow reserve of individual coronary vessels in patients with limited discrete atherosclerosis. The application of these techniques and data should facilitate assessment of the physiologic significance of coronary arterial lesions in the catheterization laboratory.

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