Effect of coronary stenotic lesions on regional myocardial blood flow at rest

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ABSTRACT To determine the effect of atherosclerotic coronary lesions on myocardial blood flow in patients at rest, regional myocardial blood flow was measured distal to stenotic lesions in 29 patients with isolated proximal lesions of the left anterior descending artery. Severity of coronary stenosis was measured by computer-assisted cinevideodensitometric analysis of digitized coronary arteriograms. Regional myocardial blood flow was measured from the clearance rate of intracoronary $^{131}$Xe injected into the left main coronary artery and recorded with a multicrystal scintillation camera. In 21 patients with stenotic lesions ranging from 19% to 84% area reduction, distal regional myocardial blood flow was normal. In all eight patients with reduced regional myocardial blood flow distal to left anterior descending lesions, the minimum area of each stenotic lesion was less than 0.80 mm$^2$ (mean 0.34 ± 0.2 mm$^2$), minimum calculated diameter was less than 1 mm (mean 0.59 ± 0.3 mm), and percent stenosis, based on the reduction in cross-sectional area, was greater than 85% (mean 94 ± 4%). For all patients, distal flow, expressed as a fraction of normal flow, correlated with the lesion cross-sectional area ($r = .84$), minimum luminal diameter ($r = .84$), and percent area stenosis ($r = -.70$). Thus, resting myocardial blood flow distal to stenotic lesions of the proximal coronary arteries remains normal until the degree of narrowing is severe. The dimensions observed for critical coronary stenotic lesions correlate well with theoretical predictions based on fluid mechanics and with experimental preparations in laboratory animals.


CRITICAL STENOSIS is generally defined as that degree of stenosis for which a small further reduction in luminal area will cause significantly reduced blood flow distally.1 Numerous experimental studies in canine preparations of the relationship between regional myocardial blood flow and severity of coronary arterial stenosis have shown that, as an artery is gradually constricted, distal flow remains normal until a critical degree of stenosis is reached.2–6 Typically, the luminal area must be severely reduced before distal flow falls. Flow is maintained at normal levels, until the stenosis is severe, by autoregulatory vasodilation of the distal vascular bed.6,7 Peripheral vasodilation lowers arterial pressure distal to the lesion and thus widens the pressure drop across the stenosis. This increased pressure gradient enhances the driving pressure, which maintains flow at normal or near-normal levels.

Studies in canine preparations have consistently reported values of approximately 80% to 95% reduction in luminal area as the critical stenosis causing reduced blood flow under resting conditions.2–5 Of the many geometric and rheologic variables that affect blood flow through a stenosis, the most important variable is the ratio of the minimum cross-sectional area of the stenosis to the unobstructed luminal area.1 This ratio is commonly expressed as percent stenosis and calculated as $(1 - A_{s}/A_{n}) \times 100$.

The degree of coronary stenosis that reduces regional myocardial blood flow in patients at rest has never been determined, largely because techniques for measuring regional myocardial blood flow and magnitude of coronary stenosis have been imprecise. Recently we have developed a method for quantifying coronary stenosis based on computer-assisted videodensitometric analysis of the radiographic density of intra-arterial contrast medium.8 This method for calculating percent stenosis is based on relative luminal areas and has been validated in both phantom and postmortem heart studies.

We used this technique to measure the dimensions of coronary stenotic lesions in 29 patients with isolated
proximal lesions of the left anterior descending (LAD) artery. Regional myocardial blood flow distal to each stenosis was measured scintigraphically from the clearance rate of intracoronary \(^{133}\)Xe and was related to the degree of stenosis to define critical coronary stenosis in patients under resting conditions. The objective of this study was to determine the critical degree of stenosis that causes distal coronary blood flow to fall in patients with coronary artery disease.

**Methods**

**Patient selection.** Selected for study were patients undergoing coronary arteriography for clinical indications who had isolated lesions of the proximal LAD artery. Patients with total occlusion of the LAD artery, heavily calcified lesions, or extensive collateral arteries were excluded. Also excluded were patients with valvular heart disease, congenital heart disease, or cardiomyopathy. Patients with prior myocardial infarction were excluded, because Engel et al.\(^8\) have shown that segmental left ventricular contraction abnormalities after myocardial infarction are often associated with reduced regional myocardial blood flow. Left ventriculograms were reviewed in all patients, and patients with segmental akinesis documenting prior infarction were excluded. Also, one patient with a technically poor coronary arteriogram was excluded from analysis. Informed written consent was obtained from each patient under a protocol approved by the Institutional Review Board and Joint Radiosotope Committee of the Columbia-Presbyterian Medical Center.

**Coronary arteriography.** Coronary cineangiograms were recorded on 35 mm cine film (Kodak CFR) at 32 frames/sec.

A coronary cine frame was selected for analysis that met the following criteria. First, the frame was selected from the middle phase of the contrast injection when the stenotic lesion was well opacified. Second, the selected frame had to display the long axis of the arterial segment without foreshortening. Therefore, a radiographic projection was chosen in which the x-ray beam was approximately perpendicular to the long axis of the artery. Third, the frame had to display the stenotic segment and an adjacent normal segment clearly, with both segments located away from extreme margins of the field.

The 35 mm film was projected with a modified Vanguard projector (model M-35 C, Vanguard Corp., Melville, NY) and the frame selected for analysis was scanned with a Panasonic model WV-1500A videocamera. The projector was mounted on a moveable stage, which could be adjusted both vertically and horizontally for selecting the quadrant of the cine frame showing the stenosis. Light from the illuminated cine frame was projected into the vidicon tube in the camera with approximately twofold magnification. The vidicon camera was operated with the automatic light compensation circuit off so that the target voltage of the pick-up tube was fixed rather than automatically adjusted.

**Cinevideodensitometry**

**Videodensitometric equipment.** The RS-170 signal produced by the vidicon camera was digitized and processed by a video digitizer interface and analyzed with a software system (A3: Medical Data Systems, Ann Arbor, MI) on a Nova 4 computer consisting of a central processor with a 256 kbyte mainframe memory, 10 and 300 mbyte disk drives, and a separate pipeline processing rack with 2 mbyte image memory.

**Measurement of relative stenosis.** The selected frame was then digitized to a 512 \(\times\) 512 pixel matrix with 254 gray scale levels and stored in the video analyzer memory. The digitized image was then analyzed quantitatively by positioning regions of interest (ROIs) on the digitized image displayed on the monitor screen with a manually operated controller, as described previously.\(^8\) Briefly, rectangular ROIs, two pixels in width, were positioned across the stenotic and normal segments of the artery, as shown in figure 1, A. Each ROI was long enough to extend beyond both margins of the arterial lumen. Both ROIs were positioned perpendicular to the long axis of the artery and bilinear interpolation was used to compute density values for ROIs positioned at oblique angles over the image data, which were in the form of a square array. Two smaller ROIs (each 2 \(\times\) 2 pixels) were positioned adjacent to the ends of each of the other ROIs for determining average background videodensity. The background-corrected videodensitometric value \((V_a)\) across the arterial segment was then calculated as: \(V_a = V - nb\), where \(V\) is the total videodensitometric value in the ROI across the arterial segment, \(n\) is the number of pixels in the ROI, and \(b\) is the average background density per pixel. Percentage relative stenosis was then calculated as: \(\%\) stenosis = \(100 \times (V_a - V_s)/V_n\), where \(V_n\) and \(V_s\) are background-corrected videodensitometric values for the normal and stenotic arterial segments, respectively.

Since optical density of the contrast-filled arterial segment recorded on cine film reflects the volume of contrast medium within the arterial lumen, videodensitometric analysis measures the relative cross-sectional area of the stenotic arterial lumen. The accuracy and reproducibility of this method for measuring relative coronary stenosis based on reduction in cross-sectional area was validated previously in radiographic phantom experiments and in experiments with postmortem human coronary arteries measured histologically.\(^8\)

**Measurement of coronary luminal dimensions.** After measurement of percent relative reduction in cross-sectional area by cinevideodensitometry as described above, absolute dimensions were calculated with use of the diameter of the catheter as a spatial reference to correct for radiographic magnification (figure 2, A). Videodensitometric profile curves, four pixels in width, were recorded across the normal arterial segment and across the catheter shaft. The width of these two videodensitometric curves was measured in pixels at half of the vertical height of the curve above background (full width at half maximum or FWHM). The diameter of the normal arterial segment \((D_n)\) was then calculated from the known diameter of the No. 7F catheter shaft (2.33 mm) and the ratio of the FWHM values for the normal arterial segment \((FWHM_n)\) and the catheter \((FWHM_c)\):

\[
D_n = \frac{FWHM_c}{2.33} \times \frac{FWHM_n}{FWHM_c}
\]

The cross-sectional area of the normal arterial segment was then calculated from its diameter, based on the assumption that the normal arterial segment is circular in shape. From the area of the normal arterial segment and the percent reduction in cross-sectional area measured previously, the cross-sectional area of the stenotic segment was then calculated. Finally, the mean diameter of the stenosis was calculated from its cross-sectional area.

The advantage of this approach is that it obviates the need for defining the borders of the catheter, which are blurred by adsorption unsharpness due to the gradual change in x-ray attenuation as the x-ray beam penetrates the curved edge of a cylinder of contrast medium.\(^10\) By use of FWHM to determine the relative sizes of the catheter shaft and normal arterial segment, a correction factor is obtained for radiographic magnification that is based on the capacity of videodensitometry for quantifying the dimensions of cylindrical objects in three dimensions.

The validity of this approach was tested experimentally in a
FIGURE 1. A, Cinevideodensitometric analysis of a digitized image of a projected cine frame of a coronary arteriogram. Shown is one-fourth of a cine frame showing the proximal LAD artery recorded in the RAO projection. Regions of interest are positioned over the stenotic and normal arterial segments with small adjacent regions for determination of background density. Percentage stenosis (33%) was calculated from the background-corrected videodensitometric values measured over the normal and stenotic segments. B, Regional myocardial blood flow pattern (LAO projection) measured from myocardial clearance rates of intracoronary $^{133}$Xe for the same patient. Regional blood flow in the LAD distribution (74 ml/100 g/min) was equivalent to regional flow in the circumflex distribution (77 ml/100 g/min).

Plexiglas phantom. Cylindrical holes (1.78 to 4.17 mm diameter) were drilled in a Plexiglas block, measured with precision pins accurate to 0.001 inch, and filled with contrast medium (Renografin 76) diluted with saline. The Plexiglas phantom was encased in 27 mm Plexiglas to simulate chest wall radiation scatter. The phantom was cineradiographed, and the cine film was projected and acquired digitally in computer memory. The resulting digitized image was analyzed by measuring the FWHM diameters of the videodensitometric profile curves recorded across the contrast-filled cylinders. The FWHM widths in pixels of these profile curves correlated linearly with the actual diameters of the contrast-filled cylinders ($r = .99$). Furthermore, videodensitometric analysis of the phantom was repeated after inserting a short segment of a contrast-filled...
coronary catheter (barium-impregnated, polyurethane Judkins-Schmidt catheter, U.S.C.I., Billerica, MA) into one of the cylindrical holes. With use of this segment of No. 7F (2.33 mm diameter) coronary catheter as a spatial reference and the equations above to calculate cylinder diameters from relative FWHM diameters, the actual diameters of the contrast-filled cylinders could be predicted to within a 2.7% (figure 2, B) for cylinder diameters ranging from 1.78 to 4.17 mm, which are typical diameters of catheters and normal arterial segments.

Pixel density was determined by relating the number of pixels measured across each contrast-filled cylinder to actual cylinder diameter. For radiographic magnification typically used in coronary arteriography and the additional twofold magnification resulting from projection of the cine film into the videocamera, the resulting pixel density was 30 pixels/mm².

Measurement of regional left ventricular blood flow. Regional left ventricular myocardial blood flow was measured by recording regional clearance rates of intracoronary ¹³³Xe from the left ventricular myocardium with a multicrystal scintillation camera (System 70; Baird Atomic, Inc.) as previously reported.¹¹ The measurements of ¹³³Xe clearance were obtained 10 min after the initial diagnostic coronary arteriograms, to allow the effect of contrast medium on regional myocardial blood flow to dissipate.

Briefly, 20 mCi of ¹³³Xe dissolved in 1 to 2 ml of sterile pyrogen-free saline was injected rapidly through the left coronary catheter into the left main coronary artery. The regional clearance of ¹³³Xe from the left ventricle was recorded in the 30 degree left anterior oblique projection for 2 min. The slope (k) of the initial portion of the myocardial ¹³³Xe clearance curve recorded by each crystal was calculated by monoeponential analysis of the activity recorded for the first 40 sec after the peak count rate. Regional myocardial flow rates were calculated by the Kety¹² formula: F = 100 × k × λ/ρ, where F is the myocardial capillary blood flow (ml/100 g/min), λ is the blood/myocardium partition coefficient (0.72) for xenon determined for the normal dog heart,¹³ and ρ is the specific gravity of tissue (1.05). Mean left ventricular myocardial blood flow per unit mass measured by the ¹³³Xe clearance technique has been found to correlate well with blood flow measured by the radioactive microsphere technique in anesthetized dogs with heterogeneity of local perfusion induced by partial coronary occlusion.¹⁴

The pattern of regional myocardial blood flow rates measured by individual crystals was then superimposed on a tracing of the left coronary arteriogram filmed in the left anterior oblique (LAO) projection. Correct alignment and appropriate magnification were achieved with radiopaque-radioactive markers positioned on each patient’s chest. Regional myocardial blood flow distal to proximal stenosis of the LAD artery was expressed as a fraction of regional flow in the circumflex distribution to normalize for the effect of variations in heart rate and systolic blood pressure among different patients, since these variations have major effects on absolute levels of myocardial blood flow. In previous studies of regional myocardial blood flow measured by ¹³³Xe clearance, we observed that absolute levels of left ventricular myocardial blood flow varied considerably both in patients with normal coronary arteriograms and in patients with coronary artery disease, and that most of this variation was closely related to spontaneous differences in double rate product.¹⁵,¹⁶ In patients with normal coronary arteriograms, regional flow rates in the LAD and circumflex distributions were consistently equal. In patients with coronary artery disease, subtle regional flow abnormalities may be detected by comparing flow rates in segments supplied by stenotic and normal arteries to normalize for the effect of spontaneous pressure-rate differences. These regional flow abnormalities would otherwise be obscured by the effect of spontaneous pressure-rate differences. Myocardial

FIGURE 2. A, Schematic illustration of the method used for measuring the absolute dimensions of coronary stenotic lesions by videodensitometry. Three videodensitometric profile curves were generated by computer for the catheter shaft, the normal arterial segment, and the stenotic segment. The diameter of the normal arterial segment was calculated from the known diameter of the catheter and the ratio of the widths of the catheter and normal arterial segment was expressed as FWHM. The area of the normal arterial segment, calculated from its diameter, was used to calculate the area of the stenotic segment from percent area stenosis measured by videodensitometry, as described in the text. B, Correlation between diameters of contrast-filled cylinders predicted by FWHM measurements of videodensitometric profile curves and actual cylinder diameters in a radiographic phantom.
blood flow rates measured in a rectangular matrix of six crystals overlying the myocardium supplied by the LAD artery were averaged and compared with the average myocardial blood flow measured in a similar six-crystal matrix overlying myocardium supplied by the circumflex artery (figure 1, B).

The validity of expressing regional myocardial blood flow in the LAD distribution as a fraction of flow in the circumflex distribution was documented in a previous study from our laboratory in which it was shown that LAD/circumflex ratios of regional myocardial blood flow rates correlate highly with LAD/circumflex ratios of myocardial 201Tl uptake for patients with normal coronary arteriograms and for patients with coronary artery disease both at rest and during the stress induced by rapid pacing or by treadmill exercise. The LAO projection is optimal for comparisons of regional flow rates in the left ventricular segments supplied by the LAD and circumflex arteries, because these two segments are viewed tangentially in this projection and are well separated by the left ventricular cavity. 133Xe activity is maximal in these segments when viewed tangentially, affording high activity levels. None of the patients in the present study experienced angina or had electrocardiographic evidence of ischemia during the measurement of flow with 133Xe.

For analysis, the 29 patients with proximal lesions of the LAD were separated into two groups based on whether regional blood flow in the LAD distribution was normal or reduced compared with regional flow in the circumflex distribution. To establish criteria for abnormally reduced regional flow, 133Xe regional flow measurements were obtained in 16 additional patients with normal coronary arteriograms, normal left ventricular angiograms, and normal intracardiac pressures. For these patients, the mean flow in the LAD distribution at rest was 65.1 ± 13 ml/100 g/min and mean flow in the circumflex region was 64.9 ± 13 ml/100 g/min. The mean LAD/circumflex flow ratio was 1.01 ± 0.07 (range 0.90 to 1.18). LAD/circumflex ratios less than 2 SDs of this mean value (i.e., less than 0.87) were defined as representing abnormally reduced regional flow in the LAD distribution.

Statistical analysis. Group differences were evaluated by Student’s t test. Ratios of regional myocardial blood flow were correlated with the dimensions of coronary stenotic lesions by power-curve analysis.

Results

Figure 1, A, shows a representative digitized coronary arteriogram from a patient with a minor proximal stenosis of the LAD artery. The digitized image shown represents one-fourth of a projected cine frame recorded in the right anterior oblique (RAO) projection. For videodensitometric analysis, ROIs two pixels in width were positioned over the normal and stenotic segments of the artery with small adjacent ROIs for measurement of background videodensity. The percent area stenosis calculated from the videodensitometric values for these background-corrected ROIs was 33%. The calculated cross-sectional area of this lesion was 3.23 mm², and the minimal diameter was 2.03 mm.

Figure 1, B, shows the pattern of regional myocardial blood flow recorded over the left ventricle in the LAO projection for the same patient. Regional myocardial blood flow measured for the six-crystal rectangular region in the LAD distribution (74 ml/100 g/min) was equivalent to the mean flow in the six-crystal region of the circumflex distribution (77 mg/100 g/min), and the LAD/circumflex flow ratio was 0.96. Shown in figure 3, A, is a digitized cine frame of a coronary arteriogram recorded in the left lateral projection in a patient with a severely stenotic proximal lesion of the LAD artery. Videodensitometric analysis demonstrated a 95% stenosis, with a minimal diameter of 0.72 mm and cross-sectional area of 0.41 mm². Shown in figure 3, B, is the regional myocardial blood flow pattern recorded scintigraphically from the clearance of myocardial 133Xe for this patient. Mean flow in the LAD distribution (44 ml/100 g/min) was reduced compared with flow in the circumflex distribution (54 ml/100 g/min) (LAD/circumflex ratio = 0.81).

Twenty-one patients had normal myocardial blood flow in the LAD distribution as reflected by LAD/circumflex ratios greater than 0.87 (table 1). For these patients the mean LAD/circumflex ratio was 0.98 ± 0.07, and mean dimensions of the proximal stenotic lesions of the LAD artery were 2.2 ± 0.6 mm diameter, 4.15 ± 2 mm² cross-sectional area, and 47 ± 19% stenosis based on reduction in cross-sectional area. Three of these patients (14%) had unstable angina, defined as recurrent chest pain at rest despite medical therapy. None of these patients had collateral arteries supplying the LAD artery. The mean ejection fraction for this patient group was 58%, and anterior wall motion appeared normal in 18 of the 21 patients.

Eight patients had reduced regional myocardial blood flow in the LAD zone with LAD/circumflex flow ratios less than 0.87 (table 2). For these patients with abnormally reduced LAD regional flow, the mean LAD/circumflex ratio was 0.79 ± 0.03, and mean dimensions of the stenotic lesions of the proximal LAD artery were 0.59 ± 0.3 mm diameter, 0.34 ± 0.2 mm² area, and 94.1 ± 4% stenosis based on reduction in cross-sectional area. Six of these patients (75%) had unstable angina, and five (62%) had small collateral arteries supplying the LAD artery from the right coronary artery. Mean ejection fraction for this patient group was 60% and four (50%) had reduced anterior wall motion.

For all 29 patients, regional myocardial blood flow in the LAD distribution, expressed as a ratio of circumflex flow, correlated inversely (r = −0.70) with percent stenosis determined by cinevideodensitometry (figure 4). LAD/circumflex ratios correlated linearly (r = 0.84) with minimum luminal diameters of stenotic lesions of the LAD artery (figure 5) and with cross-sectional area of the stenoses (r = .84) (figure 6).
Discussion

This study describes the effects of coronary stenotic lesions on regional myocardial blood flow in patients with single-vessel coronary artery disease and defines the dimensions of critical coronary stenotic lesions that reduce regional myocardial blood flow at rest. The study demonstrates in patients the pathophysiologic principle that regional myocardial blood flow remains normal until the degree of stenosis is severe. Abnormally reduced myocardial flow was consistently observed distal to proximal lesions of the LAD artery with mean diameters less than 1 mm, cross-sectional areas less than 0.8 mm², and percent reduction in cross-sectional area greater than 85%. These dimen-
TABLE 1
Stenotic coronary dimensions and regional myocardial blood flow in patients with normal LAD/circumflex (CX) flow ratios (>0.87)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/age (yr)</th>
<th>Angina</th>
<th>% Area stenosis</th>
<th>Diameter (mm)</th>
<th>Cross-sectional area (mm²)</th>
<th>Regional myocardial blood flow (ml/100 g/min)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>LAD</td>
</tr>
<tr>
<td>1</td>
<td>F/35</td>
<td>Atypical</td>
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<td>2.2</td>
<td>4.0</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
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<td>3.4</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>M/47</td>
<td>Atypical</td>
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<td>1.8</td>
<td>2.7</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
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<td>3.7</td>
<td>40</td>
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<tr>
<td>5</td>
<td>M/50</td>
<td>Atypical</td>
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<td>2.2</td>
<td>3.9</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
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<td>11</td>
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<td>12</td>
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<tr>
<td>21</td>
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<td>Atypical</td>
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<tr>
<td>Mean ± SD</td>
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<td></td>
<td>51.5 ± 8</td>
<td>47.0 ± 19</td>
<td>2.21 ± 0.6</td>
<td>4.15 ± 2</td>
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sions are highly consistent with luminal dimensions of flow-limiting lesions predicted on the basis of theoretical fluid mechanics,17-20 observed in experimental studies in laboratory animal preparations,2-6 and suggested by clinical studies in patients with angina at rest.21-23

Based on classic fluid mechanics, Young and his colleagues17-19 demonstrated that the loss of perfusion pressure caused by a stenotic lesion can be accounted for by viscous friction according to the Poiseuille equation and by flow separation or eddy formation just distal to the lesion. Gould et al.24 demonstrated experimentally in canine preparations the applicability of these equations for predicting the effect of coronary stenotic lesions on regional myocardial blood flow. These equations indicate that the most important single determinant of the hemodynamic effect of a coronary stenotic lesion is its minimal cross-sectional area or

TABLE 2
Stenotic coronary dimensions and regional myocardial blood flow in patients with reduced LAD/circumflex (CX) flow ratios (<0.87)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/age (yr)</th>
<th>Angina</th>
<th>% Area stenosis</th>
<th>Diameter (mm)</th>
<th>Cross-sectional area (mm²)</th>
<th>Regional myocardial blood flow (ml/100 g/min)</th>
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<td></td>
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<td>LAD</td>
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<td>Stable</td>
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<td>0.6</td>
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<tr>
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<td>Unstable</td>
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<td>57</td>
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<td>0.3</td>
<td>54</td>
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<tr>
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</tr>
<tr>
<td>8</td>
<td>F/55</td>
<td>Unstable</td>
<td>86.5</td>
<td>0.9</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td>47.4 ± 10</td>
<td>94.1 ± 4</td>
<td>0.59 ± 0.3</td>
<td>0.34 ± 0.2</td>
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</table>
diameter. Using these equations, Brown et al. predicted that for typical proximal coronary arteries 3 mm in diameter, flow-limiting stenotic lesions would have luminal diameters in the 0.5 to 1.0 mm range. This prediction agrees with the observation in the present study that stenotic lesions less than 1 mm diameter consistently reduce distal myocardial blood flow under resting conditions. This prediction, however, is based on the assumption that blood flow through the arterial segment is 1 ml/sec. Different flow rates would be expected to be associated with different dimensions for flow-limiting critical stenosis. The dimensions for critical stenosis observed in the present study are applicable only to the proximal coronary arteries and to resting conditions.

Experimental studies of the relationship between the severity of a stenotic lesion and the pressure gradient across it have demonstrated that flow resistance increases markedly with slight increments in the degree of narrowing for stenotic lesions greater than approximately 80% area reduction. This principle has been demonstrated in hydraulic models, in post-mortem experiments with atherosclerotic human coronary arteries, and in animal studies and reflects the dominant effect of the fourth power of the radius on flow. The present data are consistent with this nonlinear principle of fluid mechanics. Studies reported by Gould et al. demonstrated that a reduction in diameter of approximately 85% is necessary to reduce coronary blood flow in open-chest anesthetized dogs studied at rest. This degree of narrowing is equivalent to a 97% reduction in cross-sectional area, which is consistent with the mean value of 94% reduction in area observed for the eight patients with reduced regional flow in the present study.

The dimensions of the coronary stenoses for the
eight patients with reduced regional flow in the present study are also consistent with the coronary dimensions reported by McMahon et al. for patients with unstable angina and subendocardial infarction. In patients with severe isolated proximal stenoses of the LAD artery, chest pain at rest, and subendocardial infarction, minimum dimensions of coronary stenoses were mean diameter 0.64 ± 0.08 mm, mean area 0.35 ± 0.11 mm², and percent area stenosis 95 ± 2%. These values correspond closely to the dimensions obtained in the present study for patients with reduced flow at rest and unstable angina. Smith et al. recorded intraoperative 133Xe clearance curves in patients undergoing coronary artery bypass surgery and observed that myocardial flow was reduced distal to lesions causing a greater than 80% reduction in diameter, as measured from the preoperative coronary arteriogram. This degree of diameter stenosis corresponds to 94% area stenosis, which matches the magnitude of stenosis observed in the present study for patients with reduced regional flow. It is also interesting that Schwartz et al. observed reduced regional left ventricular wall motion and reduced ejection fractions for patients with coronary stenotic lesions exceeding 80% diameter stenosis as measured by quantitative coronary arteriography.

The Poiseuille equation and the separation loss equation indicate that slight changes in the minimum diameters of significant stenotic lesions will have profound effects on predicted pressure loss across the lesion, whereas the diameter of the normal artery can vary considerably without any significant effect on the predicted stenosis resistance. Thus, absolute dimensions are more precise determinants of the physiologic effects of a stenotic lesion in a proximal coronary artery than is percent relative stenosis. Quantitation of coronary stenotic lesions in terms of percentage measurements relative to normal arterial segments may also be misleading because normally appearing arterial segments may be atherosclerotic and are often tapered. Harrison et al. demonstrated in patients with proximal lesions of the LAD artery and multivessel coronary artery disease that percent stenosis predicts the coronary reactive hyperemic response poorly but that minimal cross-sectional area can predict which stenotic lesions will cause abnormal reactive hyperemic responses. In the present study, reduced regional myocardial blood flow correlated best with minimum luminal diameter and cross-sectional area and correlated less well with percent coronary stenosis.

None of the eight patients with reduced regional myocardial blood flow experienced chest pain or mani-fested electrocardiographic signs of ischemia during the 133Xe clearance measurements. This observation that regional flow may be reduced without causing ischemia may be explained by several different mechanisms. First, several groups of investigators have recently reported experimental studies in anesthetized dogs demonstrating that reduced resting myocardial flow does not imply exhaustion of distal vasodilator reserve. Second, reduced anterior wall contraction, which was observed for four of the eight patients with reduced flow in the LAD distribution, may partially account for the absence of ischemia. Reduced contractile performance of the anterior wall would be expected to lower regional myocardial blood flow requirements, since many studies have demonstrated that left ventricular myocardial flow rates are closely coupled to hemodynamic performance. In a previous study of patients with multivessel coronary artery disease, we observed that reduced left ventricular blood flow per 100 g myocardium was closely related to the hemodynamic determinants of myocardial oxygen consumption. Left ventricular myocardial blood flow was reduced in these patients without signs of ischemia, implying that lower myocardial oxygen needs were adequately supplied by reduced myocardial blood flow. Third, since six of eight patients with reduced resting blood flow had unstable angina, impaired segmental left ventricular function caused by repeated ischemic injury may have contributed to the reduction in distal blood flow observed. Chronic stunning of the myocardium would be expected to result in reduced regional myocardial blood flow, because impaired left ventricular contractility lowers myocardial blood flow requirements per 100 g of myocardium. Finally, localized myocardial fibrosis in the left ventricular segment supplied by the LAD artery may have contributed to reduced regional flow. This mechanism is less likely, however, because clearance of 133Xe from scar tissue requires a much longer time period than 40 sec. Since monoexponential analysis of the 133Xe clearance curves was limited to the initial 40 sec after the peak counting rate, it is unlikely that fibrotic tissue contributed to the 133Xe clearance rates. Furthermore, patients with prior myocardial infarction were excluded from the study.

For the eight patients with severe proximal stenotic lesions, the absolute magnitude of the reduction in regional flow averaged 21% less than flow in the circumflex region. Collateral arteries supplying the LAD artery probably prevented a further reduction in regional flow rates. Five of the eight patients with reduced regional myocardial blood flow had angio-
graphically visible collateral arteries from the right coronary artery to the LAD artery, whereas none of the patients with normal flow in the LAD distribution had collateral arteries. This observation that collateral arteries were present only in patients with reduced distal blood flow at rest is consistent with a recent report by Aran et al.\textsuperscript{37} demonstrating that resting flow in collateral-dependent myocardium is consistently reduced.

In a study reported previously from this laboratory,\textsuperscript{38} regional myocardial blood flow data measured by the \textsuperscript{133}Xe clearance technique were tabulated for patients with proximal lesions of the LAD artery evaluated by visual estimation. Although mean regional flow in the LAD distribution was not reduced compared to flow in the remainder of the left ventricle, reduced regional anterior descending perfusion was noted in several patients with severe proximal lesions, which were described as causing almost total occlusion. Similarly, in the present study, the majority of patients with proximal lesions of the LAD artery had normal regional flow in the LAD distribution; only patients with very severe lesions had reduced distal flow. The present study demonstrates that quantitative coronary arteriography is capable of predicting which patients will have reduced distal blood flow at rest. Recently, Wilson et al.\textsuperscript{39} have shown that quantitative coronary arteriography is capable of predicting coronary vasodilator reserve in patients with single-vessel coronary artery disease.

Klocke et al.\textsuperscript{40} also reported reduced regional flow distal to severe lesions of the LAD artery. In patients with stenotic lesions reducing the diameter of the LAD artery by 70\% by more, distal flow was consistently reduced compared with regional flow in patients with normal coronary arteriograms. In some patients in whom the diameter of the LAD artery was reduced by 50\%, distal flow was also reduced. Interestingly, during rapid atrial pacing in these patients, the increase in distal flow in the anterior descending distribution was curtailed despite a large increase in rate-pressure product. In the present study, rapid pacing or pharmacologic intervention was not performed.

An important advantage of cinevideodensitometric analysis is that precise identification of arterial borders is unnecessary. Cinevideodensitometry compares the total videodensity of contrast material in the stenotic arterial segment to the videodensity in the normal arterial segment without the need for precise edge detection. After subtraction of average background density per pixel from the video value for each pixel across the arterial lumen, the videodensity values are summed, and the total videodensity value reflects the amount of contrast material in the arterial lumen. Since the video values are larger in the central region of the arterial lumen and smaller toward the borders, the boundary regions contribute relatively little to the summed value.

A second advantage of cinevideodensitometric analysis is its capability for measuring eccentric stenotic lesions, since the total videodensity of contrast medium within the arterial lumen does not change in different radiographic projections.\textsuperscript{8} Therefore, videodensitometry requires analysis of a lesion in only one radiographic projection. Other methods require manual tracing of the borders of projected coronary arteriograms obtained in multiple angiographic projections.\textsuperscript{25}

However, cinevideodensitometric analysis yields percentage values of relative stenosis, rather than the absolute dimensions of coronary stenotic lesions. In the present study, a method was introduced for calculating absolute dimensions of stenotic lesions based on the videodensitometric value of relative stenosis and videodensitometric profile curves of the normal arterial segment and catheter shaft, which was used as a spatial reference to correct for radiographic magnification. Phantom experiments in the present study demonstrated that the actual diameters of contrast-filled cylinders could be predicted to within $\pm 2.7\%$ by FWHM analysis of videodensitometric curves of the catheter shaft and contrast-filled cylinders.

Measuring the diameter of the catheter shaft and normal arterial segments by FWHM analysis has several advantages. First, FWHM measurements are based on objective computer analysis of videodensitometric profile curves rather than subjective visual analysis of profile curve width. Second, FWHM analysis eliminates the difficulty associated with attempting to measure diameters by identifying the borders of the catheter and normal arterial segment, which are indistinct on projected cine film. FWHM analysis uses videodensitometric data, which reflect the cylindrical shape of the arterial segment, eliminating the need for estimation of the borders of the arterial segment and catheter. Third, FWHM is used only for measuring the diameters of the catheter and normal arterial segment, which are cylindrical in shape and relatively large. The stenotic segment, which is often eccentric and much smaller, is not measured by the FWHM technique. Instead, the videodensitometric signal across the stenosis is summated and related to the videodensitometric signal across the normal arterial segment; i.e., the areas under the two videodensitometric curves are compared. Since the same site on the normal-appear-

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ing arterial segment is measured for calculation of both FWHM and for the summed videodensity value, relative stenosis is accurately converted to absolute dimensions.

A major advantage of videodensitometric analysis is that percent stenosis is calculated based on relative cross-sectional area, rather than relative diameter. Postmortem experimental studies in atherosclerotic human coronary arteries have demonstrated that percent reduction in cross-sectional area is the most important single determinant of blood flow through a stenotic artery. Other dimensional factors besides cross-sectional area, however, such as length of stenosis, eccentricity, and tapering of the lesion, also affect blood flow to a lesser extent. None of these geometric factors were measured in the present study. Therefore, the present study should not be interpreted as indicating that regional myocardial blood flow distal to a lesion falls when the degree of stenosis exceeds a single precise dimension. Instead, this study demonstrates in patients at rest the pathophysiologic principle that regional flow remains normal until the degree of stenosis becomes very severe, i.e., approximately 85% to 90% stenosis based on relative reduction in cross-sectional area.

Potential limitations of the 133Xe clearance technique for measuring regional left ventricular myocardial blood flow have been discussed previously. It should be noted that regional flow rates are heterogeneous within each of the regional areas sampled, and that flow rates for the LAD and circumflex regions represent mean values. Furthermore, the primary data obtained are differences in local clearance constants calculated by monoexponential analysis of the initial portion of each tracer curve. These regional clearance rates reflect clearance of a diffusible indicator by local myocardial capillary circulation and, by inference, local tissue perfusion with diffusible nutrients. Expression of these clearance constants in terms of myocardial blood flow must be interpreted cautiously, however, because of the assumptions required with use of the Kety principle.

The present study demonstrates that cinevideodensitometric measurements can predict the hemodynamic effects of stenotic lesions on regional myocardial blood flow. Cinevideodensitometric analysis of coronary arteriograms may provide an objective and practical method for evaluating the physiologic significance of coronary stenotic lesions in individual patients. These quantitative measurements may facilitate the selection of patients for coronary bypass surgery or for coronary angioplasty.

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