DIAGNOSTIC METHODS

CORONARY ARTERY DISEASE

The value of lesion cross-sectional area determined by quantitative coronary angiography in assessing the physiologic significance of proximal left anterior descending coronary arterial stenoses

DAVID G. HARRISON, M.D., CARL W. WHITE, M.D., LOREN F. HIRATZKA, M.D., DONALD B. DOTY, M.D., DOUGLAS H. BARNES, B.S.S., CHARLES L. EASTHAM, B.A., AND MELVIN L. MARCUS, M.D.

ABSTRACTS The results of previous work from this laboratory have shown a poor correlation between percent stenosis (determined visually with calipers) and the coronary reactive hyperemic response (an index of maximal coronary vasodilator capacity) determined during cardiac surgery. This study was performed to determine whether other parameters of lesion severity could predict the reactive hyperemic response and thus the hemodynamic significance of coronary stenoses in human beings. Twenty-three patients with lesions in the proximal left anterior descending coronary artery were studied. To account for differences in expected vessel size, patients with large diagonal branches (greater than one-half the diameter of the left anterior descending artery) arising before the lesion were excluded. Computer-assisted quantitative coronary angiography was used to measure percent diameter stenosis, percent area stenosis, and minimal stenosis cross-sectional area. With a pulsed Doppler velocity probe, reactive hyperemic responses were recorded after a 20 sec coronary occlusion of the left anterior descending artery at cardiac surgery before cardiopulmonary bypass and were quantified by the peak/resting velocity ratio (normal greater than 3.5:1). Percent area stenosis ranged from 7% to 54% for vessels with normal reactive hyperemic responses and from 27% to 94% for vessels with abnormal reactive hyperemic responses. With both percent diameter stenosis and percent area stenosis there was substantial overlap between vessels with normal and abnormal reactive hyperemic responses. In contrast, nine of nine vessels with normal reactive hyperemic responses had lesion minimal cross-sectional areas of greater than 3.5 mm² and 13 of 14 vessels with abnormal reactive hyperemic responses had minimal cross-sectional areas of less than 3.5 mm². We conclude that (1) the hemodynamic significance of a coronary stenosis in patients with coronary atherosclerosis is not accurately predicted by percent area or percent diameter stenosis, even when the angiograms are analyzed with quantitative coronary angiography and (2) minimal cross-sectional area can identify vessels with normal vs abnormal reactive hyperemic responses and thus can be used to predict the hemodynamic significance of stenosis of the proximal left anterior descending coronary artery.


CORONARY ARTERIOGRAPHY is widely accepted as a useful clinical and investigative tool. Despite this, there exist substantial data suggesting that the traditional methods of analysis of the coronary arteriogram are inadequate, and several investigators have shown that there is considerable intraobserver and interob-

server variability. The results of postmortem studies have shown a poor correlation between angiographic findings and anatomic findings. Although there is little controversy regarding the usefulness of coronary arteriography in separating patients with entirely normal coronary arteries from those with severe high-grade obstructions (greater than 95% diameter steno-

sis), the potential of the coronary arteriogram in predicting the hemodynamic significance of lesions that angiographically appear mild to moderate remains controversial.

In the experimental animal the physiologic signifi-

cance of artificially produced arterial stenoses has been extensively studied. Gould et al. produced varying
degrees of coronary narrowing and showed that short stenoses in excess of 50% diameter narrowing reduced coronary vasodilator responses in a predictable fash-

ion. Thus there is a close relationship between the coronary vasodilator response to a given stimulus and the degree of luminal narrowing.

Recently, it has become possible to record mean and phasic coronary flow velocity in human beings at the time of cardiac surgery by means of a pulsed Doppler velocity probe. With this device, reactive hyperemic responses from individual coronary arteries can be obtained before the patient is placed on cardiopulmonary bypass. This response can be used to assess the vasodilator reserve of a stenosed vessel and thus provides an estimate of the functional significance of the stenosis.

We have previously shown that measurements of percent stenosis analyzed by the traditional method failed to correlate significantly \( r = -0.22 \) with the reactive hyperemic response. Because of these findings, this study was performed to determine whether parameters other than percent diameter stenosis can be used to predict the reactive hyperemic response subsequently obtained at cardiac surgery. Estimates of percent area stenosis, percent diameter stenosis, and residual lumen cross-sectional area were obtained by computer-assisted quantitative coronary angiography and were compared with a physiologic parameter of lesion severity, the reactive hyperemic response obtained during cardiac surgery.

### Methods

**Patient selection.** Twenty-three adult patients undergoing coronary arteriography and cardiac surgery at the University of Iowa were studied. Most operative procedures were performed to place coronary artery bypass grafts. However, four patients had mitral valve surgery for correction of mitral stenosis. To be included in the study, each patient had to have an isolated lesion in the proximal one-third of the left anterior descending artery or a left anterior descending artery containing only minor luminal irregularities. Many patients had lesions in other major coronary arteries as well. Patients with disease of the left main coronary artery were excluded. Each patient underwent either contrast left ventriculography of radionuclide ventriculography and those with abnormalities of left ventricular contraction were excluded. Because left ventricular hypertrophy can independently alter the reactive hyperemic response, patients with hypertension, valvular heart disease (other than pure mitral stenosis), or evidence of left ventricular hypertrophy by echocardiography, left ventriculography, or electrocardiography (Estes criteria) were not studied. In addition, patients who appeared to have left ventricular hypertrophy at the time of cardiac surgery were excluded. Patients with coronary collaterals visible on the coronary arteriogram were excluded. All patients included in the study had to have a coronary arteriogram suitable for analysis by quantitative coronary angiography, which required that the lesion be clearly seen in two orthogonal views. To be included in the study, each patient also had to undergo a technically adequate reactive hyperemia study performed in the left anterior descending artery at cardiac surgery.

Because percent stenosis compares the narrowest portion of the stenosis to the normal vessel size, it should, if measured properly, reflect the hemodynamic significance of a coronary obstruction regardless of the location of that obstruction in the coronary vasculature. In contrast, the significance of any single measurement of minimal cross-sectional area of a coronary stenosis is dependent on the normal expected vessel size of the vascular segment containing that stenosis. For example, a coronary stenosis producing a minimal cross-sectional area of 2 mm\(^2\) may produce a severe reduction in intraluminal area of the proximal left anterior descending artery. In contrast, a lesion with a similar minimal cross-sectional area in the middle portion of the left anterior descending artery may produce only a minor reduction in intraluminal area. Therefore, for purposes of comparing minimal cross-sectional area to the maximal vasodilator capacity, it was necessary to study vessels with similar expected normal sizes. Thus to compare minimal cross-sectional area with the reactive hyperemic response, patients with a large diagonal branch proximal to the stenosis were excluded. A large diagonal branch was defined as a vessel one-half the diameter of the parent left anterior descending artery.

Although the subjects were drawn from a large pool of patients, they represent a consecutive series meeting the above requirements. Each patient gave informed written consent before entering the study. The studies were approved by the Human Use Committee at the University of Iowa.

**Cardiac catheterization.** All patients were premedicated with atropine (0.6 mg sc) before catheterization. Sublingual nitroglycerin (0.4 mg) was given to each patient immediately before coronary angiography. The Seldinger approach from the right femoral artery was used. Multiple views of the left coronary artery were obtained with a No. 8F Judkins catheter. These views were selected so that at least two matched perpendicular views of the proximal left anterior descending artery were available for analysis.

**Quantitative coronary angiography.** The lesion in the left anterior descending artery was projected on a large screen marked in rectilinear coordinates and was carefully traced along with as much of the adjacent left anterior descending artery as could be seen in either view. Additionally, a portion of the catheter near its tip was traced. The position of the catheter and the vessel in each view was noted on the rectilinear grid and subsequently entered into the computer. The tracings of the lesion and the catheter tip were then digitized with a Tektronic digitizing tablet interfaced with the computer.

The steps used by this program to analyze each lesion have been previously described in detail by Brown et al. Briefly, the x-ray magnification and pin cushion distortion characteristics of the x-ray equipment have been determined and previously entered into the computer. With this information, each view is corrected for magnification and distortion. The center line of the vessel and lesion in each view are matched, thus allowing the computer to create a three-dimensional reconstruction of the vessel and the lesion. The computer is then able to calculate the cross-sectional area of the apparently normal portion of the vessel, the minimal cross-sectional area of the vessel, a percent diameter stenosis in both the right anterior oblique and the left anterior oblique views, and the percent area stenosis obtained from the paired views.

**Validation of quantitative coronary angiography.** Computer-assisted quantitative coronary angiography has been extensively validated by Brown et al. Before beginning these clinical studies, we performed three separate validation studies to confirm the previous studies of Brown and co-workers in our laboratory. Initially a brass artery containing a simulated steno-

sis (minimal diameter of 1.94 mm, maximal diameter of 4.1 mm) together with a portion of a No. 8F catheter tip were filmed.
in orthogonal views. To simulate usual catheter and vessel positions, the brass artery and the catheter were placed at widely varying positions in the x-ray field. Additionally, their positions were changed in relationship to the distance from the x-ray tube and the distance from each other. After some initial experience with this technique, we were able to consistently measure the brass artery to within 3% of its known size from all positions in the x-ray field.

Intraobserver variability was examined. For this purpose, one observer traced one lesion from each of 18 patients from three different paired views. The range of minimal cross-sectional areas studied was from 1.5 to 11.5 mm². The mean percent difference between each of the three paired views was 7 ± 1% (mean ± SE).

To assess variability, two independent observers analyzed 10 lesions. The range of the cross-sectional areas included in the interobserver studies was from 1.3 to 11.5 mm². Each observer traced and digitized each lesion three times using three different paired views. For each lesion the average of the three minimal cross-sectional areas were computed and the average difference between the values of the observer 1 and those of observer 2 was found to be 7 ± 1% (SE).

**Reactive hyperemia studies at cardiac surgery**

**Preparation of patients.** All patients were anesthetized, usually with halothane. An endotracheal tube was inserted and ventilation was accomplished with a mechanical respirator. Blood gases were maintained in the physiologic range by varying the depth and rate of respiration and the oxygen concentration in the inspired gas. The studies were performed during surgery through a midsternal incision for cardiac exposure after appropriate preparations for cardiopulmonary bypass. Arterial pressure, measured with a radial arterial catheter, and the electrocardiogram were monitored continuously. A catheter placed in the left atrium via a pulmonary vein was used to monitor left atrial pressure. Just before measurements of coronary velocity, heparin was administered intravenously to raise the activated clotting time to 480 sec. All measurements of coronary reactive hyperemia were obtained before the onset of cardiopulmonary bypass when the patient’s hemodynamic status was stable.

**Measurements of coronary blood flow velocity.** Mean and phasic coronary blood flow velocity were obtained with a specially designed pulsed-ultrasonic probe previously sterilized for intraoperative use. The probe, which has been described in detail, consists of a 1 mm 20 MHz piezoelectric crystal placed at a 45 degree angle in a silicone suction pad, 2.5 cm in diameter. Continuous contact of the crystal to the coronary vessel was accomplished by suction applied to the silicone pad through a separate vacuum line. The probe was connected to a pulsed Doppler flowmeter constructed by the bioengineering resource facility at the University of Iowa according to the design originally described by Cole and Hartley. With this system, high-quality coronary velocity tracings were routinely obtained from the left anterior descending artery. Simultaneous measurements of mean and phasic coronary velocity, phasic arterial pressure, and the electrocardiogram were recorded.

After the Doppler probe was placed over the left anterior descending coronary artery, the position of the probe was adjusted until a recording of coronary blood flow velocity of excellent. Quality was obtained. A 20 sec coronary occlusion was accomplished by obstructing the coronary artery with gentle pressure by means of vascular forceps just proximal to the Doppler probe. The time of occlusion was determined by measuring the time during which coronary blood flow velocity was zero. Previous studies from this laboratory have shown that 20 sec coronary occlusions produce maximal reactive hyperemic responses in human beings under these conditions.

Each reactive hyperemic response was quantified by measuring peak coronary velocity and dividing this by resting velocity before the onset of transient coronary occlusion. Traditionally, coronary reactive hyperemic responses are quantified by measuring peak/resting velocity ratios, debt/repayment ratio, and duration of occlusion/duration of repayment ratios. Initial experience has shown that in patients with coronary artery disease, changes in peak/resting velocity ratio parallel changes in the debt/repayment ratio. Thus, in this study the reactive hyperemic response was quantified by measurements of peak/resting velocity ratios only.

**Protocol.** For purpose of data analysis, patients were divided into two groups: those with normal maximal coronary vasodilator responses, defined as a peak/resting velocity ratio of greater than 3.5:1, and those with abnormal maximal vasodilator responses with peak/resting velocity ratios of less than 3.5:1. Initial experience in studying vessels with no evidence of intraluminal atherosclerosis supplying normal ventricles has shown that the normal peak/resting velocity ratio after a 20 sec coronary occlusion is 5.5, with a range of 3.5 to 9. Thus a peak/resting velocity ratio of 3.5:1 represents the lowest extreme of what we consider to be a normal response.

Each patient’s coronary angiogram was carefully reviewed and two orthogonal views were selected in which the lesion could be clearly visualized. If more than one pair of views were available, the paired orthogonal views in which the lesion appeared most severe was selected. Three frames from each pair were analyzed by quantitative coronary angiography. This yielded three values for minimal cross-sectional area and percent area stenosis and six values for diameter stenosis and minimal diameter. The peak/resting velocity ratio of the reactive hyperemic response was subsequently compared with the average of the three values for each of these as well as the “most severe” of the values for each of these parameters. In addition, the size of the apparently normal vascular segment adjacent to the lesion in question was determined. To accomplish this, the cross-sectional areas of either the proximal or distal portion of the vessel (whichever was largest) were averaged from the three paired frames.

Analysis of the arteriogram and determination of reactive hyperemic responses were performed by two independent observers, each of whom was unaware of the other’s result.

**Statistical methods.** Results are expressed as mean ± SE. Comparisons between patients with normal and abnormal reactive hyperemic responses were made with an unpaired Student’s t-test. The relationship between the peak/resting velocity ratio of the reactive hyperemic response and the various angiographic parameters examined were compared by both linear regression and least-squared multivariate regression analyses to obtain a ‘best fit’ curve.

**Results**

The patients were found to have lesions ranging from 7% to 94% area stenosis and 4% to 73% diameter stenosis. The average diameter stenosis for all patients was 35 ± 3.5% and the average area stenosis was 44 ± 4.4%. In general, percent area stenosis was greater than percent diameter stenosis; however, because of lesion eccentricity an occasional patient had a percent diameter stenosis greater than percent area stenosis. The majority of the patients studied had lesions of mild-to-moderate severity as indicated by percent stenosis.
TABLE 1

Hemodynamics of patients at time of reactive hyperemia study in operating room

<table>
<thead>
<tr>
<th>PRVR &gt; 3.5:1</th>
<th>PRVR &lt; 3.5:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(normal, n = 9)</td>
<td>(abnormal, n = 14)</td>
</tr>
<tr>
<td>AoP (mm Hg)</td>
<td>68 ± 3.8</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>72 ± 6.8</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>21 ± 3.7</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE.

PRVR = peak/resting velocity ratio; HR = heart rate; AoP = mean aortic pressure; LAP = left atrial pressure.

The hemodynamics at the time of cardiac surgery for patients with normal and abnormal reactive hyperemic response are shown in table 1. The mean left atrial pressure was higher in the group with normal reactive hyperemic responses because this group included four patients with mitral stenosis. The heart rates of patients with normal and abnormal reactive hyperemic responses were not significantly different. Of particular importance, the coronary driving pressure (mean arterial pressure), a major determinant of the reactive hyperemic response, was highest in the group with the diminished peak/resting velocity ratio. Blood hemoglobin concentration averaged 13.8 ± 0.5 and 14.2 ± 0.5 g/dl for patients with normal and abnormal reactive hyperemic responses, respectively. The left ventricular ejection fraction averaged 0.67 ± 0.04 and 0.65 ± 0.03, respectively, for these two groups. Neither the mean hemoglobin nor the mean ejection fraction was significantly different between groups.

Relationship between maximal vasodilator response and percent stenosis. The relationships between percent diameter stenosis, percent area stenosis, and the reactive hyperemic response are shown in figure 1. Both percent diameter and area stenosis correlated poorly with the reactive hyperemic response (table 2). The distribution of percent diameter and percent area stenosis (average of three paired frames) in patients with normal and abnormal maximal vasodilator responses is shown in figure 2. Considerable overlap exists between patients with normal and abnormal reactive hyperemic responses for both percent area stenosis and percent diameter stenosis. Although certain values for percent area stenosis or percent diameter stenosis may be specific for hemodynamically significant obstructions, the same values lack sensitivity. For example, lesions greater than 60% area stenosis were always associated with a blunted reactive hyperemic response. However, many lesions with area stenosis of substantially less than 75% were associated with abnormal reactive hyperemic responses.

In addition to averaging the three values for percent area stenosis and percent diameter stenosis, we determined the "worst" percent area stenosis and diameter stenosis for all of the frames analyzed for each lesion. With this value, the degree of overlap between patients with normal and abnormal reactive hyperemic responses was virtually unchanged.

Relationship between minimal cross-sectional area and maximal vasodilator response. Figure 3 shows the relationship between minimal cross-sectional area and the reactive hyperemic response quantified by the peak/resting velocity ratio. Although the correlation coefficient for this relationship was low (r = .58) it was highly significant (table 2). This relationship was best fit with a quadratic equation, and the correlation between predicted and observed y values for each minimal cross-sectional area was also significant (table 2). Figure 4 shows the distribution of minimal cross-sectional areas in vessels with definitely normal and abnormal reactive hyperemic responses. In contrast to percent area stenosis, vessels with minimal cross-sectional areas of greater than 3.5 mm² consistently demonstrated a normal maximal coronary vasodilator response. A minimal cross-sectional area of less than 3.5 mm² was associated with an abnormal coronary reactive hyperemic response in 13 of 14 instances.

In addition to using the average of three paired frames for determination of minimal cross-sectional area, we also compared the smallest cross-sectional area from these three pairs for each lesion with the

FIGURE 1. Relationship between percent diameter stenosis (left) and percent area stenosis (right) vs the peak/resting velocity ratio of the reactive hyperemic responses. There is a poor correlation (r = −.34 and −.33, respectively) for each of these relationships.
reactive hyperemic response. This analysis yielded similar results.

Relationship between minimal lesion diameter and the vasodilator response. The minimal lesion diameter was determined from the average of either three right anterior oblique frames or three left anterior oblique frames, depending on which showed the lesion to be most severe. The correlation coefficient for the relationship between the minimal lesion diameter and the reactive hyperemic response was .73 (p < .005). This correlation was greatly influenced by one patient with a reactive hyperemic response of 7:1. Excluding this patient, the correlation coefficient of this relationship was .61.

The minimal lesion diameters of vessels with normal and abnormal reactive hyperemic responses overlapped substantially. All vessels with a minimal lesion diameter of less than 1.5 mm had abnormal reactive hyperemic responses. All vessels with minimal lesion diameters in excess of 2.3 mm had normal reactive hyperemic responses. Of eight vessels with minimal lesion diameters between 1.5 and 2.3 mm, three had normal and five had abnormal reactive hyperemic responses.

Relationship between the largest adjacent segment cross-sectional area and the vasodilator response. The average apparently normal segment cross-sectional area for vessels with normal reactive hyperemic responses was 9.2 ± 1.2 mm² compared with 5.1 ± 0.4 mm² for vessels with abnormal reactive hyperemic responses. These values were significantly different (p < .001). The relationship between this value and the peak/resting velocity ratio is shown in figure 5. The correlation coefficient for this relationship was .68 (p < .0005). In addition, the size of the apparently normal segment closely correlated with the minimal cross-sectional area of the same vessel (r = .86, p < .0001).

Comparison of diameter stenosis determined by quantitative coronary angiography and visually with calipers. In all patients, percent diameter stenosis was determined by quantitative coronary angiography and by hand-held calipers. The correlation coefficient between these two techniques was .93, the slope of this relationship was .81 (with the hand-held caliper technique

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**TABLE 2**

Correlations between angiographic parameters and reactive hyperemic response

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Regression equation</th>
<th>Correlation coefficient</th>
<th>SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Area stenosis vs PRVR</td>
<td>3.77 - 0.02x</td>
<td>-.33</td>
<td>1.35</td>
<td>.12 (NS)</td>
</tr>
<tr>
<td>% Diameter stenosis vs PRVR</td>
<td>3.77 - 0.03x</td>
<td>-.33</td>
<td>1.35</td>
<td>.12 (NS)</td>
</tr>
<tr>
<td>Cross-sectional area vs PRVR (linear regression)</td>
<td>1.61 + 0.34x</td>
<td>.59</td>
<td>1.12</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Cross-sectional area vs PRVR (&quot;best fit&quot;)</td>
<td>0.417 + 0.946x - 0.052x²</td>
<td>.69^</td>
<td>1.07</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Minimal diameter vs PRVR</td>
<td>y = 0.151 + 1.56x</td>
<td>.73</td>
<td>0.98</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

PRVR = peak/resting velocity ratio of the reactive hyperemic response; SD = standard deviation about the regression line of y on x.

^Calculated by linear regression of observed responses vs those predicted by this equation.
as the x value), and the intercept was 7.0. The average absolute difference between caliper and quantitative coronary angiographic estimates of percent stenosis was $4.6 \pm 0.9\%$. Thus, these two methods of determining percent diameter stenosis yield quantitatively similar results.

**Discussion**

The new findings in this study are that (1) percent stenosis as calculated by quantitative coronary angiography does not accurately predict the physiologic significance of coronary stenoses, particularly for lesions of mild-to-moderate severity, and (2) residual lumen area of lesions proximal to any major diagonal branch of the left anterior descending artery serves to better define the physiologic significance of the stenosis.

One explanation of these findings is schematically presented in figure 6. Both of the vessels pictured would appear to have a 50% reduction in luminal diameter at coronary arteriography. The vessel on the right, however, contains diffuse intimal atherosclerosis, and the superimposed plaque results in a substantial reduction of the vessel cross-sectional area. The physiologic significance of the angiographically apparent 50% stenosis on the right is much greater than that of the stenosis pictured on the left. The major difficulty in differentiating these two lesions, therefore, is not in identifying the stenosed portion of the vessel but in identifying the truly normal diameter of the vessel. Thus vessels with angiographically apparent mild degrees of stenosis may demonstrate very blunted reactive hyperemic responses because their cross-sectional areas are substantially reduced.

This hypothesis is supported by our observations related to the apparently normal adjacent segments. First, the cross-sectional areas of these segments was significantly smaller in the group of vessels with abnormal reactive hyperemic response compared with the group with normal responses. Second, a significant correlation ($r = .68$) existed between the reactive hyperemic peak/resting velocity ratio and the size of the normal segment. For this group of vessels, this measurement correlated as well as the minimal cross-sectional area to the peak/resting velocity ratio. Third, the minimal cross-sectional area could be shown to be a function of the size of the apparently normal segment of the vessel. Thus the overall reduction in luminal area produced by the atherosclerotic process was significantly influenced by the severity of the diffuse narrowing in the adjacent (and underlying) vessel. This

![FIGURE 3](image-url). Relationship between the peak/resting velocity ratio of the reactive hyperemic response and the lesion minimal cross-sectional area. This relationship is best fit by the quadratic equation $y = 0.417 + 0.946x - 0.051x^2$.

![FIGURE 4](image-url). Distribution of lesion minimal cross-sectional areas of vessels with normal and abnormal reactive hyperemic responses. PRVR = peak/resting velocity ratio.

![FIGURE 5](image-url). Relationship between the peak/resting velocity ratio of the reactive hyperemic response and the cross-sectional area of the largest adjacent segment of the left anterior descending artery.
would be expected when a condition such as that depicted in figure 6 exists.

A number of studies in animals have shown that coronary stenoses greater than 75% severity significantly limit coronary vasodilator capacity.\textsuperscript{9,17,18} Furthermore, such obstructions in patients are often associated with evidence of inducible myocardial ischemia.\textsuperscript{19-23} Our data do not challenge these concepts. Our results, however, suggest that some lesions of apparent mild-to-moderate severity, ranging from 21% to 73% diameter stenosis, may also produce alterations in coronary reserve. Furthermore, by use of percent area or diameter stenosis these lesions may be indistinguishable from stenoses that are hemodynamically insignificant.

In contrast to percent stenosis, residual lumen area more adequately separated vessels with normal and abnormal reactive hyperemic responses. These findings should not be interpreted as challenging traditional concepts of fluid dynamics across a stenosis. Because we examined a group of vessels with relatively homogeneous normal expected sizes (the left anterior descending artery proximal to any major diagonal branch), changes in minimal cross-sectional area should be inversely related to changes in the "true percent stenosis" (percent stenosis calculated with the normal lumen diameter free of diffuse atherosclerosis). Although normal lumen diameter was unknown in these patients, our observations in the few patients with nearly normal vessels suggests this value was somewhere between 7 and 10 mm\textsuperscript{2}. Thus a lesion minimal cross-sectional area of 3.5 mm\textsuperscript{2} represents a 50% to 70% true area stenosis. This critical value associated with an abnormal reactive hyperemic response compares favorably with estimates of percent stenosis altering vasodilator reserve in animal preparations of experimental stenoses.\textsuperscript{9,17,18}

It should be stressed that because our observations were limited to the proximal left anterior descending artery, the critical value of 3.5 mm\textsuperscript{2} should not be applied to other epicardial coronary arteries. Whether or not other segments of the coronary vasculature can be similarly characterized is uncertain. It is possible that variability in the coronary branching pattern from one individual to another is so great that critical values of minimal cross-sectional area associated with abnormal coronary vasodilator capacity cannot be defined for stenoses in distal vessels.

The coronary arteriogram has frequently been used as a gold standard to evaluate the accuracy of a number of noninvasive techniques in detecting the significance of coronary artery disease.\textsuperscript{19-23} In general, these studies have arbitrarily defined significant stenoses as those greater than 50% to 75% diameter narrowings and have considered patients with lesser degrees of stenosis as having insignificant coronary artery disease. These data and those from our previous work\textsuperscript{10} suggest that the design of future studies should be altered. The group of patients considered normal or having insignificant coronary artery disease should comprise only patients with less than 20% diameter stenoses. The group considered as having significant lesions should include only patients with greater than 50% diameter stenoses. In the absence of other acceptable criteria to ascertain the significance of coronary lesions, the group of patients with 20% to 50% lesions cannot be classified as having either significant or insignificant coronary artery disease and therefore should not be included in such studies. In this study we used a technique that provided minimal observer variability. We also included only patients with angiograms of excellent quality suitable for quantitative coronary angiography. It is likely that this range of overlap is substantially greater when more traditional methods of analyzing the coronary arteriogram are used.

Brown-Dodge quantitative coronary angiography, although clearly superior to more traditional methods of analysis of the coronary arteriogram, has certain

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Hypothetical explanation for this study's findings. Both vessels would appear to contain 50% lesions at coronary angiography. The hemodynamic significance of the superimposed lesion on the right is greater than that of the lesion on the left. CSA = cross-sectional area.}
\end{figure}
limitations. Although two views of the lesion are selected for analysis, it is possible that the severity of eccentric, irregular lesions may be underestimated because of improper angulation. Although slitlike eccentric lesions may occasionally preclude accurate assessment of lesion size and severity, previously published data have estimated the frequency of such lesions to range from 5% to 29%. These earlier studies have shown that the majority of lesions are either round or oval in appearance and thus are accurately visualized by the coronary arteriogram.

With the Brown-Dodge quantitative coronary angiographic system, the borders of the lesion are manually traced and digitized by the operator. Identification of the true lumen border requires high-quality, high-contrast angiograms. While this technique is time consuming, the results of our validation studies as well as of the extensive validation studies of Brown et al. and Gould et al. support the accuracy of this method. It is possible that a system of automatic edge detection may facilitate analysis of the coronary arteriogram by quantitative coronary angiography and conceivably improve accuracy.

An estimate of lesion diameter can be obtained from the unprocessed projected cine image, with the catheter tip used as a scaling device. Scoblionko et al. have shown that estimates of lesion diameter obtained with an electronic digital caliper system that uses this approach agree reasonably well with estimates of lesion diameter obtained with Brown-Dodge quantitative coronary angiography. It should be cautioned that this method does not correct for pin cushion distortion or differential magnification of the catheter tip and the vessel, which results when these are different distances from the x-ray source. In our experience, estimates of lesion diameter obtained with the unprocessed cine image and the catheter tip as a scaling device correlate well (r = .94, n = 26) with similar estimates derived from the Brown-Dodge system. However, occasional estimates of lesion diameter vary as much as 0.4 mm.

The Doppler velocity probe used in these studies does not permit the measurement of absolute flow. Use of this device to record reactive hyperemic responses in humans is based on the premise that alterations in coronary velocity parallel changes in coronary flow. The lines of evidence supporting this concept are as follows: (1) phasic coronary velocity and flow tracings are remarkably similar and change in parallel in response to vasoactive stimuli, (2) changes in mean coronary velocity are related closely to changes in coronary flow measured by either timed venous outflow or an electromagnetic flow probe, and (3) the characteristics of reactive hyperemia in coronary circulation of patients as determined by the Doppler velocity probe are similar to those obtained with an electromagnetic flow probe in other large animals. These data therefore suggest that the Doppler system can measure changes in the coronary flow accurately.

There are two factors that might alter the reactive hyperemic response measured by the Doppler velocity probe and result in an overestimation of the hemodynamic significance of a coronary stenosis. Marcus et al. have previously shown that reactive hyperemic responses obtained from vessels supplying hypertrophied ventricles are extremely blunted. To avoid this potential confounding factor, we did not study patients with hypertension, aortic valve disease, mitral insufficiency, or patients with left ventricular hypertrophy by echocardiographic or electrocardiographic criteria. Additionally, the left ventricle was inspected at surgery and the patient was not included in the study if the left ventricle appeared to be hypertrophied.

It is conceivable that coronary collaterals prevented the development of regional ischemia during transient occlusions and thus blunted the reactive hyperemic response. This would have led to an overestimation of the physiologic significance of the coronary stenosis being studied. To avoid this factor we did not study patients with coronary collaterals visible on the coronary arteriogram. That collateral flow is not likely to have played a role in blunting the reactive hyperemic response is supported by previous work by Schwarz et al. These investigators used quantitative coronary angiography to assess the percent diameter stenosis in human beings and found that collaterals did not form in patients with stenoses of less than 90% diameter. None of the 23 patients analyzed in the present study had a percent diameter stenosis greater than 90%.

In conclusion, the present study demonstrates that measurements of percent stenosis, even when determined by quantitative coronary angiography, do not predict the physiologic significance of coronary atherosclerotic lesions ranging from 20% to 60%. In contrast, when vessels of similar expected normal sizes were examined, minimal cross-sectional area more accurately delineated physiologically significant from insignificant lesions.

The findings of this study do not detract from use of percent stenosis to define the significance of lesions when true normal vessel diameter is known. In particular, these findings are not relevant to studies of experimental stenoses performed in animal preparations. Furthermore, if a technology were available that would allow identification of the true normal lumen size in
patients with diffuse coronary atherosclerosis, our ability to differentiate significant from insignificant lesions would be greatly enhanced.

We gratefully acknowledge the technical assistance of Mr. Steven M. Cooper.

References
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*Circulation*. 1984;69:1111-1119
doi: 10.1161/01.CIR.69.6.1111

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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