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Quantitative Coronary Angiography: Measurement of the "Critical" Stenosis in Patients with Unstable Angina and Single-Vessel Disease Without Collaterals

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SUMMARY Quantitative angiographic assessment of proximal coronary artery stenosis was performed in 15 patients with consecutive presentations in two categories defined by clinical and angiographic criteria. Group 1 consisted of 10 patients who had new onset of refractory rest angina and ischemic ST-T changes, but no infarction, single-vessel coronary disease without collateralization, and normal left ventricular (LV) angiograms. Group 2 consisted of five patients who were similar to patients in group 1, but had subendocardial infarction (SEI). Quantitative coronary arteriography, using paired perpendicular angiographic views and digital computation, yielded statistically different lesion dimensions and hemodynamic predictions for the two groups. Minimum stenosis diameters were 0.88 ± 0.14 (SD) and 0.64 ± 0.08 mm, respectively, for groups 1 and 2. This corresponded to 72% and 78% diameter reduction and 92% and 95% cross-sectional area reduction for the two groups. These small dimensional differences among lesions in the two groups resulted in large differences in their hemodynamic impact as predicted from classic fluid mechanics theory. We conclude that there are characteristic lesion dimensions for the isolated "critical" stenosis in these selected patients with rest angina. Further small increases in lesion severity result in SEI. Certain practical applications and limitations of these observations are discussed.

THE TERM "CRITICAL LESION" is commonly used but poorly defined in human disease. Are there, in fact, identifiable characteristics of the "critical" human coronary stenosis? A critical lesion may be

defined clinically as one that results in ischemic symptoms at rest, or physiologically as one that permits only marginally sufficient levels of myocardial perfusion in the basal state. Various clinical and experimental reports have contributed to our understanding of the degree of coronary constriction necessary to impair normal basal myocardial perfusion.¹⁻¹⁸ In spite of this information, the relationship between symptoms of coronary disease and the magnitude of stenosis is widely known to be inconsistent.¹⁹⁻²¹ For example, patients with total obstruction of a large coronary branch sometimes have enough collateral development to preserve both ventricular function and the asymptomatic state. Conversely, patients with variant angina²² may have only minimal atherosclerosis.²³ Thus, one might anticipate similar inconsistencies in

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attempting to characterize the coronary lesion responsible for ischemia at rest. One experiment of nature does occur relatively rarely to provide us with a clinical model that resembles the isolated experimental coronary constriction. This is the patient with recent onset of exertional angina that rapidly progresses to refractory intermittent rest pain who, on angiography, has proximal single-vessel stenosis, an apparently normal left ventricular contractile pattern, and no evidence of collateral development.

This report describes the analysis of lesions in such patients using a computer-based technique. To avoid the variability and error associated with visual interpretation of the coronary angiogram,²⁴⁻²⁶ we have developed a method²⁷ that generates a true-scale, three-dimensional representation of a diseased coronary segment with $\pm 150\mu$ dimensional accuracy and $\pm 4\%$ variability on estimates of percent stenosis. By this technique, the isolated stenosis in patients with rest angina, no infarction, and no collateral development has been shown to have consistent dimensional characteristics. And in a group of similar patients with associated subendocardial myocardial infarction, a slightly but significantly greater stenosis has been identified.

Methods

Quantitative Angiography

Fifteen patients presented clinically with angina at rest, refractory to medical therapy. Each had single-vessel disease. The 15 stenotic arterial segments were analyzed using a newly developed, digital computer method.²⁷ We obtained coronary cineangiograms in routine fashion using Judkins technique in multiple projections, including cranial angulation projections. For each left anterior oblique (LAO) projection, we filmed a perpendicular right anterior oblique (RAO) projection. For example, a perpendicular pair might be a 60° LAO and a 30° RAO. Our radiographic equipment is the General Electric Fluoricon 300 system, operating at less than 7 msec/frame, 70-120 kV maximum. Individually adjusted film processing²⁸ results in high-contrast images, as shown in figure 1. Cine frames were selected from the perpendicular pair of projections that showed the lesion most clearly. For each of the two views, frames were selected at end-systole, end-diastole and midcycle. These frames were projected at about fivefold arterial magnification onto a large screen marked off in x,y coordinates.

Three trained observers separately traced the out-

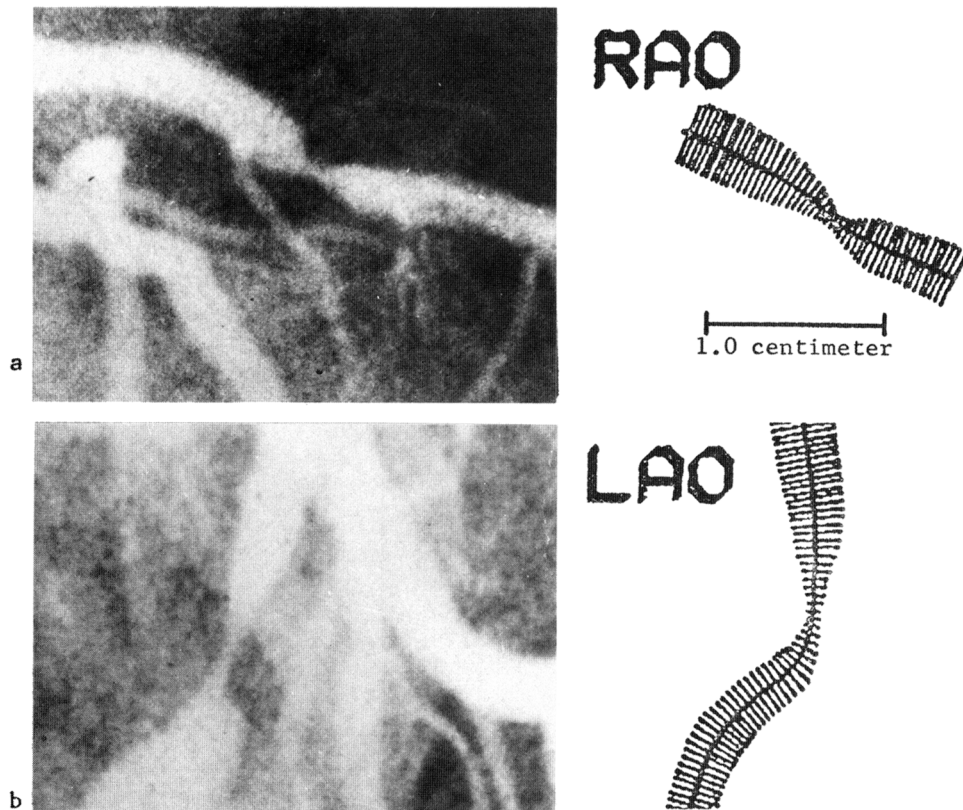


FIGURE 1. Examples of highly magnified areas from angiographic frames showing the diseased arterial segments analyzed. Considerable image clarity was lost in preparing this illustration. A) Example of a lesion from a patient in group 1 (unstable angina) selected because its calculated dimensions were closest to the group 1 average. On the left is the magnified lesion image; on the right is the computer representation of the lesion. B) Example of the average group 2 lesion (subendocardial infarct) and its digital representation. Kodak 2474 35-mm cine film was used. All images are at the same scale, or given. RAO = right anterior oblique; LAO = left anterior oblique.

line of the magnified, projected lesion image from the selected frame pairs. The diseased arterial segment was traced from the "normal" proximal to the "normal" distal portion. A traced section of the catheter tip, of known dimensions, provided a scaling factor. These traced images were transmitted, using a digitizer, to a PDP 11/45 computer. The computer program reduces the lesion image to true scale by compensating for pincushion distortion, x-ray beam divergence and magnification. These true-scale images from the two perpendicular projections were then matched along their center lines. This combination of data from the perpendicular projections allowed a three-dimensional characterization of the diseased arterial segment. Figure 2 shows the hard-copy computer printout of a typical processed lesion. The segments are displayed as they would appear in true scale in each of the two perpendicular projections, LAO and RAO. Matched portions of the two views are mathematically stretched out to true length in the center panels. The computer determines the length of the lesion as the distance between the two points which are 10% reduced in cross-sectional area from the normal proximal and distal areas. From these data, the computer calculates and prints vessel diameter and cross-sectional area (assuming an elliptical cross sec-

tion) in the "normal" proximal and distal portions, and at the point of maximum narrowing. Percent diameter and area stenosis are calculated according to the formulas of figure 3. More complex geometric functions of the lesion are estimated, including atheroma mass and flow resistance. Resistance is estimated assuming fully developed flow in the converging portion of the lesion and turbulent flow in the diverging portion. A pressure drop across the lesion may be predicted by multiplying the estimated resistance by a selected flow value.

Since the lesions from each of these patients were traced by three independent observers at three different points in the cardiac cycle, each lesion dimension represents an average of nine repeated measurements. The variability of repeated measurements for a given lesion was small. For example, the average standard deviation of the minimum diameter estimate among the 15 lesions was 103 μ .

Patients

Fifteen patients who underwent cardiac catheterization for symptomatic coronary artery disease presented with one of two clinical syndromes: 1) unstable angina with medically refractory rest pain, or

U1 SU1 GS					CATH. DATE: 8-13-76	
IS THIS THE CRITICAL LESION?					REPORT DATE: 15-MAY-76	
CATH TIP TYPE IS 7 FR, SIZE IS 2.30 MM.						
	PROXIMAL	DISTAL	MINIMUM	STEN.	ATHEROMA	
LAO (MM)	3.347	2.832	1.008	67.4%	LENGTH =	10.197 MM ³
RAO (MM)	3.254	2.577	0.814	72.1%	MASS =	30.2608 MM ³
AREA (MM ²)	8.554	5.732	0.709	90.1%	MASS/LENGTH =	2.9676
RESISTANCE (MMHG/CC/SEC) = 2.4106 (Poiseuille)						
RESISTANCE/LENGTH = 2.3639 RESISTANCE RATIO = 14.4354						
FLOW (CC/SEC)	ORIFICE RES.		TOTAL PRESSURE DROP (MMHG)			
1	7.3643		9.7748			
2	14.7286		34.2781			
3	22.0929		73.5100			

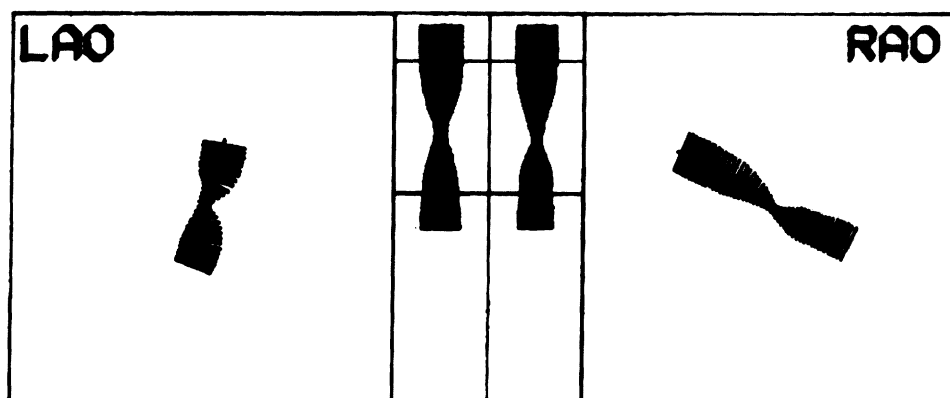
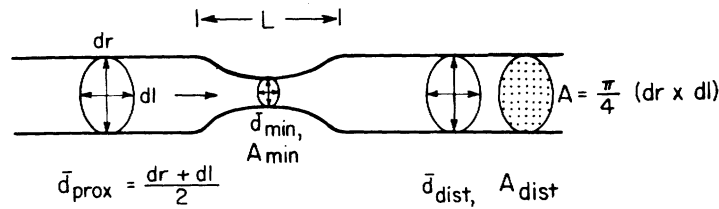


FIGURE 2. Example of the hard-copy computer printout of the lesion analysis of a typical group 1 (unstable angina) patient. Diameters of approximately 3 mm were measured in the normal portions of the vessel. In the left anterior oblique (LAO) projection, the minimum lumen diameter (d_{min}) in the stenosis is 1 mm, a 67% reduction from its averaged normal diameters (%DS). The minimum cross-sectional lumen area (A_{min}) is 0.71 mm², a 90% reduction from the averaged normal areas (%AS). Lesion length is 10.2 mm. The Poiseuille resistance (R_p) is 2.4 mm Hg/ml/sec. The turbulent (orifice) resistance (R_t) is calculated for a range of flow values. The predicted pressure drop across the stenosis is thus 9.8 mm Hg for 1 ml/sec flow, 34 mm Hg for 2 ml/sec flow, and so on. RAO = right anterior oblique.



$$\% \text{ DIAMETER STENOSIS} = \left(1 - \frac{2 \bar{d}_{\min}}{\bar{d}_{\text{prox}} + \bar{d}_{\text{dist}}} \right) \times 100$$

$$\% \text{ AREA STENOSIS} = \left(1 - \frac{2 A_{\min}}{A_{\text{prox}} + A_{\text{dist}}} \right) \times 100$$

	No MI	SEI
\bar{d}_{\min} (mm)(\pm S.D.)	.88 \pm .14	.64 \pm .08
% DIAM. STENOSIS	72 \pm 5	78 \pm 3
LENGTH (mm)	14 \pm 6	15 \pm 3
A_{\min} (mm ²)	.63 \pm .19	.35 \pm .11
% AREA STENOSIS	92 \pm 3 (n=10)	95 \pm 2 (n=5)

2) subendocardial myocardial infarction (SEI) with persistent refractory rest angina. Patients with ST-segment elevations on the ECG during rest pain were excluded from both groups. All patients were male veterans. None had had previous bypass surgery. Patients with each of the above clinical presentations who also fit the angiographic criteria described below represent consecutive cases of each syndrome studied in the Wadsworth VA Hospital's cardiovascular diagnostic laboratory during the periods given. Group 1 consisted of 10 patients who underwent catheterization between October 1972 and November 1977 (mean age 52 years; range 38–61 years) with 1) recent onset of exertional angina whose severity had progressed rapidly to refractory rest pain unresponsive to medical therapy, with localizing ischemic ST-T changes on the ECG and no evidence of a previous myocardial infarction. The average interval between onset of angina and arteriography was 3 weeks; 2) single-vessel coronary artery disease without collateral development; 3) apparently normal wall motion on left ventricular (LV) angiograms. Group 2, who underwent catheterization between March 1974 and December 1977, consisted of five patients (mean age 51 years; range 42–60 years) similar to patients in group 1, but who had ECG or enzymatic evidence of a subendocardial infarction (i.e., persistent T-wave inversion for longer than 72 hours without new q waves and/or CPK elevation > 111 IU/ml (upper limit of normal for our laboratory), but < 360 IU/ml. Three of these five patients had very mild segmental hypokinesis in the LV angiogram. All 15 patients of groups 1 and 2 were studied during their clinical syndrome of intermittent rest pain.

In group 1, eight patients had left anterior descend-

FIGURE 3. Calculated values (\pm SD) for minimum lesion diameter (d_{\min}), percent diameter stenosis, lesion length (L), minimum lesion cross-sectional area (A_{\min}) and percent area stenosis for each of the three clinical groups. Diameters are calculated as the average from the two views (e.g., see formula for \bar{d}_{prox}). L represents the computed distance between the two apparently normal portions of the vessel. The length of the most severely narrowed portion of the stenosis was generally much shorter than the overall length. Local cross-sectional area is computed assuming that the vessel is elliptical in cross section, with major and minor axes (dr and dl) determined from the two angiographic views (e.g., see formula for A). We defined d_{\min} as the average of the two minimum values determined from the two views. A_{\min} is the minimum value of A, determined by computer search along the lesion axis. MI = myocardial infarction; SEI = subendocardial infarction; dist = distal; prox = proximal.

ing (LAD) lesions, one patient had a dominant left circumflex, and one had a right coronary artery (RCA) lesion. In group 2, four patients had LAD lesions and one patient had an RCA lesion.

Results

Figure 2 presents typical values for group 1 patients. Table 1 summarizes the data for both groups, and presents the statistical comparison. Figure 3 shows the mean minimum lumen diameter (d_{\min}), percent diameter stenosis (%DS), minimum cross-sectional lumen area (A_{\min}), percent area stenosis (%AS), and length of lesions in both groups. The mean local diameter was averaged from the two perpendicular views. Table 1 shows that there were significant differences in d_{\min} between the two groups ($p < 0.01$). There were also significant differences in %DS. In group 1 patients, the mean d_{\min} was 0.88 \pm 0.14 mm (SD), a 72% diameter reduction. Group 2 patients had a mean d_{\min} of 0.64 \pm 0.08 mm, a 78% diameter reduction. The mean lesion length in group 1 was 14.4 \pm 5.5 mm; in group 2 it was 15.3 \pm 3.1 mm.

Average local cross-sectional area is calculated assuming that the vessel is elliptical in cross section. The local diameters determined from the two angiographic views were used as the major and minor axes of the ellipse. As shown in table 1, there were significant differences in A_{\min} between the two groups. The mean A_{\min} was 0.63 \pm 0.19 mm² (SD) in group 1, and 0.35 \pm 0.11 mm² in group 2. There were also significant differences in %AS.

Resistance to flow through the stenosis was calculated according to classic theory for steady flow.

TABLE 1. Averaged Determinations of Lesion Geometry and Derived Resistance and Pressure Functions for Each of the Patient Groups

	Geometric determinations				Derived functions				
	D _{min} (mm)	%DS	A _{min} (mm ²)	%AS	Length (mm)	Atheroma mass (mm ³)	R _p (mm Hg/ml/sec)	R _t (Q = 1) (mm Hg/ml/sec)	ΔP (Q = 1) (mm Hg)
Group 1 n = 10	0.88 ± 0.14 (0.69–1.07)	72 ± 5.3% (62–81%)	0.63 ± 0.19 (0.99–0.94)	92 ± 3% (87–97%)	14.4 ± 5.5 (7.9–22.6)	54 ± 29 (23–120)	5.3 ± 2.8 (2.4–10.3)	11.4 ± 7.7 (3.3–24.8)	16.6 ± 9.5 (7.1–31.9)
Group 2 n = 5	0.64 ± 0.08 (0.53–0.73)	78 ± 2.9% (76–83%)	0.35 ± 0.11 (0.22–0.51)	95 ± 1.6% (93–97%)	15.3 ± 3.1 (10.7–18.9)	52 ± 18 (31–78)	13.7 ± 2.7 (10.4–16.4)	37.8 ± 24.2 (14.1–76.6)	50.2 ± 24.4 (27.5–87.1)
Statistical comparison									
(group 1 vs group 2)	†	*	†	*	NS	NS	†	†	†

Values are given as mean \pm SD. Values in parentheses represent the range.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.005$.

Abbreviations: D_{min} = minimum lumen diameter; %DS = percent diameter stenosis; A_{min} = minimum cross-sectional lumen area; %AS = percent area stenosis; R_p = Poiseuille resistance; R_t = turbulent resistance; ΔP (Q = 1) = estimated stenosis pressure based on hypothetical stenosis flow of 1 ml/sec.

The formulas and the hemodynamic estimates based on those calculations for each group are shown in figure 4. The Poiseuille resistance (R_p) is an integrated function, independent of flow, and proportional to lesion length, viscosity and the inverse fourth power of diameter. Significant R_p differences existed between the two groups (table 1). Turbulent resistance (R_t) is an estimate of energy dissipation in the turbulent deceleration process distal to the lesion. It is similar in form to the Gorlin estimate for valvular stenosis,²⁹ being proportional to flow, fluid density and, approximately, to the inverse second power of minimum area in the stenosis. Significant R_t differences existed between groups 1 and 2.

The loss of pressure (ΔP) across the stenosis, which is a physiologically important consequence of luminal narrowing, can be estimated by multiplying stenosis resistance by stenosis flow. Unfortunately, we cannot accurately estimate the stenosis flow from angiographic or other clinical data. In order to predict ΔP , we used the hypothetical value of Q = 1.0 ml/sec (60 ml/min). This value is probably somewhat less, in these patients, than the generally accepted normal myocardial flow requirement, approximately 80 ml/min/100 g,¹⁴ but is probably not much more than 40 ml/min/100 g necessary to maintain contractile function.¹³ The estimate of ΔP for group 1 patients was 17 mm Hg (table 1); for group 2, it was 50 mm Hg. There were highly significant differences between groups 1 and 2 in ΔP estimated by this method (table 1).

Two patients whose ΔP (Q = 1) values were the highest in group 1 (31.9, 30.8 mm Hg) and whose minimum areas were least (0.39, 0.37 mm²) progressed to a documented anterior subendocardial infarction 12 hours and 33 days after catheterization.

Discussion

We have attempted to identify quantitatively the features of the isolated "critical" coronary stenosis in a well-defined subset of patients with coronary disease. From the clinical perspective, a critical stenosis may be defined as one resulting in frequent angina at rest. From the physiologic perspective, a critical stenosis may be defined as one diminishing segmental myocardial perfusion below the basal requirement. The magnitude of relative flow reduction necessary to cause symptomatic ischemia is not well-defined, although ischemic contractile abnormalities appear at about 50% of basal flow.¹³ Factors that determine coronary flow limitation include the narrowness and length of the stenosis (and other geometric factors), blood viscosity, arterial pressure, collateral development, and the capacity of the peripheral bed to autoregulate. The coronary flow requirement further depends on the mass of viable myocardium beyond the stenosis, heart rate and contractility. With such a complex interaction it is not surprising that there is little agreement on the nature of the "critical" stenosis. For example, May et al.¹⁸ produced uniform stenoses 10 mm long in canine iliac arteries and showed that

$$R_p = \sum_{i=a}^w 15\mu \frac{(dr_i^2 + dl_i^2)}{(dr_i^3)(dl_i^3)} \Delta Z_i$$

$$R_t = \frac{pQ}{0.266} \left(\frac{1}{A_{\min}} - \frac{1}{A_w} \right)^2$$

$$\left. \begin{array}{l} R_p \\ + \\ R_t \end{array} \right\} = R \quad \boxed{\Delta P = Q \cdot R}$$

	No MI	SEI
R_p [mmHg/cc/sec]	5 ± 3	14 ± 3
R_t " " "	11 ± 8	38 ± 24
$\Delta P_{Q=1}$ [mmHg]	17 ± 10	50 ± 24

FIGURE 4. Hemodynamic predictions for lesions in each of the two clinical groups. Calculations are based on classic fluid mechanics theory for steady flow. Flow is assumed to be laminar and fully developed in the converging portion of the lesion, and to "separate" from the luminal surface in the diverging portion, forming large-scale eddies whose turbulent energy is dissipated during the deceleration process. Poiseuille resistance (R_p) represents energy dissipation due to viscous forces. Turbulent resistance (R_t) represents energy losses due to eddy formation and dissipation in the diverging, distal portion of the lesion. R_t is computed based on an hypothetical flow of 1 ml/sec. $\Delta P_{Q=1}$ is the estimated pressure loss across the stenosis for an hypothetical flow of 1 ml/sec. MI = myocardial infarction; SEI = subendocardial infarction; dr and dl = major and minor axes.

flow and distal pressure were not reduced until an 85% area reduction (i.e., a 61% diameter reduction) was present.

Increasing degrees of stenosis resulted in precipitous drops in flow and distal pressure. Their numbers correspond fairly well to those measured in our group 1 patients when differences in length are considered. Gould et al.,¹⁶ using highly localized wire-noose constrictors of canine coronary arteries, showed that resting flow measurements did not decrease until there was an 85% "diameter" reduction, although the hyperemic response to contrast media (the coronary reserve) began to decrease at 60% "diameter" reduction. These authors point out that percent reduction of the outer arterial circumference may not linearly reflect the reduction in lumen diameter; thus, the 85% figure is somewhat difficult to interpret angiographically. In addition, the length of their artificially created lesions was much shorter than that of clinically observed stenoses. Thus, 85% could well be an overestimate of the severity of the "critical" stenosis.

Asokan et al.,¹⁶ using ^{86}Kr washout to measure flow in human coronary arteries and angiographic estimates of disease severity, showed that $\geq 90\%$ lumen

diameter reduction resulted in a "critical" decrease in coronary blood flow, and that "significant" but less severe lesions (50–90%) had normal flows. This study was subject to the reported difficulties with the ^{86}Kr technique and to the subjective tendency to overestimate the severity of the stenosis from the angiogram³⁰ (see below). Our group 1 category was defined to select patients with "critical" stenosis. In these patients with medically refractory unstable angina and proximal single-vessel disease without infarction or evident collateralization, the lesion under consideration threatened the total flow available to a defined, fully viable segment of the left ventricle. It appears that the stenosis necessary to produce this syndrome is 0.9 mm in minimum diameter and 0.6 m^2 in minimum area, with an overall length of 14 mm. This represents a 72% reduction in diameter and 92% area reduction. Further increased narrowing of the coronary artery was associated in five cases with subendocardial infarction.

The characteristic lesion parameters in our patients with symptomatic single-vessel disease show considerably less variability than the results of Rafflenbeul et al.,³⁰ who reported coronary constrictions ranging from 30–80% diameter reduction in "symptomatic" patients with single-vessel disease. However, the clinical symptoms of their patients were not defined. For example, in variant angina, a relatively mild coronary stenosis may be associated with ischemic symptoms,²² and this clinical presentation was excluded from our analysis. Furthermore, while these investigators used an objective, "morphometric" technique, they analyzed only a single angiographic projection. This can result in a considerable error in measuring the degree of constriction, as lesions are often narrower in one projection than in others.

Interpretation of the finding of characteristic lesion dimensions in these two coronary syndromes requires certain qualification. The minimum lumen diameter necessary to cause arterial flow reduction depends in part on the mass, and thus the metabolic requirements, of myocardium distal to the stenosis. Although a 0.9-mm lumen diameter in the proximal LAD or dominant RCA may cause unstable angina, it is a nearly normal measurement in a small diagonal or marginal branch, and yet it may be incompatible with life in the left main coronary artery. Thus, arteries with different flow loads will have different dimensions of critical stenosis or, more appropriately, different critical resistances. Our stenosis dimensions show little variability in these two coronary syndromes because, in part, these diseased LAD and dominant RCAs perfused approximately similar myocardial beds.

Despite the general unavailability of computer-based systems for quantitative angiography, there is certain clinical utility in the above information. First, quantitative methods may become more widely available. Our telephone link to the Seattle PDP 11/45 computer by means of a video terminal and digitizer is accurate, relatively inexpensive (about

\$15,000 in equipment), and technically reliable with commercially available hardware. Analysis of a given lesion takes about 20–25 minutes of operator time. For this reason, we continue to regard this as a clinical research technique.

Second, the complexity of these measurements does not diminish their validity. They may be compared to reasonably accurate estimates which can be made simply from measurements of lumen dimensions in magnified, projected views of a lesion. Using the known catheter diameter for scale, dimensional errors due to uncorrected angiographic distortion will seldom exceed 15%. Such direct measurements of minimum diameter and percent stenosis would provide an estimate of how nearly critical a given lesion is. For example, a 2-mm narrowing in a 4 mm, dilated RCA is certainly not flow-limiting and should not be bypassed at surgery, even though it represents a 50% stenosis. And if intermittent ischemia is demonstrated in the distribution of this lesion, the possibility of a coronary vasospastic disorder should be considered. In two of our patients, minimum LAD stenosis diameters of 0.7 mm were predictive of impending subendocardial infarction.

Third, these measurements define the minimum catheter tip diameter necessary for percutaneous transluminal coronary angioplasty³¹ in patients with unstable angina as 0.5 mm.

Fourth, the expressions of figure 4 provide a conceptual framework for our understanding of the hemodynamic impact of coronary lesions. In theory, the pressure loss across a moderately severe stenosis is estimated by a relationship of the form^{17, 18, 32–34}

$$\Delta P = \frac{k_1 Q + k_2 Q^2}{d_{\min}^4}$$

where ΔP is the pressure drop across the stenosis, Q is flow, d_{\min} is the minimum stenosis diameter and k_1 and k_2 are constants based on blood viscosity and density, lesion length and shape, and certain flow assumptions. In these patients, k_2 was more than twice k_1 . The theoretical resistance expressions of figure 4 are based on classic fluid mechanics. While they remain to be validated in comprehensive studies, they have predicted accurately the Poiseuille and turbulent contributions to stenosis resistance in the basal state in high-instrumented, unanesthetized dogs (Gould KL, Brown BG: preliminary observations).

Fifth, these measurements further illustrate our tendency to overestimate the severity of stenosis from the angiogram.³⁰ These lesions were graded clinically by experienced cardiac angiographers upon review of the coronary cineangiograms. Lesions which were graded as $87 \pm 5\%$ (SD) in the 10 group 1 patients were measured at $72 \pm 5\%$. In the five group 2 patients, lesions graded as $96 \pm 2\%$ measured $78 \pm 3\%$. We have found that the subjective visual interpretation of "percent stenosis" correlates fairly well with percent diameter reduction for mild and moderate stenosis, but with the percent area reduction for severe stenosis.

These measurements support the hypothesis that atherosclerotic progression of coronary artery stenosis

results in a clinical progression from ischemia to subendocardial infarction. Even more severe coronary narrowing is found in association with transmural infarction.³⁵ Various other etiologies of unstable angina have been proposed, such as platelet emboli,^{36–38} arterial spasm,³⁹ or hemorrhage into an ulcerated plaque.^{40–43} Our measurements do not exclude these mechanisms; they suggest, however, that in the patient with atherosclerotic heart disease and lacking collaterals, the major determinant of the severity of ischemia is the degree of luminal narrowing. Other factors such as coronary arterial constriction, transient microthrombus formation, or increased inotropic or chronotropic state could induce small perturbations in the oxygen supply-demand balance. In the setting of severe stenosis these would result in intermittent clinical manifestations of ischemia.

These measurements were purposely restricted to a highly specific subset of patients. Attempts to extrapolate these results to the broad spectrum of patients with ischemic heart disease are to be undertaken with caution, except as discussed above. The "typical" patient with coronary disease may have multiple stenoses, collateral development, previous myocardial necrosis, and compensatory myocardial hypertrophy, all of which can alter dramatically the relationship between lesion severity and the clinical manifestations of ischemia.

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