

Quantitative Coronary Angiography to Measure Progression and Regression of Coronary Atherosclerosis

Value, Limitations, and Implications for Clinical Trials

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There have been five primary prevention trials of which the purpose was to determine whether reducing hypercholesterolemia would also decrease the incidence of coronary heart disease (CHD).¹⁻⁵ Two were dietary studies, and three were pharmacological studies. Although there were inconsistencies in the findings among the trials, largely due to differences in design and method of intervention, each demonstrated significant reduction in the incidence of CHD, particularly CHD morbidity, although none showed a convincing reduction in total mortality. However, there is evidence to suggest that a synergistic effect occurs when interventions are combined, especially when one intervention is aimed at reducing hypercholesterolemia. For instance, the Oslo Heart Study showed an impressive reduction in CHD morbidity and mortality in previously healthy men with the combined interventions of reducing cigarette smoking and lowering serum cholesterol levels by diet.⁶

Very recently, three trials showed, using repeated coronary angiography, that cholesterol lowering was associated with less progression of coronary artery disease and that the frequency of regression of lesions was increased.⁷⁻⁹ The establishment and successful conduct of new primary prevention trials of the effectiveness of lowering hypercholesterolemia are very expensive and complex. Therefore, one of the most important questions now facing the medical and scientific community is whether it is possible to show that significant regression of coronary atherosclerotic lesions can be achieved by new and more powerful interventions that reduce

high concentrations of low density lipoprotein and of triglycerides or that increase low concentrations of high density lipoprotein. It is particularly important to be able to prove with conviction that a new pharmacological (or dietary) measure, such as HMG Co-A reductase inhibitor, aimed at reducing hypercholesterolemia prevents the progression of coronary atheromatous lesions and, hopefully, causes regression of existing lesions. The acquisition of convincing evidence to this effect will make it probable that the regimen under test will also reduce the clinical manifestations of CHD. However, this is not axiomatic because other very important mechanisms leading to clinical manifestations, such as thrombosis, may continue relentlessly.

Ideally, we would like to know whether all newly introduced interventions are able to reduce CHD morbidity and mortality, but the cost of such prospective studies is prohibitive. There is, therefore, a pressing need to identify a method that can reliably evaluate a different, possibly softer, end point. Coronary angiography is the obvious candidate, even though it tests only one part of the overall pathophysiology of CHD. It allows us to assess the impact of the process of atherosclerosis on the lumen of the coronary artery and to establish over time whether an intervention attenuates progression or regression of atherosclerotic disease. Computer-assisted assessment of progression or regression of coronary artery disease is currently the only acceptable method to study the efficacy of such interventions, but even this technique has inherent limitations and difficulties related to interpretation of the angiographic information. This article reviews the value, limitations, and implications for clinical trials that use quantitative coronary angiography to measure progression or regression of coronary atherosclerosis.

Pathophysiological Aspects of Coronary Atherosclerosis and Limitations of Quantitative Coronary Angiography

Coronary angiography has been used as a diagnostic tool for more than 25 years. Visual interpretation of

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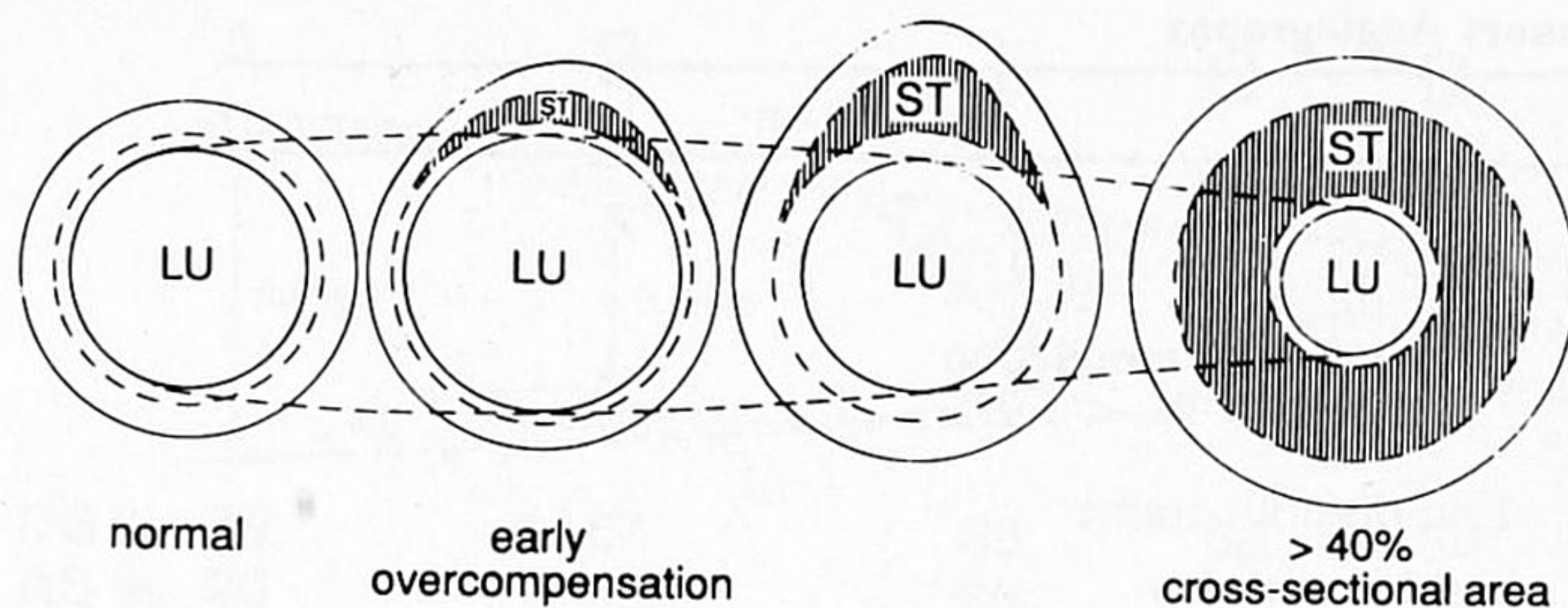


FIGURE 1. Diagram of the sequence of luminal changes during the development of an early lesion to a severe atherosclerotic plaque. LU, lumen vessel; ST, stenosis; dashed circle, internal elastic lamina. (Adapted with permission^{26,28}).

coronary angiograms has its acknowledged limitations,¹⁰⁻¹³ and results of intervention trials based on visual interpretation should be interpreted cautiously.

If all patients with manifestations of clinical CHD had one isolated lesion in one coronary artery, the problem of demonstrating that there was no progression or even regression of that lesion after a period of treatment for hypercholesterolemia would be simple. But this is not the case. Most patients have a number of lesions in a number of coronary arteries. These lesions are variable in obstruction, distribution, and pathological composition.

Although quantification of coronary artery disease with a computer-assisted analysis is a major step forward compared with visual assessment, the interpretation of the computed measurements is not as straightforward as one would wish or expect and may easily lead to erroneous conclusions. After all, coronary angiography is nothing more than a two-dimensional shadowgram of an opacified vessel. It merely demonstrates the effect of arterial wall disease on the contour of the arterial lumen, and the underlying pathological process can be identified only by inference. The use of coronary angiography to measure progression or regression of atherosclerosis is based on the assumption that a change of volume of the atherosclerotic plaque will have an effect on the size and shape of the contrast-filled lumen. However, atherosclerotic changes of the arterial wall are not reflected precisely enough by changes in the lumen.

Many studies¹⁴⁻²² have shown that coronary angiography frequently underestimates the severity of coronary artery lesions or even misses significant narrowings. The major reason appears to be the diffuseness of the atherosclerotic process. Diffuseness of the atherosclerotic process will narrow the entire lumen of a segment of a vessel smoothly and evenly, and angiography is unable to detect its existence. When the caliber of the arteries is unexpectedly small, diffuse coronary atherosclerosis can only be inferred, and angiographic quantification is impossible. Underestimation of coronary arterial stenosis at clinical arteriography also has been explained by inadequate radiological views of crescentic or slit-shaped lumens.²³⁻²⁵ However, a recent, carefully performed postmortem study showed that it is no longer correct to assume the existence of a crescentic or slitlike lumen and that most stenotic lesions result in circular, elliptical, or D-shaped lumens.¹⁸ Depending on the radiological view, elliptical or D-shaped

lumens not only result in underestimation of stenosis, but they may also result in serious overestimation.

Recently, compensatory enlargement of human atherosclerotic coronary arteries was shown to occur during the early stages of plaque formation.²⁶⁻²⁸ Compensatory enlargement results in preservation of a nearly normal lumen cross-sectional area so that angiography severely underestimates or is unable to detect early stages of coronary atherosclerosis. Glagov et al²⁶ showed that increases in artery size parallel increases in intimal plaque in the human left coronary artery that prevent a decrease in lumen caliber until the plaque occupies about 40% of the internal elastic lamina area (Figure 1). Progression of disease beyond the 40% resulted in narrowing of the lumen, and only then is angiography able to detect progression of coronary artery disease. The phenomenon of compensatory enlargement also has been shown in the left anterior descending coronary artery, the right coronary artery, and the proximal circumflex coronary artery.²⁸ This issue is further complicated by the finding that small plaques (early lesions) were associated with a larger-than-normal lumen area, suggesting that overcompensation of the artery may have occurred in the very initial phase of disease.²⁷ Angiographically, this compensatory widening of the lumen would be misinterpreted as regression of atherosclerotic disease. Also, in advanced atherosclerosis, the media has been shown to undergo striking atrophy beneath atheromatous plaques so that the vascular lumen tends to be preserved.²⁹

Furthermore, processes other than atherosclerotic changes such as arterial spasm, intimal dissection, thrombosis, or embolism that may cause abnormalities on the angiogram cannot always be distinguished angiographically from atherosclerosis.

Sources of Error Related to Quantitative Coronary Angiography

To obtain adequate films, brisk injection of up to 10 ml dye is needed because the concentration of contrast medium is an important determinant of vessel edge resolution. Also, certain technical considerations such as magnification, tube, voltage, film type, and frame exposure time must be adjusted to optimize the contrast and the signal to quantum noise and to minimize motion blur.

The various sources of errors, related to the patient, the technique, the methodology, and the at-

TABLE 1. Sources of Error Related to Quantitative Coronary Angiography

Sources of Errors	Prevention
Patient related	
Patient size	...
Vasomotor tone	Standardized vasodilation
Vessel motion (blurring)	
Cardiac	End-diastolic-frame
Respiratory	Held inspiration
Cyclic variation in diameter	End-diastolic-frame
Geometric considerations	
Vessel curvature, stenosis irregularity, relation to other vessels or branches	Many projections
Technique related	
Difference of x-ray gantry setting between first and second film	On-line annotation of x-ray gantry settings
Foreshortening	X-ray gantry setting: object of interest parallel to image intensifier
Insufficient mixing of contrast	7F catheter, big bolus injection, with blood pump triggered isoviscous, isoosmolar contrast
Pincushion distortion	Lesion or segment of interest centrally located
Methodology related	
Fully automated versus computer-assisted	No or minimal observer interaction
Edge-detection algorithm	1-derivative: overestimation 2-derivative: underestimation weighted sum 1st and 2nd derivative: precise
Definition of normal	Interpolated method
Calibration technique	Catheter tip caliper measurement
Pincushion distortion	Correction for each particular image intensifier

tempts to correct these, are listed in Table 1.^{30,31} The most important are potential differences in vasomotion, or unequal x-ray gantry settings between the two films, and the problems with the exact calibration, or with pincushion distortion. Differences in vasomotion should be avoided by standardization of vasodilation by the routine administration of a standard dose of nitroglycerin before each angiogram is obtained. Important coronary artery segments or lesions must be visualized in radiographic projections that are roughly perpendicular to their epicardial planes. This requires different views to obtain maximal information and not to miss lesions or vessel areas with diffuse atherosclerosis. Obviously, segments or lesions of interest should not be analyzed from projections that are foreshortened.

Coronary contrast catheters have been used increasingly for calibration in the quantitative assessment of coronary arterial dimensions. It should be realized that the size of the catheter as given by the manufacturer may deviate from its true size, especially disposable catheters. Therefore, it is advisable to measure the actual size of the catheter with a micrometer after the catheterization procedure.³² Also, use of woven Dacron, polyvinylchloride, or polyurethane catheters are recommended because they provide an image quality superior to that of a nylon catheter.³² Pincushion distortion is the selectively increased magnification of objects viewed in the periphery of the angiographic field. This may also

introduce a substantial error in dimensional estimates and, if not corrected, may have an intolerable effect on the absolute dimensional estimates.

Value of Quantitative Coronary Angiographic Measurements

Visual analysis of the angiogram only provides us with relative measurements of narrowings. Quantitative coronary angiography provides, in addition to relative measurements (which otherwise are more reliably obtained with quantitative coronary angiography than with visual analysis), absolute measurements (in mm) and "functional" measurements (pressure gradient across stenosis or stenosis resistance).

Relative measurements. Relative percent diameter stenosis is commonly used as a measure of stenosis severity, but a number of important problems arise with these relative measurements.¹³⁻¹⁵ First, they do not accurately reflect the functional significance of a coronary lesion because they fail to account for other geometric-anatomic lesion characteristics such as lesion length and absolute diameters of diseased and normal segments.^{13-15,33-39} For instance, a 50% narrowing in a vessel with a diameter of 4 mm has a totally different hemodynamic impact than a 50% narrowing of a vessel with a 2-mm diameter.

Second, the relative diameter is usually determined by comparing the diameter at the site of maximal reduction with the diameter in adjacent

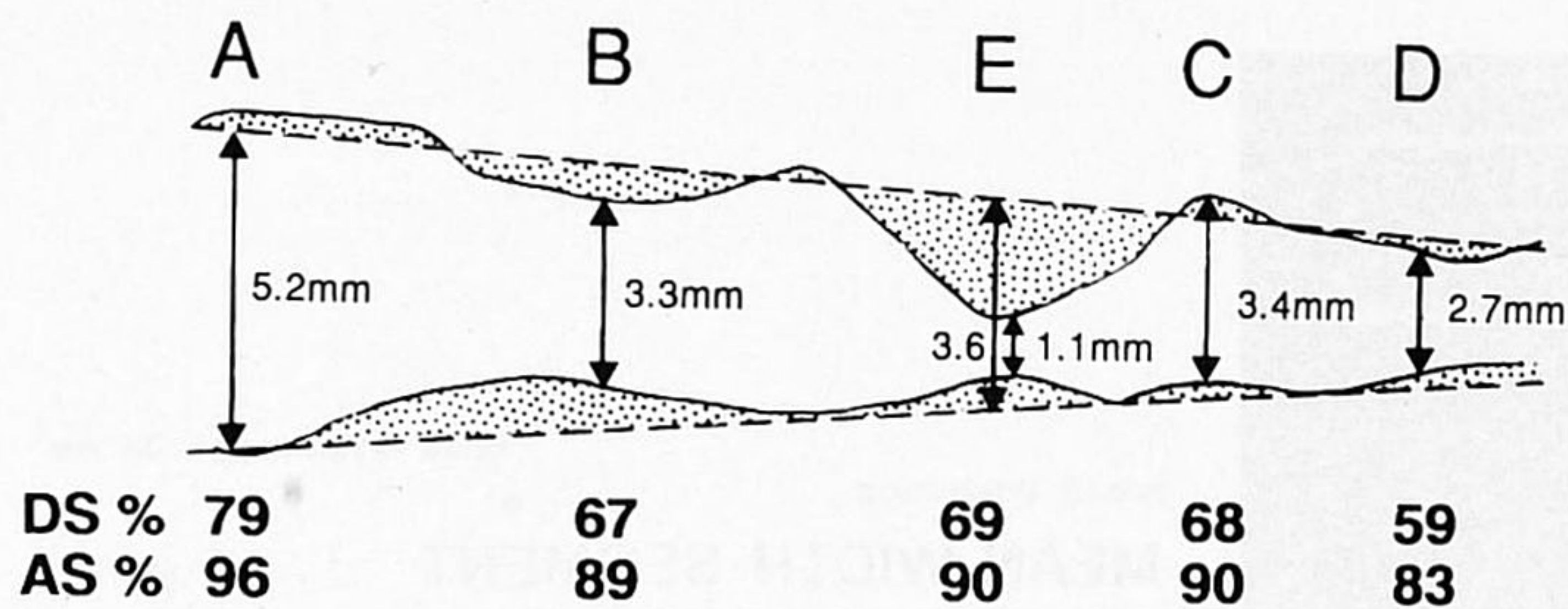


FIGURE 2. Diagram of influence of determining reference area in a tapering vessel with diffuse atherosclerosis on relative percent diameter (DS) and area stenosis (AS).

areas that appear either normal or only minimally diseased. Therefore, these measurements are highly dependent on the diameter of the reference area. In cases with focal obstructive disease and a proximal nondiseased angiographic area, the determination of a reference area is simple and straightforward. However, the nearby "normal" portion of the vessel lumen, the diameter of which forms the denominator of the percent stenosis estimate, may be dilated by the aging process⁴⁰⁻⁴² or by poststenotic turbulence,^{43,44} or it may be narrowed by diffuse atherosclerotic narrowings⁴⁵⁻⁴⁷ so that these segments show combinations of stenotic and ectatic areas, and determination of a "normal" reference diameter poses important problems (Figure 2). Furthermore, one also has to take into account the normal tapering of the caliber of the vessel. A computer-assisted method to determine a more reliable reference diameter should be used to take into account the effects of either prestenotic or poststenotic luminal irregularities and the tapering of the vessel.

Third, progression of atheromatous change in mildly-to-moderately diseased vessels may occur in a diffuse manner involving only the "normal" diameter used for comparison to calculate severity of stenosis. This may result in a calculated less severe lesion (Figure 3), suggesting regression that actually should be regarded as pseudoregression, or this may have no effect on percent stenosis severity, suggesting no progression of disease, when in actuality progression has occurred.

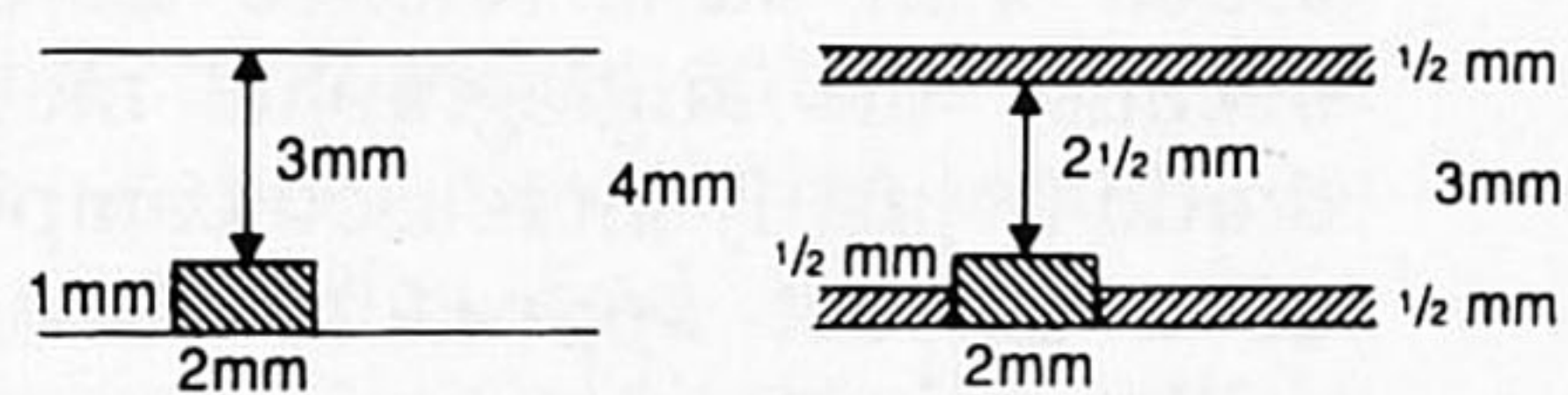
Last, relative measurements are unable to detect progression or regression if the process of atherosclerosis is predominantly diffuse.

Absolute measurements. The mean width (mm) is an absolute measurement of a particular segment, which is independent of a reference diameter. It is the only parameter that is able to measure progression or regression of diffuse atherosclerosis in angiographically "normal-appearing" segments or of dif-

fuse atherosclerosis in combination with focal atherosclerosis (Figure 3). Recent reports¹³⁻¹⁵ proposed that absolute measurements such as mean coronary diameter, minimal luminal diameter, or minimal cross-sectional area of narrowings are better measures of stenosis severity, and absolute measurements have been shown to be better markers of progression or regression of coronary atherosclerosis.^{37,48-50}

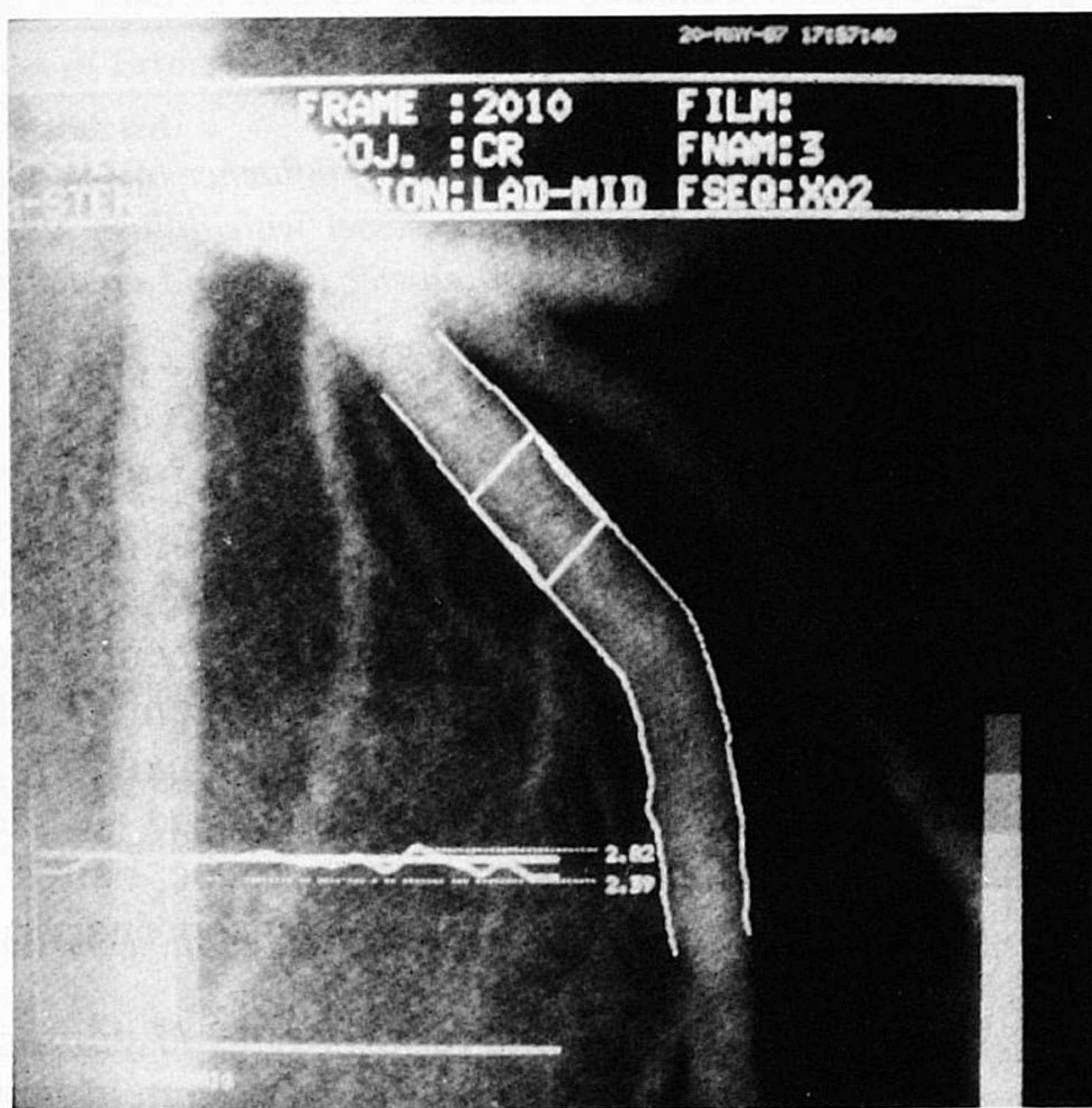
Many previous reports^{33-39,51,52} demonstrated that the absolute value of the minimum lumen diameter is the greatest single determinant of the hemodynamic impact of a coronary narrowing because the luminal stenosis diameter affects flow by a fourth-power term.

Plaque area is a recently developed absolute measurement. This area is a measure of the atherosclerotic plaque in a particular angiographic view,^{30,53} calculated as the difference between the computer-estimated predisease reference contours and the actual detected luminal contours at an obstructive lesion (Figure 4). The plaque area measurement appears to be an attractive method to measure progression or regression of coronary atherosclerosis. However, this measurement is flawed by three objections. First, it is highly dependent on the length of the stenosis. Even with the use of a computer-assisted method, the determination of the beginning and end of the proximal and distal part of a lesion may be subject to considerable variation. Second, its estimate is highly dependent on the determination of the border of the artery in the presumed prediseased state. A complicated algorithm is required to "calculate" the prediseased border of the artery. Third, plaque area measurement may underestimate progression of diffuse atherosclerosis or even misinterpret this as pseudoregression (Figure 3), and it is completely incapable of evaluating progression of diffuse coronary artery disease.

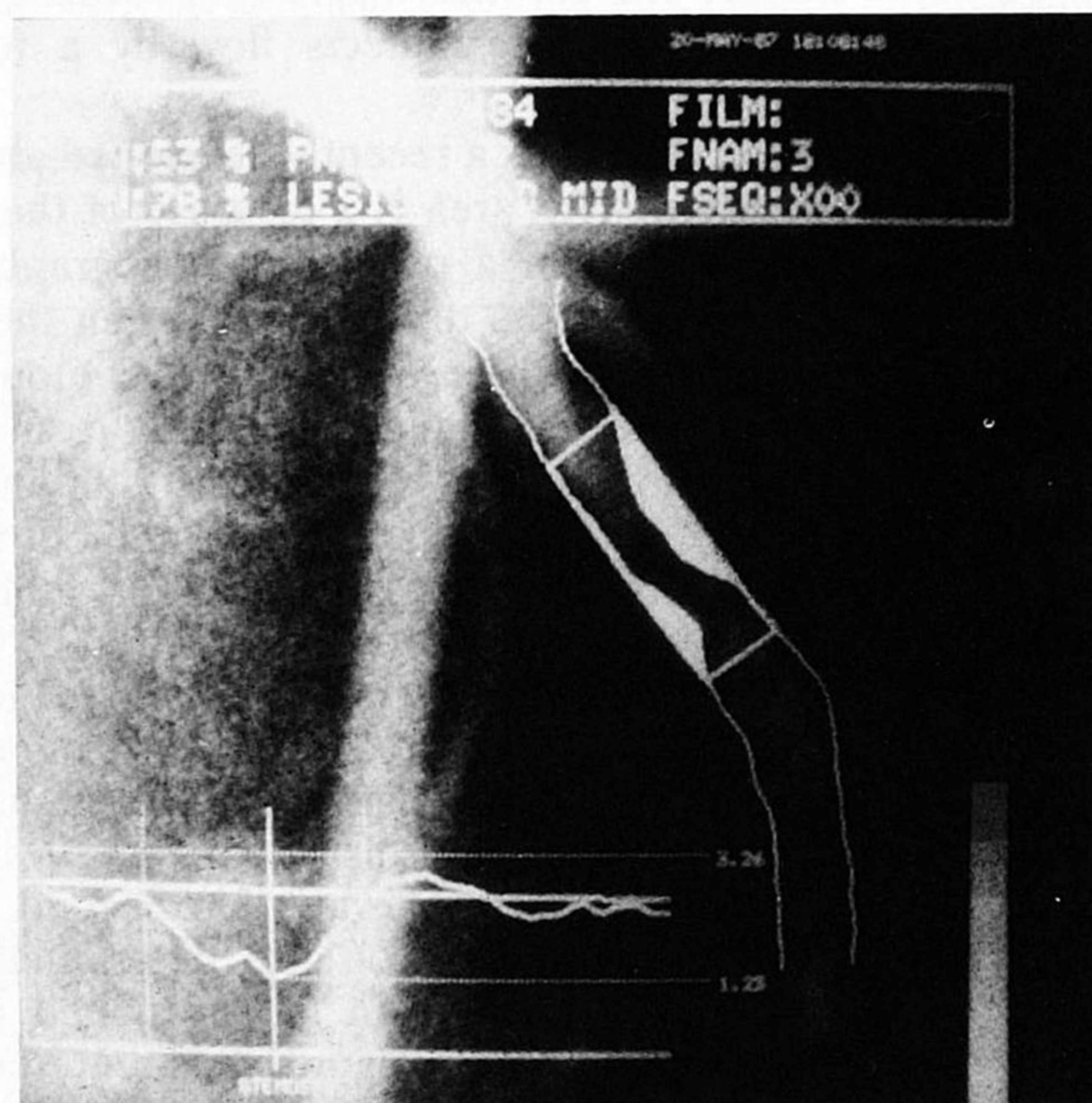


MEASUREMENTS:		
DS%	25	17
Mean width segm. (mm)	3.75	2.9
Min. lum. diam. (mm)	3.0	2.5
Plaque area (mm ²)	2.0	1.0

FIGURE 3. Diagram of progression of diffuse coronary atherosclerosis in a segment with preexisting stenosis. Relative measurement (DS%, percent diameter stenosis) and plaque area suggest regression of severity of lesion, whereas, in reality, absolute measurements show progression of disease.



MEAN WIDTH SEGMENT
LENGTH SEGMENT MM
MAXIMAL WIDTH MM
MINIMAL WIDTH MM



REFERENCE DIAMETER MM
LENGTH OBSTRUCTION MM
DIAMETER STENOSIS %
OBSTRUCTION DIAMETER MM
AREA STENOSIS %
REFERENCE AREA MM²
OBSTRUCTION AREA MM²
PLAQUE AREA MM²
△ P MMHG

FIGURE 4. Example of quantitative angiographic measurements in a coronary artery segment with diffuse atherosclerosis (panel A) and focal atherosclerosis (panel B). In this example, boundaries were automatically detected with the Coronary Angiography Analysis System. Adapted with permission.³⁰ Estimated predisease dimensions of the vessel at the site of the obstruction (reference edges) are shown; white area is a measure of the extent of the obstruction or plaque area.

“Functional” estimate. Until now, in the years when measurement of vessel luminal width from angiograms was not made with a computerized image analysis system, the relative narrowing was widely accepted as the main clinical predictor of the functional severity of a stenosis, and crude equations were used to estimate the corresponding pressure drop. That approach was never adequate in its relation to available basic knowledge of fluid dynamics. It was accepted partly because its users were out of

touch with basic science developments and partly because the angiographic measurements were too crude to justify increased computational effort by use of a correct approach. Now, we have improved accuracy in the determination of arterial dimensions, the accumulation of 50 years of knowledge of fluid dynamics, and the widespread availability of enhanced programs for computation of flows and pressure losses in channels of arbitrary geometry, so the time for crude estimates is over. The channel shape

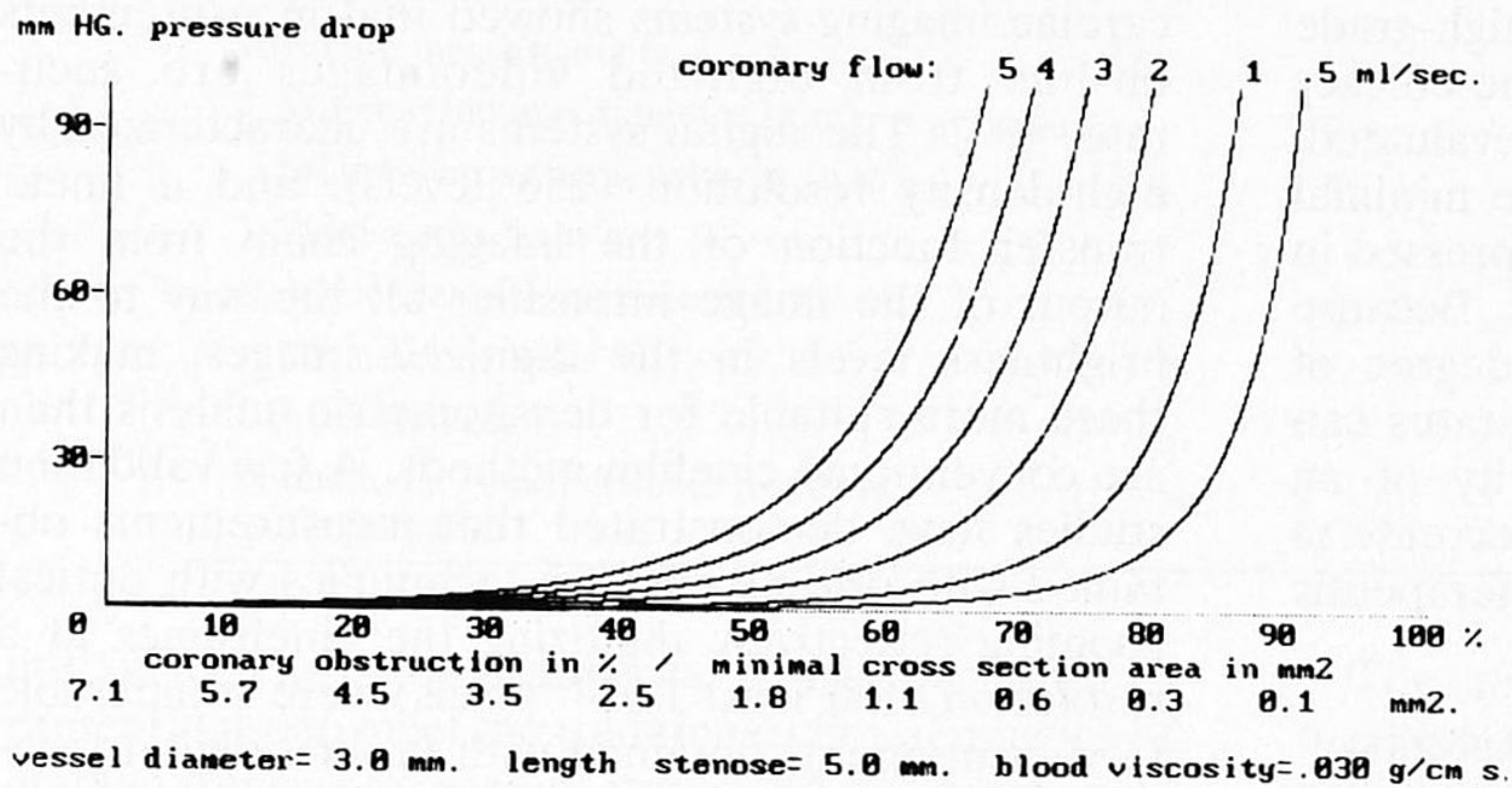


FIGURE 5. Plot of a computer-derived functional estimate, using quantitative angiography to measure dimensions of percent narrowing, absolute diameter, and lesion length. These were combined into a fluid dynamic equation to provide a single integrated measure of hemodynamic severity, that is, pressure gradient over the lesion. The following equation was used:

$$\Delta P = fQ + sQ^2.^{39}$$

$$\text{Where } f = \frac{8\pi\mu L}{A_s^2} \text{ and } s = \frac{\rho}{2} \times \left[\frac{1}{A_s} - \frac{1}{A_n} \right]^2$$

where ΔP is pressure loss across the stenosis, μ is absolute blood viscosity, L is stenosis length, A_n is the cross-sectional area of the normal artery, A_s is the cross-sectional area of the stenotic segment, Q is volume flow, and ρ is blood density. From the available morphological data of the obstruction, the Poiseuille and turbulent resistances at different flows range from 0.5 to 5 ml (simulating conditions at rest or maximal exercise) and, thus, the resulting transstenotic pressure gradients can be computed.

of a stenosis is not a sudden shift to a tube of lesser, uniform diameter, nor is the exit from it an equally sudden divergence, but there are converging and diverging portions with distinct flow characteristics.⁵⁴ The velocity profile is flattened in the middle of the lumen for the convergent portion, and steepened near the walls, whereas for the divergent portion, the velocity gradient near the walls becomes very low, and if the effective angle of divergence in the distal direction is large enough, the flow can separate at some distal position. Most vessels are not straight, and for more than 50 years, curvature has been known to alter steady flow velocity profiles and friction away from the Poiseuille values,^{55,56} with swirling secondary flow being generated. The flow in coronary arteries is not steady, but pulsatile, and the general problem of analysis of such flows, with specific reference to physiological applications, has been presented.⁵⁷ Blood vessels are compliant, and the compliance can be a factor in determining flow and resistance. Early studies of unsteady flow in compliant tubes⁵⁸ treated the flow as one dimensional, that is, as having no variation of velocity across the lumen.

Progress in computing methods has been so fast in the past 10 years that we find treatments of flow that include various wall shapes, Newtonian and non-Newtonian fluid characteristics, and the beginnings of computational representation of the wall elasticity as well. In particular, we see an emerging account of sometimes paradoxical consequences of wall elasticity, for example, a decrease in flow when resistance is reduced distal to a stenosis.⁵⁹ Although the analysis of the effects of vessel wall compliance is still in a

research phase, the use of computer codes for flows and pressure drops in rigid tubes of nonuniform geometry has become routine and should be seriously considered now as an appropriate complement to determination of vessel geometry by computer-assisted angiography; indeed, such codes are the emerging reference standard on which functional assessment can be based and have the intrinsic prospect of handling a series of discrete lesions in vessels as overall entities. An example of a functional estimate, using a rather crude computer code for flows and pressure drop, is shown in Figure 5.

The calculated transstenotic pressure gradient over a particular stenosis derived from quantitative coronary angiography describes the hemodynamic impact that a particular lesion would have under a range of flow conditions, within the range of "normal" aortic pressures. This calculation represents merely an approximation because the formula used is based on a nonpulsatile flow in a rigid and straight tube. It does not account for the effects of pulsatile flow or of curved and tapered vessels, more than one lesion in a vessel, the collateral circulation, or perfusion of areas of nonviable myocardium; and it assumes a noncompliant stenosis. It would be erroneous to extrapolate from these equations an absolute hemodynamic impact on the global perfusion in an effort to evaluate the significance of a coronary artery lesion in a specific patient. However, it enables us to estimate the relative hemodynamic impact of a stenosis between patients, and it enables us to estimate the hemodynamic impact of progression or regression of a particular lesion, assuming certain conditions.

Four conclusions can be reached: 1) Minimal cross-sectional area within the stenosis is the single most important determinant of stenosis resistance. 2) Stenosis length plays a less important role for most clinically important lesions. 3) Flow requirements importantly determine the steepness of the relation between pressure decrease and flow for high-grade stenoses (Figure 5). 4) Therefore, when the efficacy of an intervention on a stenosis is being evaluated, primary emphasis should be placed on the minimal cross-sectional area within the stenosis, expressed in absolute terms, that is, square millimeters. Because of the relation between resistance and degree of stenosis, an important change in clinical status can result from a small increment in severity of an established stenosis. Conversely, a small decrease in stenosis severity could have an important therapeutic benefit (Figure 5).

Quantitative Coronary Angiography: Edge Detection Versus Densitometry

Computer-assisted techniques provide the most reproducible and accurate methods for assessing stenosis severity. Variability in repeated measures of percent diameter stenosis or in absolute coronary dimensions using several different computer algorithms has been reported in the 3–7% range.^{30,33,60,61}

Basically, two techniques are currently available for quantitative coronary angiography: edge-detection algorithms and densitometric computer-aided analysis. Theoretically, densitometry seems the ultimate solution for the computation of a vessel's cross-sectional area from a single angiographic view.^{62–67} Perspex phantom studies have shown that densitometry is a very attractive, precise, and accurate technique for the assessment of the severity of coronary obstructions from only a single view. In particular, if the cross-sectional shape is highly irregular, densitometry is expected to be more reliable than edge-detection methods. However, the reality in routine clinical practice is different.^{62–67} This is due to various error sources. Densitometry is much more sensitive than is edge detection to densitometric nonlinearities (x-ray scatter, veiling glare, and beam hardening), orthogonality of vessel beam (foreshortening vessel), overlapping with other structures (arterial branches), patient structure noise (background noise), and inaccurate contrast filling of vessels. This is also demonstrated by the fact that only a few investigators have demonstrated a very close agreement of densitometric results from different views taken from the same vessel.^{62,65}

A potential advantage of densitometry is that it is independent of image resolution (blur or unsharpness), unlike edge-detection methods, which tend to overestimate vessel diameter when there is motion unsharpness.⁶³

We believe that, at this time, the role of videodensitometry should be in rapid calculation of relative cross-sectional areas in a single view, and if repeated studies are anticipated, then the same view must be

used to avoid large errors due to potential differences in foreshortening, background, veiling glare, and scatter.^{62,66,68}

Until now, computer-based techniques have been developed primarily for off-line applications with cinefilm. However, recent developments in digital cardiac imaging systems showed that measurements on-line from digitized videoimages are accurate.^{65,68–76} The digital systems are characterized by high-density resolution (256 levels), and a linear transfer function of the imaging chain from the output of the image intensifier all the way to the brightness levels in the digitized images, making these more suitable for densitometric analysis than are conventional cinefilm methods. A few validation studies have demonstrated that measurements obtained with off-line cinefilm techniques with optical zooming (effectively digitizing the cineframes at a resolution of at least 1,024² pixels) were comparable to measurements obtained with on-line digital techniques.^{62,64,69,76} However, many problems, in addition to those inherent to videodensitometry as described above, must be solved before widespread application of on-line digital angiography is recommended.^{63,68}

For long-term intervention studies, in which small changes in vessel dimensions in obstructed and nonobstructed segments need to be detected, a precision in the repeated measurements should be in the order of 0.1 mm. With the use of modern small field-of-view image intensifier (resolution, 512² × 8 bits at 25 or 30 frames/sec), the digital angiograms may even be of sufficient quality. However, validation studies need to be performed to establish this firmly.

Which Measurements Should Be Used to Detect Progression or Regression of Coronary Atherosclerosis?

Widely accepted criteria for arteriographic evaluation of progression or regression of coronary atherosclerotic disease are not yet established and may depend, in part, on methodology. Conceptually, one might distinguish progression or regression of coronary atherosclerosis as a focal pathological process or as a diffuse pathological process. However, in patients with coronary artery disease, both processes often occur in combination.^{19,42}

In Table 2, we propose a set of measurements derived from quantitative coronary angiography that may be used to assess progression or regression of disease. Preferably, absolute measurements should be used. The mean width of segment (mm) is the most important measurement because it can be used to assess progression or regression of diffuse atherosclerotic disease, it can also be used to measure changes of focal atherosclerotic disease, and it is the single measurement that can be used to assess the combination of diffuse and focal atherosclerosis.^{19,42}

In addition, other absolute measurements (minimal luminal diameter or minimal cross-sectional area), which are predominantly able to assess focal atherosclerosis, are useful. Although relative measurements

TABLE 2. Significance of Measurements Used to Assess Progression or Regression of Coronary Atherosclerosis

	Diffuse atherosclerosis	Focal atherosclerosis	Combination of diffuse and focal atherosclerosis
Coronary segment score			
Mean width per vessel segment (mm)	++	+	++
Coronary lesion score			
Absolute measurements			
Minimal luminal diameter (mm)	±	++	+
Minimal cross-sectional area (mm ²)	±	++	+
Plaque area (mm ²)	...	++	+
Relative stenosis measurements			
Diameter stenosis %	...	+	±
Area stenosis %	...	+	±
"Functional" stenosis measurements			
ΔP (mm Hg)	...	+	+

are subject to many drawbacks, it may be useful to present these to meet the traditional clinical practice of grading stenoses as percent stenosis. Also "functional" estimations based on modern computer codes for flows and pressure drops may be useful to inform the reader about the clinical significance of progression or regression of focal coronary atherosclerosis.

How Should Arteriographic Information Be Presented?

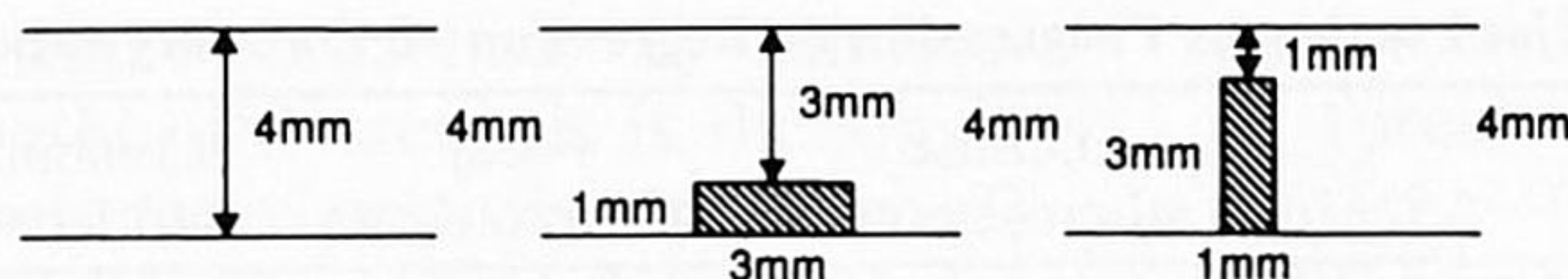
It is a common clinical practice to present efficacy of an intervention on a patient-oriented basis. However, in trials studying the effect of an intervention on progression or regression of coronary artery disease, a patient-oriented assessment of progression only can be ambivalent because it is not uncommon for one lesion to worsen while another one improves in the same patient. To provide the reader with sufficient data to gain appropriate insights into the potential efficacy of an intervention, we believe that data should be presented on a patient-based assessment as well as on a lesion- or segment-based assessment (Table 3). Although it is clinically useful to classify individual patients, lesions, or segments (either with or without a lesion) discretely, as progressing, regressing, or not changing, atherosclerosis may proceed in a continuous fashion. Any cutoff for defining progression or regression suffers from the arbitrary nature of such a definition. Therefore, assessment of changes in coronary artery disease should also be performed with the variables analyzed as a continuous variable. Patient-based analysis should include: 1) a coronary tree score that measures all analyzable segments (including those with lesions) and serves as a total score to assess diffuse and focal atherosclerosis, 2) a coronary lesion score to assess focal atherosclerosis, and 3) a coronary segment score (segments without lesions) to assess changes in diffuse atherosclerosis. Lesion-based analysis should include absolute, relative, and "functional" measurements, and a segment-based analysis should include absolute and relative measurements.

The absolute measurements should be the best markers of progression or regression of coronary artery disease. Although subjective visual estimate of "percent stenosis" lacks accuracy and repeatability and provides no accurate insights into the hemodynamic impact of a lesion, the simplicity of the percent stenosis estimate and the force of clinical tradition will compel us to continue its use as an imperfect measurement and should, therefore, also be presented. It will also enable us to compare results of future trials with those from the past that have used percent stenosis as a parameter.^{77,78}

Even with quantitative measurements, however, anatomic changes in stenoses that may be seen during a natural history study or during therapeutic interventions may be difficult to interpret from a practical clinical standpoint. The same "volume" of progression or, conversely, of regression of coronary heart disease, depending on the location and orientation within the vessel, will have profound different

TABLE 3. Assessment of Progression or Regression of Coronary Atherosclerosis

<i>Patient based</i>	
Coronary tree score	Mean width (mm) of all segments
Coronary lesion score	Minimal luminal diameter (mm)
	Minimal cross-sectional area (mm ²)
	Plaque area (mm ²)
	Diameter stenosis (%)
	Area stenosis (%)
	ΔP (mm Hg)
Coronary segment score	Mean width (mm)
<i>Lesion based</i>	
Coronary lesion score	Minimal luminal diameter (mm)
	Minimal cross-sectional area (mm ²)
	Plaque area (mm ²)
	Diameter stenosis (%)
	Area stenosis (%)
	ΔP (mm Hg)
<i>Segment based</i>	
Coronary segment score	Mean width (mm)

**MEASUREMENTS:**

DS %	0	25	75
Mean width segm. (mm)	4.0	3.6	3.6
Min. lum. diam. (mm)	4.0	3.0	1.0
Plaque area (mm ²)	0	3.0	3.0
ΔP mmHg for:			
Coronary flow 1 ml/s	0	0	8
Coronary flow 3 ml/s	0	0	60
Coronary flow 5 ml/s	0	0	"164"

FIGURE 6. Diagram of progression of the same "volume" of atherosclerosis with a different distribution within the vessel lumen to demonstrate the significant differences in stenosis measurements and functional estimates using the equation described in Figure 5. ΔP mm Hg is "calculated" for coronary flow of 1 ml/sec (at rest), for 3 ml/sec (moderate exercise), and 5 ml/sec (maximal exercise). The value of "164" obviously is theoretical.

impacts on relative, absolute, and "functional" measurements (Figure 6). The progression or regression of disease also should be expressed as a cumulative effect of all geometric changes on the hemodynamic characteristics of the stenosis. And the clinical relevance of progression or regression of disease may best be presented as the hemodynamic impact of the change of the lesions in terms of changes in pressure drop across the lesion provided, of course, that these are computed using modern methods. Because the total number of patients enrolled in serial angiographic studies will be low and because the expected frequency of clinical end points such as angina pectoris, myocardial infarction, or cardiac death will be too low to be of statistical significance, these data cannot be used as an end point.

Unresolved Problems

Currently, many questions remain unanswered. Is progression of atherosclerosis episodic or linear? If the former, then serial angiography may not be the most accurate method to detect this process. Distinguishing between two types of progression is difficult: 1) fast progression up to total occlusion due to the sequence of events after plaque fissuring, that is, intraplaque and intramural thrombosis, and 2) slow progression developing over years.

Is there a difference in the capability of lesions to progress or regress, and if so, can we identify the predictive variables? For instance, evidence suggests that severe lesions have a higher tendency to progression or regression than do mild lesions.⁷⁹⁻⁸¹ Is there a difference in pattern of progression of coronary heart disease in the three main coronary arteries? The right coronary artery may show more progression than the left anterior descending and circumflex arteries.⁸² Does progression of preexisting lesions or development of new lesions occur more frequently in vessels already "diffusely" diseased compared with that in "normal" vessels? How can we distinguish between the rate of progression of disease of a severe stenosis due to local hemodynamic forces (wall shear stress) and that due to the atherosclerotic process?

To what extent might differential compensatory enlargement of artery segments in response to enlarging atherosclerotic plaques impair the interpretation of angiographic information?²⁶⁻²⁸ It appears that the rate of increase of compensatory enlargement in different segments of the arterial tree is not equal and that the rate of increase of distal parts of the tree is greater than in the more proximal parts.²⁷

How should we account for the effects of progressive dilation of the artery with aging?⁴⁰⁻⁴² Does a proximal, severe coronary artery stenosis inhibit the development of distal lesions, or does a mild proximal stenosis potentiate the progression of distal atherosclerosis and the development of lesion complication as has been shown in human aortic disease?^{83,84}

Do lesions over a prolonged period of time undergo "molding," whereby lesions may change dimensions while retaining the same volume? A stenosis may become longer with a less severe minimal diameter, or it may become more severe in one part but less severe in another part.

What should be used as the statistical criterion to distinguish between "probably due to actual change" and "possibly due to variability of the method?"

Conclusion

Clinical trials that attempt to alter the progression of coronary artery disease require accurate and reproducible methods for assessing end points that ideally would show a high prevalence of change over a reasonable follow-up time period. Despite certain limitations, quantitative coronary arteriography is presently the definitive procedure for assessing progression and regression of coronary atherosclerosis in living humans.

Furthermore, quantitative angiography is useful in revealing the mechanisms of coronary atherosclerotic progression or regression and is being refined so that it will further enhance the understanding of the pathophysiology of human coronary arteries.

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