Arteriographic Assessment of Coronary Atherosclerosis

Review of Current Methods, Their Limitations, and Clinical Applications

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The safety and utility of direct intracoronary injection of contrast medium for radiographic visualization of the coronary arteries was first reported by Sones et al.1 in 1959. This relatively new technique is regarded as the definitive procedure at present for demonstrating the distribution and severity of coronary atherosclerosis in living humans. As such, coronary arteriography now forms the basis for much of the decision-making in the medical and surgical therapy of this prevalent disease.

To produce these arterial images, one of a number of specially designed catheters is advanced from the arterial entry point (femoral or brachial) into the ostium of one of the two (right or left) coronary arteries. Iodine-containing radiopaque contrast medium is injected through this catheter directly into the cannulated artery. The cineangiogram is a sequence of images formed when the moving x-ray shadow of the transiently opacified arterial lumen is cast upon the input phosphor screen of the image intensifier. This electronic tube converts the energy of incident gamma radiation into light, and produces an amplified, focused optical image of the coronary lumenal shadow which is then recorded on 35 mm cine film at 30 frames per second. The clinical objectives of arteriography, and thus the focus of various modes of interpretation, are to demonstrate the anatomic and pathophysiologic basis for the patient’s clinical findings, and to provide information useful in guiding future therapy.

Over the past two decades, clinical interpretation of these arteriograms by radiologists and cardiologists has been entirely subjective or, at best, semiquantitative. Gensini et al.2 observed in 1971 that the coronary arteriogram “offers a wealth of data which is, at present, only partially used and seldom measured in clinical practice.” Theirs was the first of several approaches to arteriographic image measurement that have emerged during the past decade. This review discusses certain of these methods in the context of the clinical and investigational objectives and the technical limitations of coronary arteriography.

Subjective Interpretation of the Arteriogram

Figure 1 illustrates several different views of the left coronary injection in a patient suffering a recent anterior subendocardial myocardial infarction. How do we assess this information clinically? At present, cardiologists and radiologists inspect these coronary images projected at a magnification of 2 to 3 times true scale. Disease location is specified in terms of the “standard” arterial anatomy; and disease severity is specified as the “percent stenosis,” i.e., the percent of segmental reduction in lumen diameter relative to an appropriate nearby “normal” diameter. Thus, the arterio-
Figure 1. Four views of the proximal left coronary artery and its branches in different arteriographic projections. 
A. 30° right anterior oblique (RAO) view. The catheter (2.7 mm diameter) enters the left main artery from the upper left. The left anterior descending (LAD) artery and its branches course to the right and downward. B. 50° left anterior oblique (LAO) view, as seen by the observer looking from the right of A. The proximal LAD is forshortened. C. LAO with 20° cranial angulation of the x-ray axis. The proximal LAD narrowing is well-visualized due to the appropriate projection and to drug-induced focal coronary constriction. D. Same view as C, after nitroglycerin.

gram of figure 1 would be interpreted as essentially normal if only views A, B, and D were available, and as showing a 50% narrowing at the origin of the anterior descending artery if only view C were available. Coronary vasomobility explains this apparent paradox.

Unfortunately, subjective assessment of disease severity has considerable intra- and interobserver variability. Errors occur in specifying disease location and its severity. For example, when 11 experienced cardiac angiographers were asked to estimate the severity (percent stenosis) of the worst lesion in 10 different standard arterial segments in each of 10 angiograms, the average variability (standard deviation of 11 estimates) was about ± 25%. When potential errors in locating lesions were eliminated, five angiographers estimated the severity of specified lesions with a variability averaging ± 12%; and they substantially overestimated the severity of lesions in the 60% to 90% range. These studies are illustrated in figure 2. Thus, even in the best of circumstances, a 50% coronary stenosis (the threshold value for placing a saphenous vein bypass graft) may very frequently be misread subjectively as 40% or less, or as 60% or greater.

If it were more precise, would "percent stenosis" be an appropriate measure of atherosclerosis severity? And what, specifically, is meant by "severity of atherosclerosis?" The two most relevant aspects of disease severity are the hemodynamic impact of the lumenal stenosis and its prognostic significance — how likely further progressive narrowing is to occur and what the consequences will be.

The factors determining the hemodynamic impact of a coronary lesion are now reasonably well understood. The relationships among viscous and turbulent pressure losses, lesion dimensions, and blood flow are presented in figure 3.
Figure 2. The mean variability of "percent stenosis" estimates are compared for three different methods. Upper curve. Eleven subjective visual estimators using standard artery forms. Middle curve. Five visual observers grading specified lesions. Lower curve. Two observers making multiple computer-assisted measurements of specified lesions. For lesions ranging between 20% and 80% stenosis, the variability (standard deviation of multiple estimates) averaged 30%, 12%, and 3%, respectively, for these three methods. The upper two curves are taken from published data (see refs 5 and 6).

for the dimensionally average human coronary stenosis. These curves and expressions clearly demonstrate that the greatest single determinant of the hemodynamic impact of a coronary narrowing is the minimum stenosis lumen diameter, \( d_{\text{min}} \). The inverse fourth power function of \( d_{\text{min}} \), which appears in both terms of the pressure loss formula, is mathematically very powerful. Thus, one weakness of the "percent stenosis" parameter is that it is a relative estimate of luminal narrowing, while the hemodynamic impact depends on the absolute value of the minimum lumen diameter.

If there were a generally definable relationship between \( d_{\text{min}} \) and percent stenosis, then the latter would be a useful index of hemodynamic impact. But this is simply not the case. The nearby "normal" portion of the vessel lumen, whose diameter forms the denominator of the percent stenosis estimate, may be dilated by the aging process or by poststenotic turbulence; or it may be substantially narrowed by diffuse arteriosclerotic thickening of the intima. For example, Arnett et al. examined 467 histologic coronary cross sections from 10 patients dying of coronary disease, and found that 74% of all randomly selected cross sections were greater than 50% obstructed relative to the "original" normal lumen area. Thus the "normal" coronary segment near a stenosis is very seldom normal. The superiority of absolute dimensional measures for predicting the hemodynamic severity of coronary stenosis has been demonstrated in human studies. Stenosis length is another variable that is not mentioned in the subjective visual assessment of disease severity. While the length of the constriction should add little to the hemodynamic impact of \( \geq 50\% \) stenoses (see figure 3), the contribution of length to the apparent severity of moderate stenoses has been demonstrated experimentally.

Less is known about the second aspect of atherosclerosis severity—the prognostic significance of a stenosis. We know that the number of major coronary branches that are significantly narrowed strongly influences prognosis, and that a stenosis of the left main coronary artery is much more dangerous than comparable lesions in other major branches. Thus, predictably, the amount of myocardium in jeopardy distal to ath-

Figure 3. Theoretical pressure loss under conditions of normal flow through an average stenosis in a 3.0 mm diameter human coronary artery. The abscissa is the absolute diameter of the lumen at the point of greatest narrowing and (in parenthesis) the corresponding % reduction from the normal diameter. Stenosis pressure loss is scaled logarithmically on the ordinate. The equations are those of classical fluid mechanics. Here, \( \mu \) is blood viscosity, \( Q \) is blood flow, \( \rho \) is density, \( d \) is lumen diameter, \( L_e \) is stenosis equivalent length determined from 560 human coronary lesions, and \( \Delta P \) is pressure lost in flow through the stenosis.
Technical Aspects and Limitations of Arteriography

The clinical objectives of catheterization require: 1) comprehensive visualization of the coronary anatomy; 2) evaluation of potential pathophysiologic mechanisms suggested by the patient’s symptoms; 3) careful attention to certain technical considerations relating to image quality; and 4) proper interpretation of the arteriographic information. While this review focuses on quantitative methods of arteriographic interpretation, the first three of these requirements encompass the fundamental principles of good clinical arteriography. If these are neglected, no method of interpretation, however sophisticated, will succeed in recovering the lost information. Because of their importance, certain of these principles are discussed below.

Since coronary atherosclerosis focally narrows short segments of the arteries, very commonly at the arterial branch points, good technique demands that the important arteries and especially all major bifurcations be visualized in x-ray projections that are roughly perpendicular to their epicardial planes. Since the heart is nearly spherical, a number of different angiographic views are necessary if disease is not to be missed. Figure 1 illustrates this point; proximal anterior descending disease is obscured by overlapping vessels in the 30° RAO view (A), is viewed end-on in the 50° LAO view (B), but is clearly revealed in the 50° LAO projection after the x-ray beam axis is tilted 20° cranially. Thus, a sufficient number of logically selected projections must be filmed to examine the coronary tree completely. We routinely obtain four to six left coronary and two to four right coronary views plus any modified views needed to better define a suspected segment.

Sometimes the arteriographic findings do not explain the clinical presentation, as in the patient in figure 1. This 42-year-old man presented with transient episodes of angina at rest and, after a particularly prolonged and severe episode, was admitted with a well-documented anterior subendocardial myocardial infarction. Yet the first views of his suspected vessel, the anterior descending, showed only mild proximal narrowing. Pharmacologic alpha-adrenergic stimulation caused a focal constriction at the origin of the vessel (figure 1 C), which virtually disappeared with nitroglycerin (D). Thus, coronary vasospasm was the basis for this patient’s clinical syndrome; and chronic nitrate therapy has abolished his symptoms.

Good arteriographic image quality requires careful attention to certain technical considerations. In particular, the constellation of interrelated factors — magnification, tube voltage, film type, and frame exposure time — must be adjusted to optimize the contrast and the signal (arterial lumen) to quantum noise (film grain size) ratio, and to minimize motion blur. System resolution and film exposure characteristics should be checked daily and adjusted if they exceed defined quality control limits. Finally, attention to certain details at the time of arteriography can greatly enhance the quality of the image. Selective panning and the use of adjustable lead shields to screen out radiolucent lung-field regions can improve cardiac penetration. And since the concentration of contrast medium is an important determinant of vessel edge resolution, the injected arteries must be filled entirely with dye, using brisk injections of up to 10 ml, which are well tolerated. The faint-hearted injector of contrast will be rewarded with faintly visualized arteries.

Let us assume that all of the recommendations above have been carefully observed, and arteriograms of excellent quality have been obtained. Can we then be assured that we have all of the information necessary to characterize the disease? Those who assert that the arteriogram is an inaccurate descriptor of the arterial pathology would say no. Pathologists raise two principal objections in their dispute with the arteriogram: First, in segments judged arteriographically to be “normal,” 50% to 70% of the "actual"...
normal cross sectional area (defined as that circumscribed by the internal elastic lamella) may be obstructed by diffuse arteriosclerotic thickening of the smooth muscle layer of the arterial intima. Second, the diseased lumen, as seen in histologic sections cut through atheromatous plaque, often displays a strikingly noncircular cross section. On such postmortem specimens, the diseased lumen is frequently seen as an exaggerated ellipse, long and narrow in shape. This so-called "slit-like" lumen has been proposed as one explanation for the reportedly frequent underestimation of stenosis severity by angiographers. In most projections, the arteriographic appearance of the slit-like lesion would be dominated by the long axis of the slit, concealing the severe obstruction caused by the narrowest dimension. The crescent-shaped (new moon) lumen, a variant of the slit-like lumen, may not appear to be severely narrowed in any arteriographic view. The only hint as to its occult severity would be a localized lucency, or reduction in contrast opacification, in an otherwise well-opacified artery.

When weighing these objections to the arteriogram, one must remember that arteriography and histology provide entirely different perspectives of arterial pathology. The arteriogram does not visualize the tissue that surrounds the arterial lumen. The two methods can be expected to agree only in measurements of their one common surface — the blood-endothelial interface that defines the lumen boundary. The size of the region circumscribed by this boundary is, once again, the principal determinant of the hemodynamic impact of arteriosclerosis. And this lumen cross-sectional area is the net result of several opposing pathologic processes: 1) progressive dilation of the musculoelastic coat of the artery with aging and poststenotic turbulence; and 2) intimal smooth muscle proliferation and atherosclerotic plaque formation. Thus, if arteriosclerotic processes have narrowed the area circumscribed by the internal elastic lamina to 30% of the apparent normal area, but still the residual lumen is greater than 2 mm in diameter due to concomitant processes of arterial dilation, this intimal pathology would impose no limitation to blood flow in a person at rest or during exercise. For hemodynamic purposes (if not for prognostic), this arterial segment should therefore be considered normal.

A second concern with the pathologist's position is that the slit-like and the crescent-shaped lumen usually occur as artifacts of postmortem arterial fixation and sectioning in the unpressurized state. Those who raise the specter of the noncircular lumen have simply ignored the principle that an elastic chamber under pressure will adopt a rounded configuration. Those who have sectioned diseased arterial segments after fixation at physiologic pressures state that: "In contrast to general belief, truly slit-like lumina did not exist in our series." In our experience and that of D. Reichenbach (personal communication), the slit-like lumen seldom occurs in coronary stenoses.

In conclusion, regarding the alleged discrepancy between arterial histopathology and the arteriogram, we believe that the pathologist and the arteriographer must meet on the common ground of absolute lumen dimensions in diseased arterial segments that are carefully examined by both in the physiologically distended configuration. Comparisons of this sort will almost certainly demonstrate an excellent agreement between these two methods of disease assessment. This has been our experience and that of others. We feel that the properly performed coronary arteriogram provides a true picture of the arterial lumen in living humans.

Quantitative Analysis of the Arteriogram

Because of the inadequacies of the visual estimate of "percent stenosis" discussed above, more precise methods for analysis of the arteriogram have been developed. Such methods should be judged in terms of their accuracy, variability, speed, cost, safety (or added risk), and the relative utility of the measurements. We describe several of these methods below, judging them where possible in terms of the criteria of merit above.

Methods Using Image Border Information

Direct Caliper Measurements of Lumen Diameter

MacAlpin et al. made direct estimates of coronary artery dimensions in several cardiac disease states using caliper measurements of projected arterial diameter and of a calibrating object filmed at the level of the left ventricle. The mean accuracy was ± 0.2 mm for measurement of known objects. Using a comparable technique, Feldman et al. reported ± 0.5 mm variability in measurements of projected dimensions.

Magnified Vernier Measurements of Lumen Diameter

Rafflenbeul et al. achieved improved dimensional accuracy using a vernier to measure arterial diameters directly from the projection screen at about X3 magnification. Feldman et al. combined high quality 105 mm photospot arteriographic images and a magnifying vernier having 0.1 mm gradations. Absolute dimensional estimates were made using the catheter tip as a scaling device with a variability of ± 0.1 mm on re-
peated dimensional estimates. The measurement variability of this method thus approximates that of a more complex computer-assisted method. Single measurements are made quickly once the photospot frame is made and selected.

**Measurements from Computer-Assisted Image Reconstruction**

While the variability of the above direct measurements of lumen diameter now approach the limits of resolution of the image intensifier, the accuracy of these measurements is diminished by two well-recognized forms of radiographic image distortion. **Pincushion distortion** is the selectively increased magnification of objects viewed in the periphery of the angiographic field. **X-ray beam divergence** causes a second form of image distortion because there is selective magnification of objects that are closest to the x-ray source. Pincushion distortion can result in a 5% to 8% error in direct-scaled dimensional estimates; and beam divergence results in an error approximating 1.5% of the estimate per centimeter separating the measured object and the scaling object along the x-ray axis. These two forms of image distortion each may introduce maximum errors of 5% to 10% on absolute dimensional estimates, errors that are seemingly trivial until one considers that the average measured coronary vasomotor change with ergonovine and with nitroglycerin approximates 10% to 20% of the lumen diameter; most other drugs and stresses produce smaller changes. Furthermore, dimensional errors of 10% are compounded to errors approximating 50% for estimates of stenosis resistance because of the fourth power of the lumen diameter in the resistance formula (figure 3). Finally, because the diseased coronary lumen is not perfectly round, the measured severity of the stenosis in one arteriographic projection may differ from that in another projection. Rafienbeul et al. attempted to correct for this by averaging estimates from several different projections. Thus, ideally, an accurate form of image reconstruction would compensate for selective magnification due to beam divergence and pincushion distortion, and would provide a mathematically tractable and physically useful three-dimensional approximation of lumen geometry.

Such a method has been developed in the cardiovascular computation laboratory at the University of Washington. Routine coronary cineangiograms are projected at approximately fivefold magnification in a darkened room. Cine frames are selected for lesion clarity at comparable points in the cardiac cycle in each view of a perpendicular projection pair (e.g., 50° LAO, 40° RAO) in which the lesion of interest is best seen. The image borders of a selected diseased arterial segment are traced from the "normal" proximal portion, through the stenosis, to the "normal" distal portion, as illustrated in figure 4. A segment of the catheter, of known dimensions, is traced as a scaling factor. This border information is digitized into a PDP 11/45 digital computer in Seattle. (This has been accomplished remotely by telephone from terminals and digitizing tablets in Seattle, Los Angeles, Iowa City, and Ann Arbor). The computer program converts the lesion image to true scale by compensating for the forms of image distortion described above, as illustrated in figure 4. Figure 5 shows the computer printout of the analysis. Here, the two images from perpendicular projections are combined in a three-dimensional characterization of the diseased segment, from which are computed the vessel diameters and cross-sectional areas in the "normal" ends and at the point of greatest narrowing. Percent diameter and area reduction in the stenosis are computed, as well as lesion length, estimated atheroma mass, and stenosis Reynolds number, flow resistance, and peak intimal shear stress. Formulas for most of these computations have been published.

The computer does not enhance the image; it depends entirely on the digital border information it receives (and thus ultimately on arteriographic image quality). Simple geometric concepts and reasonable, testable assumptions are used to create a true-scale, three-dimensional lumen representation from a pair of perpendicular angiographic views. Complex integrated calculations that would require months manually are done in milliseconds.

The performance of this system, judged by the criteria of merit above, is as follows: absolute measurements are accurate to 0.1 mm for known dimensions. The variability averages ± 3% (SD) in estimates of "percent stenosis" and ± 0.1 mm for estimates of minimum lesion diameter. Figure 2 illustrates the improved precision of computer-assisted percent stenosis estimates compared to visual estimates. This accuracy is achieved despite the requirement for subjective interpretation in tracing the magnified lumen border. We find that the human hand-eye-brain complex is an image processor that performs such functions as edge detection, border interpolation, and appropriate longitudinal smoothing remarkably well. In addition, we incorporate a blinding strategy into all comparative studies to eliminate possible errors due to observer bias. In its present form, the method is slow and tedious to apply; average times spent in film handling/frame selecting, tracing, and computer processing a lesion average roughly 5, 4, and 7 minutes, respectively. Currently we regard it as an investigational method; automation of certain of these steps can be expected to reduce the tracing and processing times to 1 and 4 minutes. The cost of the method includes hardware, computation,
and technician expenses; the option requiring the least in capital outlay costs roughly $25,000 for projector, terminal and digitizer, and accesses a central computer by telephone. This option has worked exceptionally well in our hands. The method uses high-quality routine clinical angiograms, and as such does not add to patient risk. Examples of the relative utility of this method are presented below.

**Methods Using Digital Representation of Arterial Images**

Alderman et al. have developed a method for automated, operator-interactive definition of the lumen borders of a coronary artery segment visualized during clinical arteriography. Selected portions of the arteriographic image are projected at high magnification into a television camera and stored digitally in magnetic memory as a data matrix with spatial resolution of 480 × 512 pixels and with 8-bit gray-scale resolution. By positioning the coronary segment of interest at the center of rotation of the radiographic U-arm, magnification correction factors become a defined function of the distance of the image intensifier from the x-ray isocenter, and are obtained as needed from tabular computer memory. Conventional border recognition algorithms are used to detect the lumen borders of the selected coronary segment from this digital image format. The operator uses a light pen to assist the computer program in locating the lumen borders and to override any obvious errors in edge detection. This method generates absolute measurements of lumen diameter, area, and percent diameter and area reduction from single plane angiographic views or from combined data using two perpendicular, nonsimultaneous, ECG-matched views. These investigators have not yet reported the accuracy of their measurements, but report very low variability in repeated dimensional estimates, approximating that obtained with visual/manual tracing of lesions from highly magnified projections.

Digital subtraction angiography represents a conceptual extension of digital image analysis. While this technique has been successfully applied to the visualization of large peripheral arteries following intravenous contrast injections, its application to coronary arteriography will require substantial improvements beyond
Methods Using Photodensitometry of the Arteriographic Image

Scanning photodensitometry along a trajectory that crosses the vessel image has considerable theoretical appeal. Points at which optical density changes abruptly along the trajectory mark the borders of the arteriographic lumen; and, under defined conditions, the optical density of the opacified vessel is a specified function of the depth of the contrast medium in the lumen. The optical density profile can thus generate a parameter proportional to lumen cross-sectional area; three dimensional information is extracted from a two-dimensional image. By comparing densitometric profile across the vessel image at the point of greatest narrowing with that across the nearby “normal” diameter, one may estimate the percent area reduction in the stenosis. Such methods have been described by Paulin and Sandor4546 and by Buis et al.47 They hold promise for dealing with the problem of the irregularly-shaped stenosis lumen, since the densitometric profile is theoretically a function of lumen area, independent of its cross-sectional shape. The technical difficulties facing the clinical application of this technique have been discussed;48 despite these limitations, the idea has considerable appeal as a potential means for rapid estimation of “percent area reduction” from a single angiographic projection.
Methods that Combine Border Information and Photodensitometry

The elegant approach to quantitative radiographic characterization of atherosclerosis by the collaborating USC/JPL groups has previously focused on the femoral artery.48-50 These investigators have used computer-based image scanning photodensitometry of the cut-film femoral arteriogram to estimate vessel edge roughness and lumen volume irregularity. Several indices derived from this digital pattern data appear to correlate well with the measured arterial cholesterol content and with visual grading of atherosclerosis in the opened vessels. The best of these indices, CEA (computer estimate of atherosclerosis), while not a straightforward analog of any clinical arteriographic interpretation process, is a combination of scan density and edge roughness information. This approach appears particularly useful for the angiographic analysis of early atherosclerosis. While application of these methods to the coronary arteriogram would seem much more difficult, success has been reported in an initial experimental study.51

Clinical Studies Using Quantitative Arteriography

The recent availability of accurate arteriographic measures of human coronary atherosclerosis now permits the design and conduct of objective studies of a number of clinically relevant questions in ischemic heart disease. Important investigational areas include the progression and regression of atherosclerosis, coronary vasospasm, the mechanism of action of antianginal drugs, and the relationship between the anatomic severity of atherosclerotic disease and its physiologic impact on myocardial perfusion, or ventricular function, or the clinical state. Our group has conducted clinical investigation in each of these areas. For example, we find that a major mechanism of clinical benefit from nitroglycerin is direct dilation of the coronary stenosis.52 We have observed that the calcium slow-channel inhibitor, verapamil, effectively blocks the coronary artery constriction resulting from sympathetic activation or ergonovine infusion.53 We have demonstrated that coronary spasm is due to a characteristic hyperreactivity of a specific, usually diseased, arterial segment, and not of the entire artery or the entire coronary tree. This phenomenon, illustrated in figure 1, suggests the hypothesis that the potential for coronary spasm is established primarily by the underlying anatomic substrate.54 The sympathetic neurogenic activation associated with sustained isometric handgrip causes a 15% to 20% constriction of epicardial coronary lumen area.55 We have used the angiographic measurements as the "gold standard" for determining the sensitivity and specificity of exercise-, and dipyridamole-thallium-201 myocardial perfusion imaging for "noninvasive" detection and localization of coronary stenoses.56 And objectively defined left ventricular contractile abnormalities correlate significantly with lesions having minimum area, < 0.5 mm², area stenosis > 90%, and flow resistance > 25 mm Hg/ml flow/sec.57

Coronary Lumen Caliber in Defined Ischemic Syndromes

McMahon et al.10 and Rafflenbeul et al.20,41 have measured arterial stenoses in patients with unstable angina. In an attempt to define the "critical" human coronary stenosis producing ischemia at rest, 10 patients were selected for refractory unstable angina, single vessel coronary disease, and the absence of collaterals; a companion group of five patients had a similar picture but also a documented subendocardial myocardial infarction.10 A third group (McMahon, MM, unpublished observations) of 30 consecutive patients were selected for radioangiographic and ventricular contraction patterns diagnostic of transmural infarction; 11 of these had severe stenosis proximal to the infarcted zone, and the remaining 19 arteries were completely occluded. The averaged measurements of lesion severity for each of these three clinical groups are given in figure 6. Thus, myocardial viability was barely maintained distal to lesions in the minimum area range of 0.63 ± 0.19 (so) mm²; more severe narrowing was commonly associated with myocardial necrosis.

Progression of Coronary Atherosclerosis

Studies to evaluate the effectiveness of therapeutic interventions against progressive coronary occlusion are currently based on clinical follow-up. Clinical endpoints include myocardial infarction and death, each of which occurs at an annual rate of about 4% in patients with angina. These event rates are relatively low for efficient clinical trials; thus, well-designed intervention studies must enroll several thousand patients in order to demonstrate a drug benefit at a satisfactory statistical level.58,59 Furthermore, the occurrence of one of these clinical endpoints does not necessarily reflect coronary atherosclerosis progression. For example, focal coronary spasm or cardiac arrhythmias may cause infarction or death without any worsening of coexistent coronary atherosclerosis. Conversely, mild coronary lesions may progress considerably (from 20% stenosis to 40%) without clinical changes.
QUANTITATIVE CORONARY ARTERIOGRAPHY
Brown et al.

\[
\frac{A_{\text{prox}} \cdot A_{\text{dist}}}{\pi} = \frac{1}{2} (dr \times dl)
\]

\[
\% \text{DIAMETER STENOsis} = \left(1 - \frac{2 \delta_{\text{min}}}{\delta_{\text{prox}} + \delta_{\text{dist}}} \right) \times 100
\]

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

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<tr>
<th></th>
<th>No MI</th>
<th>SEI</th>
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<tr>
<td>(\delta_{\text{min}}) (mm)</td>
<td>0.88 ± 0.14</td>
<td>0.64 ± 0.08</td>
<td>0.55 ± 0.08</td>
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<td>% DIAM STENOsis</td>
<td>72 ± 5</td>
<td>76 ± 3</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>LENGTH (mm)</td>
<td>14 ± 6</td>
<td>15 ± 6</td>
<td>20 ± 9</td>
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<tr>
<td>(A_{\text{min}}) (mm²)</td>
<td>0.63 ± 0.19</td>
<td>0.35 ± 0.11</td>
<td>0.26 ± 0.08</td>
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<tr>
<td>% AREA STENOsis</td>
<td>92 ± 3</td>
<td>95 ± 2</td>
<td>96 ± 2</td>
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<td>((n=10))</td>
<td>((n=5))</td>
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*In 11/30 patients without complete arterial occlusion

**Figure 6.** Characteristic dimensions of the "critical" coronary lesion associated with refractory unstable angina but no myocardial infarction (MI) in 10 patients, of the lesion associated with subendocardial infarction (SEI) in five patients, and with documented transmural infarction (TMI) in 11 patients. All parameters except length in the 2nd and 3rd column are significantly different from those in the first. (Modified from McMahon, et al. by permission of the American Heart Association).

Arteriographic follow-up has been proposed as an alternative to the purely clinical evaluation of progressive atherosclerosis. Indeed, several such studies have been conducted. These have been retrospective comparisons of two angiograms performed at intervals usually dictated by changes in the patient's symptomatic state. Results have been expressed, most commonly, as "percent of patients with progression," based on visual grading of arterial disease. Progression has been called present if any one of the patient's lesions underwent 20% worsening of the percent stenosis estimate, or if stenosis severity advanced by one or more levels in a six-level grading system. This patient-oriented progression assessment can be ambivalent since it is not uncommon for one lesion to worsen while another improves in the same patient. And this method of patient enrollment selects for greater-than-average progression rates. Table 1 summarizes the results of certain of these studies. Because of their retrospective nature and because of the imprecision of subjective estimates of disease, these findings must be regarded as approximations that are subject to a variety of patient selection and observer biases. Taken as a whole, these studies indicate that within 2 years, 70% of the patients selected in this manner and 40% of the observed lesions will have progressed by the specified amount at one or more of the lesion sites present in the initial study. Regression of this magnitude seldom occurred. Progression was significantly associated with lipid abnormalities in two of the three studies in which lipids were measured.

Two more recent arteriographic studies of coronary atherosclerosis progression are summarized in Table 2. In contrast with the studies of Table 1, these feature elective recatheterization of a prospectively selected patient group and a quantitative assessment of changes in the severity of focal stenoses seen on the initial angiogram. Rafflenbeul et al. used a vernier caliper method to estimate percent narrowing in all 88 significant stenoses in 25 patients initially evaluated for unstable angina, comparing the initial angiogram with an elective one obtained after 1 year of medical therapy. A 20% increase in percent area stenosis occurred in 14 lesions found in 11 patients; all six lesions initially measured at 90% area reduction became completely occluded. Five lesions found in five patients regressed by 20% area stenosis. Thus, progression was about 3 times more common than comparable regression.

In our laboratories, serial computer-assisted measurements of virtually all atherosclerotic lesions have been made in 47 patients. These men were prospectively enrolled and electively recatheterized 18 months after the initial arteriogram done for clinical indications. There were 629 coronary segments analyzed; about 50 segments appeared normal in the initial angiogram and the rest were involved with the complete spectrum of mild-to-severe atherosclerosis. Six measurements (three different frame pairs and two different observers) of each segment were made from each of the two angiograms. Luminal change in this group of segments reflects the spectrum of change in atherosclerotic coronary occlusive disease over an 18-month interval in these symptomatic patients. As shown in the histogram of figure 7, interval changes in percent stenosis were usually absent or small, although some stenoses showed measurable worsening and others, improvements. For data in this bell-shaped distribution, what should be used as the statistical criterion to distinguish between "probable actual change" vs "possibly due to variability of the method"? In addressing this statistical problem, we analyzed 39 lesions from two different injection pairs repeated at an average interval...
Table 1. Reports of Arteriographic Progression of Coronary Disease Based on Retrospective Patient Selection and Subjective Visual Assessment of Disease

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient selection</th>
<th>Criteria for progression</th>
<th>Average interval (mo)</th>
<th>Progression (%)</th>
<th>Regression (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gensini et al. 1974</td>
<td>122 CAD patients, many restudied when CABG became available. No data on symptom change. 355 arteries evaluated.</td>
<td>A</td>
<td>26 (NA)</td>
<td>76</td>
<td>46</td>
<td>0.6 0.8</td>
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<tr>
<td>Bemis et al. 1973</td>
<td>73 CAD patients with angina. 82% restudied for increasing angina.</td>
<td>B</td>
<td>24 (2-75)</td>
<td>52</td>
<td>NA</td>
<td>0 NA</td>
</tr>
<tr>
<td>Kimbiris et al. 1974</td>
<td>35 CAD patients with angina. 46% restudied for increasing angina.</td>
<td>B</td>
<td>26 (8-50)</td>
<td>69</td>
<td>NA</td>
<td>0 NA</td>
</tr>
<tr>
<td>Nash et al. 1974</td>
<td>80 CAD patients. 83% restudied for increasing angina.</td>
<td>A*</td>
<td>24 (3-108)</td>
<td>73</td>
<td>NA</td>
<td>Progression associated only with hyperlipidemia.</td>
</tr>
<tr>
<td>Rösch et al. 1976</td>
<td>58 CAD patients. 72% restudied for increasing angina. 230 stenoses and 396 initially normal segments evaluated.</td>
<td>A</td>
<td>26 (7-74)</td>
<td>66</td>
<td>33</td>
<td>New stenoses appeared in 5% of initially &quot;normal&quot; segments. All lesions with ulcerating plaques, and 58% of lesions with distal collateral progressed.</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CABG = coronary bypass graft surgery; NA = data not available in report; Pt = patient; Les = lesion.

Progression criteria: A = increase by at least one grade: (5%-24%); (25%-49%); (50%-74%); (75%-94%); (95%-99%); (100%). B = 20% increase in percent stenosis estimate, or new 100% occlusion.

* Slightly modified.

Figure 7. The spectrum of change in stenosis severity in 629 coronary artery segments in 47 patients electively recatheterized 18 months after an initial, clinically indicated coronary arteriogram. The abscissa is the difference in measured percent stenosis ($%S_2 - %S_1$). The ordinate is the frequency of occurrence of change in the various 2% difference intervals. Three standard deviations of the short-term difference distribution of the percent stenosis parameter was 10.2%. When this cutoff is used as a criterion for true change, 12% of all lesions progressed and 4% regressed.
Table 2. Reports of Arteriographic Progression of Coronary Disease Based on Prospective Study Design and Quantitative Estimates of Disease Severity

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient selection</th>
<th>Criteria for definite change</th>
<th>Prospective study interval (mo)</th>
<th>Progression (%)</th>
<th>Regression (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. 64, 1979</td>
<td>47 patients angiographically proven and symptomatic CAD. 628 lesions of all degrees of severity.</td>
<td>Absolute confidence-20% stenosis change using computer-assisted measures.</td>
<td>18</td>
<td>28*</td>
<td>3.3*</td>
<td>Serum cholesterol $\geq$ 260 mg/dl was associated with a 70% increase in the likelihood of lesion progression, as compared to normocholesterolemic risk.</td>
</tr>
<tr>
<td>Rafflenbeul et al. 20, 1979</td>
<td>25 patients catheterized during phase of unstable angina; and again after 1 year of antianginal therapy. 88 moderate-to-severe lesions.</td>
<td>20% change in vernier caliper-measured % area obstruction, roughly equivalent to 10% change in % diameter stenosis.</td>
<td>12</td>
<td>44</td>
<td>16</td>
<td>20  6 All 6 stenoses with initially more than 90% area obstruction became completely occluded.</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; Pt = patient; Les = lesion.
*Compare these figures with those of table 1.

of 21 minutes during the same catheterization. Interval changes between these two measurements reflect only changes in vasomotor tone, small variations in patient position, and the intrinsic variability of lesion analysis by this method. A histogram of this short-term percent stenosis change distribution was thus obtained, similar in format to the long-term change distribution of figure 7. The standard deviation of this distribution was called "short-term variability." We elected to use three standard deviations as the criterion for true change. Thus, a change of $\pm 10.2\%$ in the percent stenosis parameter can be designated as "true" change with a very high degree of confidence. When this criterion was applied to the data of figure 7, 12% of all lesions progressed and 4% regressed (table 2).

Certain factors were significantly predictive of the likelihood of lesion change. Initial lesion severity was a strong determinant of the likelihood of disease progression and regression. Normal segments and those with mild luminal irregularity almost never (< 1%) progressed by $\pm 10.2\%$ stenosis in this population of patients with established disease; for lesions in the 20% to 60% stenosis range, the likelihood of progression was approximately 5%; and of 37 lesions initially of 60% or greater stenosis, 19% worsened. The likelihood of comparable regression for these three lesion groups was 0%, 3%, and 14%, respectively. Progression was 70% more frequent for all lesions in patients with serum cholesterol $\geq$ 260 mg/dl than in those with normal cholesterol levels.

Using binomial probability theory for discrete variables and progression frequencies similar to those described above, we have concluded that a potentially beneficial intervention for retarding atherogenesis may be tested in 50 to 100 patients, instead of the several thousands required for trials based on clinical endpoints. Thus, the computer-assisted arteriographic approach to coronary disease intervention trials has advantages that include greatly reduced patient and physician manpower requirements, reduced costs, and more direct relevance to the mechanisms of coronary atherosclerosis progression.

Caliper-assisted and computer-analyzed assessment of changes in femoral artery atherosclerosis was performed from arteriograms in 25 hyperlipoproteinemic patients prospectively restudied at an average interval of 13 months. A continuous spectrum of measured changes occurred, similar to the observations of figure 7. Regression occurred more commonly in the treated patients experiencing substantial lowering of serum cholesterol and triglycerides. These authors are also of the opinion that the arteriographic trial is a more efficient and pathologically relevant means for evaluating progressive atherosclerosis and its prevention.
Coronary arteriography is presently the definitive procedure for characterizing the location and severity of coronary atherosclerosis; and despite certain reported limitations, we believe that the properly performed coronary arteriogram provides a true picture of the arterial lumen in life. Yet this widely-used clinical tool is currently limited by imprecise and, to a certain extent, inappropriate subjective methods of interpretation.

More objective methods for analysis of the arteriographic information content have been described. These include caliper- and vernier-based systems for measuring relative arterial narrowing, computer-assisted methods for making accurate measurements of absolute stenosis dimensions, and photodensitometric methods for extracting three-dimensional information from a planar image of the stenosis. The availability of these objective techniques has resulted in a considerable increase in our understanding of pathogenic mechanisms in coronary disease. Advances include an expanded understanding of the mechanisms of action of nitroglycerin and verapamil and of the coronary artery constriction induced by drugs or isometric stress. Stenosis measurements have served as the basis for evaluation of certain noninvasive techniques used to detect coronary disease. An analytical approach has been developed to characterize the progression (and regression) of coronary disease from serial arteriograms. We believe clinical investigations based on these techniques hold considerable promise for further advances in the understanding of human coronary pathophysiology.

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Index Terms: atherosclerosis  coronary arteriography  quantitative angiography  coronary vasomobility  progression of atherosclerosis  regression of atherosclerosis

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