Quantification of absolute luminal diameter by computer-analyzed digital subtraction angiography: an assessment in human coronary arteries

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ABSTRACT  Determination of absolute lumen diameters has been shown to be useful in predicting the functional importance of a coronary stenosis. In this study, both single-plane and orthogonal biplane digital subtraction angiograms were obtained in human cadaver coronary arteries. A single absolute diameter was calculated at the site of greatest narrowing in 20 segments by two automated computerized algorithms. Minimum and maximum diameters at the site of the stenosis were measured from pathologic sections prepared after pressure fixation. Method 1, which determines the edges by means of the first derivative of the videodensity curve, derived absolute diameters that fell between the pathologic minimum and maximum in 10 of 20 segments. Method 2, which determines the edges by an average of the first and second derivatives of the videodensity change, derived absolute diameters that fell between the pathologic minimum and maximum diameters in 15 of 20 segments. Method 1 correlated well with the maximum pathologic diameter (r = .76) and less well with the minimum pathologic diameter (r = .67). Method 2 correlated very well with the maximum pathologic diameter (r = .79) and also correlated well with the minimum pathologic diameter (r = .74). As would be expected, the computerized algorithms tended to overestimate the minimum pathologic diameter and to underestimate the maximum pathologic diameter. In six segments, two orthogonal views were analyzed; no further accuracy was discernible over single-plane determinations. Thus quantitative coronary angiography by digital subtraction angiography is sufficiently accurate to be of use in the measurement of the severity of a coronary stenosis.


THE VALUE of quantitative coronary arteriography as both a clinical and research tool is now established.1–9 Previously described methods rely on either computer-based1–5 or manual techniques6–9 to magnify the image and outline the coronary artery contours from cine angiography. However, cine film images of vessels inevitably result in indistinct borders, resulting in some inaccuracy and variability in the measurements. In addition, digitization of cineangiograms is both costly and time consuming, factors that have prevented its widespread clinical application.

Recently, two methods have been described in which digital subtraction angiograms are acquired and quantification of coronary stenoses is performed by computer algorithms.10–12 Validation of videodensiometric and geometric determination of percent stenosis by both algorithms has been performed in phantoms.13,14 However, it is likely that, in many cases, the determination of percent luminal diameter narrowing does not give an accurate appraisal of hemodynamic significance because of the fallacy inherent in assuming that there is a normal area with which to compare the visible narrowings.15–17 In addition, wide interobserver and intraobserver variability have been noted in the routine interpretation of cineangiography by percent stenosis.18,19 Conversely, absolute lumen diameter measurements have been shown to correlate well with the hyperemic response after a brief occlusion and may therefore be a better predictor of hemodynamic significance.17

Since digital subtraction angiography is a technique that is currently commercially available, we undertook to study whether automated computerized algorithms yield accurate measurements of the absolute diameter of coronary stenoses. Since phantoms fail to simulate the complex geometry of human coronary stenoses, we
used a previously validated method to test computer derived values in human coronary arteries.

Methods

Experimental protocol. Human coronary arteries obtained at autopsy were cleaned of surrounding tissue, and each branch was isolated and ligated. The arteries were harvested randomly; no clinical information was made available, although individuals with bypassed coronary arteries were excluded. To image the coronary arteries at physiologic pressures, a previously described apparatus was used to simulate coronary angiography in vivo. Briefly, each end of the coronary vessel was tied over a 2 mm vein graft cannula, forming a water-tight seal. The wider end of each adapter was fitted into flexible tubing. Two Y-port adapters were added to the tubing proximal to the site of the coronary vessel. A thin fluid-filled catheter was inserted into the sidearm of one of the adapters and was connected to pressure tubing to measure pressures just proximal to the coronary artery. Through the second Y-port, radiopaque dye was injected through another thin catheter within the larger tubing. The contrast material was injected at the ostium, simulating coronary arteriography in vivo. Saline was pumped in a pulsatile fashion from a Travenol roller pump. A screw clamp on the distal tubing was used to adjust the pressure throughout the system; by tightening or loosening the clamp and changing the pump speed, physiologic pressures were obtained. In this study, a mean pressure of 75 to 85 mm in the proximal portion of the coronary artery segment was used.

A Phillips Optimus M-200 Poly-C catheterization laboratory was used in all experiments, with the image intensifier in the 6 inch mode. An ADAC DPS 4100 digital radiography system (San Jose, CA) with a 512 × 512 × 8 bit pixel matrix was used to acquire and store the images in digital format and to perform the computer analysis.

While saline was being pumped continuously through the artery at physiologic pressures, 10 ml of meglumine diatrizoate (Renografin-76) was injected by hand through the injection Y-port. A single view of each coronary artery was obtained, using the first one or two frames before injection for background subtraction. The coronary segments were then injected with a Renografin/gelatin mixture at the same pressure as that recorded during injection, and the proximal and distal ends were ligated. The gelatin hardens upon cooling and prevents collapse of the artery during fixation.

Pathology protocol. After fixation in formalin, the artery was handled as described previously. In summary, each segment was cut into 2 mm sections, and the sections near the site identified by angiography as containing the site of interest were examined for the one containing the smallest residual diameter. Hematoxylin and eosin, as well as Verhoff’s elastic stains, were used for preparation of this section. These microscopic sections were then photographed with a Zeiss microscope with a built-in Zeiss camera at low power (4 × magnification), and Ektachrome slides were made. The Ektachrome slides were projected so that the images were five times the size of the slides. These images, which were precisely 20 times the diameter of the original pathologic sections, were traced onto paper, and measurements were made of the residual lumen at the site of each stenosis. The measured diameters were divided by 20 to obtain the actual diameters of the coronary segments at the areas of interest. Since the residual lumen in the area of greatest narrowing was frequently elliptical and often totally nongeometric, a single dimension could not accurately describe the appearance. Therefore, minimum and maximum biaxial diameters at the site of stenosis were measured.

Computer algorithms. Two algorithms were tested. Method 1, developed by Barrett et al. and validated in our laboratory, is a program in which the edges of the image are defined by the first derivative of the density curve along the vessel between two operator-identified end points. The diameter at the site of the stenosis is then determined by this algorithm and the results are given in tabular form along with the vessel diameters at the end points. Thus, for each segment, three values are determined, two end points identified by the operator and the diameter of the stenosis identified by the computer.

In method 2, developed and validated by Mancini et al., the operator enters a single point near the stenosis using a light pen. With this as a centerpoint, a computer-generated circle is drawn that can be adjusted to include proximal and distal segments of interest. Any diameter along the vessel can be rapidly determined by moving a cursor along the course of the artery. Determination of the vessel edges is performed by using an average of both the first and second derivatives of the density changes. The arterial centerline and edge detection are therefore drawn by computer and require no operator input.

In both methods, the diameter is initially calculated by summation of the pixel distance between the opposite edge locations along a line perpendicular to the centerline; an absolute value is generated based on the calibration factor of each frame (see below). The narrowest diameter generated by the computer in each analyzed segment (the site of greatest narrowing) was used for the purposes of this study.

Both methods incorporate a logarithmic transformation to correct for errors caused by the Lambert-Beer law. In addition, it should be noted that these methods are self-contained in two separate programs, and therefore the results of one would have no a priori relation to the other. The main difference between the two programs, aside from display options, is in the mathematical method used for edge detection.

Calibration. In each algorithm, a method to convert pixel diameter into absolute diameter (in millimeters) was used. This calibration factor was determined for method 1 by use of a digitally radiographed steel ball of known dimension (6.0 mm) imaged with the coronary arteriogram. By means of a light pen, the dimensions of the images of the steel ball were identified manually and the computer reproducibly calculated the number of pixels per centimeter (0.4545 mm/pixel). The calibration factor can be easily entered directly or the calculation can be performed for each analysis. In method 2, the internal diameter (1.5 mm) of the vein graft cannula was used, and a similar calculation was made.

Results

Twenty coronary segments were analyzed. Minimum pathologic diameters ranged from 0.3 to 4.0 mm (mean 1.7), and maximum diameters ranged from 1.1 to 4.3 mm (mean 2.7). The minimum and maximum diameters with the corresponding computer-derived values from both algorithms are presented in table 1.

Figure 1, A, shows the correlation (r = .67) between the minimum diameter and method 1, which overestimated the absolute minimum pathologic diameter (i.e., all the points lie above the line of unity). Method 1 results correlated better with the maximum pathologic diameter at the site of stenosis (see figure 1, B) with an r value of .76.

Figure 2, A, demonstrates the correlation of method 2 with the minimum pathologic diameter (r = .74).
TABLE I
Comparison of pathologic and angiographic luminal diameters (mm)

<table>
<thead>
<tr>
<th>Segment</th>
<th>Pathology Minimum diameter</th>
<th>Pathology Maximum diameter</th>
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<th>Angiography Method 2</th>
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All diameters by methods 1 and 2 have an error of ± 0.3 mm.

Again, the absolute minimum pathologic diameters were overestimated in that most of the points lie above the unity line. When the method 2 results were plotted against the maximum pathologic diameter, the r value was .79, the best of the coefficients (see figure 2, B). This absolute maximum pathologic diameter at the site of the stenosis generally was underestimated, however, with the points falling below the unity line. Note that the narrowest lumens, as determined by pathology, were responsible for the largest discrepancies, since the resolution of the system was less than these diameters.

Reproducibility. Two observers independently analyzed all segments using both computer algorithms, and one observer reanalyzed the segments blindly 6 months later. Interobserver variability in all segments was ± 10% with regard to absolute lumen dimension with both programs. Intraobserver variability was ± 3% with method 1 and ± 5% with method 2 in all segments.

Biplane arteriographic correlations. In six coronary segments, biplane arteriography was performed to ascertain whether a second plane might improve the accuracy of these results. In this aspect of the study, a second arteriogram was performed after rotating the artery 90 degrees to obtain an orthogonal projection. These data are summarized in table 2. Linear corre-

lations with all sets of data were similar, with values in the .65 to .75 range; no data set was significantly more accurate than another with respect to pathology. Thus the second plane added relatively little to improving the correlation with pathologic dimensions.

Limit of resolution of the cine system. To test the limit of resolution of the x-ray and digital systems used in this study, a standard line pairs apparatus was acquired onto the

FIGURE 1. Correlation between method 1 and absolute diameters at pathologic examination. A, Correlation with absolute minimum diameter; \( y = 0.95x + 1.6, \) \( \text{SEE} = 0.91. \) B, Correlation with absolute maximum diameter; \( y = 0.98x + 0.37, \) \( \text{SEE} = 0.78. \) The lines of unity are shown.
Thus, although cine film could theoretically yield more accurate results, once the cine film images are digitized this advantage will be lost. It should be recognized that no commercially available system affords more resolving capacity and that this must be regarded as state of the art.

Error analysis. Method 1 results fell between the minimum and maximum diameters in 10 of 20 segments, whereas method 2 results fell between the minimum and maximum diameters in 15 of 20 segments (assuming the margin of error to be the limit of resolution of the system, ± 0.3 mm).

Discussion

Quantitative analysis of the coronary arteriographic image requires a very precise method, which should be judged based on its accuracy, speed, and cost. Although direct caliper measurements are more objective than visual estimates, the variability is quite wide.6, 7 Magnified Vernier measurements allow very reproducible measurements, but the accuracy of the technique is limited by the visual interpretation of the luminal borders.8, 9 Furthermore, x-ray beam divergence and differential magnification cannot be corrected when analyzing standard cine angiograms. Computer-assisted image reconstruction has more recently been advocated by Brown et al.1, 2 and Gould et al.5 In this method, digital computation is used to compensate for these distortions. The strength of this method is its objective and consistent characterization of the image. However, its drawbacks include time and expense, the tediousness of tracing the lumen border, and the dependence on a high-quality cine angiogram.

Computer analysis of digitally acquired images by computer has certain theoretical and practical advantages over these previously described methods. Aside from being fully automated, which eliminates observer bias and subjectivity, the method is rapid, relatively inexpensive, and highly reproducible. Additionally, several digital angiographic systems are now commercially available. The major unresolved issue is the accuracy of the automated edge detection scheme, since one wishes to optimize the accuracy of edge detection despite variable degrees of noise in the image.

This study was therefore undertaken to determine whether videodensitometric analysis by a computer algorithm could accurately measure absolute dimensions at the site of coronary stenoses in digitally acquired images when compared with rigorously analyzed corresponding pathologic sections. An accurate assessment of coronary stenosis severity by measurement of the residual luminal diameter at the site of a
coronary stenosis is being increasingly recognized as important because (1) absolute luminal diameter measurements may provide more information than percent stenosis regarding the hemodynamic significance of an occlusion and (2) absolute measurements have been shown to correlate better with the hyperemic response than do measurements of percent stenosis.

In this study, when the results of two computer algorithms for luminal diameter determination were compared with pathologic sections, the calculated values tended to fall between the maximum and minimum pathologic dimensions. If the limit of resolution of the imaging system is incorporated into the computer-derived value, the absolute diameters of 15 of the 20 stenoses were correctly determined by method 2. This method, described by Mancini et al., was demonstrably more accurate than that of Barrett et al. for this purpose, although neither was completely accurate. Both methods gave reasonable correlations with pathologic measurements, generally yielding values between the maximum and minimum diameters, although the correlation was better with the maximum diameters than with the minimum diameters. Also, both methods appeared to be least accurate for very narrow lumen diameters, which is to be expected because the limit of the resolution of the imaging system (0.6 mm) approaches this value. In view of this limitation, which would apply to every digital system and computer algorithm, these results are excellent.

It should be noted that this validation method is perhaps the most rigorous yet devised, since human atherosclerotic stenoses are so irregular in shape. Thus, although previous validation studies in phantoms appear to yield much better correlations with the minimum lumen diameter, it would be unreasonable to expect such results in this model. To explain this further, consider that since the artery is placed without knowledge of the anatomy, there exists only a very slight probability for the artery to be lined up in such a way that the minimum diameter is parallel to the x-ray beam. Similar small changes exist to image the true maximum diameter of the stenosis. The vast majority of angiographic views of the artery will give a hybrid view that is between the minimum and maximum value. This explanation undoubtedly explains why data from a second plane did not add demonstrably to the correlation with pathologic dimensions. Thus, given the complex asymmetric and eccentric nature of the stenoses in these human coronary arteries, it is not surprising that the computer-derived values for both computer methods tended to overestimate the true minimum diameter and underestimate the maximum diameter, thus falling in between. In most of the stenoses in this study, an eccentrically placed asymmetric lumen, and even multiple lumens, were observed, which are frequent findings at autopsy. Therefore, we believe that this model is an appropriate test of any quantitative angiographic method that may be applied to human coronary atherosclerosis.

In this regard, it is well recognized that a single-plane angiographic view of ovoid lumens can either underestimate or overestimate severity of stenosis. In the study by Thomas et al., the greatest discrepancies between angiography and pathology occurred in stenoses with a large difference between the minimum and maximum diameter. In most of their reported cases, residual lumens were approximately circular, usually resembling an ellipse or a “D” shape. Slitlike lesions and crescentic shapes, the type that would cause the greatest discrepancy when analyzing only a single view, are rare when pressure fixation is used, as was done in the present study. Both in asymmetric phantoms and in human coronary arteries, they proved that any deviation from circular geometry induced a major error in stenosis calculations, although videodensitometric analysis was more accurate. Furthermore, in vessels with two or more eccentrically placed lumens in the stenosis, the computer-derived value is likely to be greater than the pathologic values, since the limits of resolution do not allow the atherosclerotic portion between the two lumens to be fully taken into account.

In addition, a possible explanation for the larger computer-generated lumen diameter values compared with the minimum pathologic diameter may be shrinkage of the arterial segment during histologic preparation. However, Siegel et al. have shown that in vessels with moderate-to-severe atherosclerosis, luminal area does not change during the process of fixation. Also, our specimens were fixed while distended under physiologic pressure (and specifically the same pres-

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**TABLE 2**

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All diameters by both angiographic methods have an error of ±0.3 mm.
sure as during angiography), and this should allow the most accurate absolute measurement. With multiple stenoses in a vessel, however, the more distal stenoses may not distend as much as the proximal stenosis, resulting in slight collapse.

Clinical applicability. With the demonstration that absolute lumen diameters can be easily and accurately obtained with this method, the potential for clinical applicability becomes significant. However, the data regarding what diameter constitutes a hemodynamically significant narrowing are somewhat unclear. McMahon et al.2 found that lesions of 0.9 mm diameter or less were "critical," producing clinical symptoms at rest.2 Harrison et al.17 demonstrated that proximal stenoses of the left anterior descending coronary artery with a minimum diameter of less than 1.5 mm caused abnormal reactive hyperemic responses, whereas vessels with minimum lesion diameters of more than 2.3 mm had normal reactive hyperemic responses. Responses of vessels with diameters between these two values were variable. Harrison found that absolute diameter measurements predicted hyperemic response far better than did percent area stenosis or percent diameter stenosis, and White et al.16 showed that hyperemic flow had no relation to percent stenosis. Nichols et al.24 provided evidence that in patients with single-vessel disease, stenoses of the left anterior descending artery with residual diameters under 1.0 mm were associated with decreased regional myocardial blood flow, whereas stenoses with residual diameters over 1.0 mm allowed normal regional myocardial blood flow. Thus lumen diameters of less than 1.0 to 1.5 mm seem to correlate best with hemodynamic significance. It is important to note that the range between 1.0 to 2.5 mm was the most accurate portion of the correlation with pathologic results in our study. Conversely, the least accurate portion, that less than 1.0 mm, is actually of least clinical relevance, since stenoses in this range are certainly significant, even if the technique becomes less accurate in deriving its absolute value. Studies in symmetric phantoms confirm that diameters less than 1.0 mm are often overestimated and those greater than 4 mm are underestimated, 25 a finding confirmed in the present study.

In conclusion, computer-assisted analysis of coronary dimensions at the site of coronary stenoses yields measurements of lumen diameter that fall between the actual minimum and maximum diameter of the stenosis as measured in corresponding pathologic sections. This intermediate value is highly representative of the severity of a stenosis.

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*Circulation*. 1988;77:484-490
doi: 10.1161/01.CIR.77.2.484

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

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