Automated quantitative coronary arteriography: morphologic and physiologic validation in vivo of a rapid digital angiographic method

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ABSTRACT  Quantitative coronary arteriography has been shown to be useful in assessing the extent of coronary disease, its functional significance, and its response to therapeutic interventions. Most current methods rely either on hand-drawn arterial contours or automatic edge-detection algorithms applied to 35 mm cineangiograms. To assess the performance in vivo of a new, fully automatic, rapid coronary quantitation program, dogs were instrumented with precision-drilled, plastic cylinders to create intraluminal stenoses in the left anterior descending and/or circumflex arteries, as well as with high-fidelity micromanometers and electromagnetic flow probes. Stenosis diameters ranged from 0.83 to 1.83 mm. Biplane, on-line, digital coronary angiograms and cineangiograms were recorded during standard selective coronary arteriography in the closed-chest preparation. The on-line digital images were analyzed in nonsubtracted and subtracted modes. Cineangiograms were digitized to allow coronary quantitation by the same computer program. There was an excellent correlation between known and measured minimal diameter stenoses \( r = .97, \) SEE = 0.09 to 0.24 mm). Interobserver and intraobserver variability analysis showed high reproducibility \( r = .90 \) to .97, SEE = 0.12 to 0.23 mm). The best results in both analyses were achieved by nonsubtracted digital imaging and the worst by cineradiography. Measures of percent diameter stenosis, percent area stenosis (geometric and videometric), and absolute minimal cross-sectional area (geometric and videometric) were all significantly correlated with independent measures of actual coronary flow reserve. This study provides direct anatomic and physiologic validation in vivo of a new and rapid coronary quantitation method suitable for analysis of both digital angiograms and cineangiograms.


QUANTITATIVE coronary arteriography has been shown to be useful in assessing the extent of coronary disease, its functional significance, and its response to therapeutic interventions such as angioplasty, thrombolysis, and diet therapy. Most current methods rely either on hand-drawn arterial contours or automatic edge-detection algorithms applied to 35 mm cineangiograms. Validation of the use of digital angiography in vivo for fully automatic edge-detection and quantitation of coronary stenoses by both videometric and geometric methods has not been previously report-
ed. The purposes of this investigation were (1) to assess the performance in vivo of a new, fully automatic, rapid coronary quantitation program by evaluating its accuracy compared with known stenosis dimensions in a range approaching dimensions likely to be encountered clinically and by comparing the analysis of biplane, on-line digital images to the analysis of cineangiograms and (2) to determine the relationship between morphologic measurements and both predicted and measured coronary flow reserve.

Methods

Sixteen mongrel dogs weighing 21.4 to 40.9 kg were anesthetized with sodium pentobarbital (35 mg/kg), intubated, and ventilated with a Harvard ventilator. Supplemental oxygen and bicarbonate were administered and ventilatory rates were adjusted to maintain pH, \( P_{O_2} \), and \( P_{CO_2} \) within normal ranges. A left thoracotomy was performed in the fifth intercostal space and the heart was suspended in a pericardial cradle. The proximal left anterior descending and circumflex coronary arteries were dissected free and encircled by appropriately sized and calibrat-
ed electromagnetic flow probes (Carolina Medical Electronics, Inc.), a soft rubber elastic tie, and a silk suture. A No. 5F high-fidelity micromanometer (Millar Instruments) was inserted through a stab wound in the ventricular apex. The left carotid artery and jugular vein were instrumented with No. 9F sheaths (Cordis). All animals received 12,000 to 15,000 U of heparin in 1000 to 3000 U intravenous boluses throughout the entire protocol to prevent clot formation.

All pressure and blood flow measurements were recorded on a Gould 2800S recorder. Baseline measurements of heart rate, systolic blood pressure, left ventricular end-diastolic pressure, peak positive and negative dP/dt, basal epicardial blood flow, and hyperemic blood flow after a 20 sec coronary occlusion were made. The left main coronary artery was then engaged with a No. 7F or 8F angiographic catheter (USCI) under fluoroscopic control. A standard 0.016 mm angioplasty guidewire was passed through the catheter and advanced into one of the main coronary arteries. The angiographic catheter was then removed, leaving the wire in place. Precision-drilled, radiolucent, nylon cylinders (Poly C Co., Ann Arbor, MI) were advanced into either or both of the proximal coronary arteries. These cylinders were 4 mm in length and No. 6F in circumference. Two sets were manufactured, one with a 2 mm long initial bore designed to fit snugly over a No. 3F (1 mm diameter) Renthrop catheter (USCI) and a second with the initial 2 mm long bore designed to fit snugly over a No. 5.4F (1.83 mm) Kifa catheter. The distal 2 mm of the cylinders were precision drilled to produce lumen diameters ranging from 0.71 to 1.83 mm. The cylinders were positioned by inserting them over the tip of the appropriately sized catheter, which was then advanced over the guidewire and into position in the proximal coronary arteries. Once in a suitable position, the cylinders were sutured into place by rapidly tying the silk suture around the segment of coronary artery containing the intraluminal cylinder while the advancing catheter and guidewire were quickly removed to reestablish antegrade flow.

After reattainment of hemodynamic stability, all pressure and flow measurements were repeated. Probes and instruments were then removed, ribs were reaproximated, and the chest wound was closed with heavy silk sutures.

Biplane digital coronary angiograms were then obtained in projections that optimized separation of the stenotic area from surrounding vessels. Angiograms were acquired on a digital angiographic computer (DPS-4100C, ADAC Laboratories, Edenvale, CA) interfaced to a standard cineangiographic system (Philips Optimus M200, Eindhoven, The Netherlands). The radiographic input signal was kept constant (fixed kVp, mA, and pulse width x-ray exposure). A 12.5 cm field of view and a small focal spot size (0.6 mm, nominal) were used. Images were acquired at 10 frames/sec in a 512 × 512 matrix with 256 gray levels. Images underwent logarithmic transformation to account for Lambert-Beer exponential x-ray absorption. Cineangiograms in the identical views were also acquired by the same radiographic technique. These images were acquired at 30 frames/sec. Care was taken to ensure that both the stenotic area and the angiographic catheter were within the central portion of the radiographic field to minimize any possible effects of pincushion distortion. Care was taken to ensure that the optical densities of interest were on the linear portion of the sensitometric curve of the film (Kodak CFR) by routinely analyzing a density step-wedge.

To analyze the cinefilm, orthogonal images that showed the lesions optimally were projected on a Vanguard viewer (Model XR-15, Melville, NY), which was optically coupled to a video camera identical to the one in the on-line digital system. With 2.4:1 optical magnification, the resulting video signal corresponding to a subregion of the 35 mm frame was digitized at 512 × 512 × 8 bit resolution onto the same digital angiographic computer system. The video noise of this method of film digitization was reduced by averaging four video frames before storage.

Both film and digital images were subjected to preprocessing before quantitative analysis. The digital images were processed both with and without mask subtraction. The single mask frame and the image best demonstrating the stenosis were selected so as to minimize any misregistration artifacts in the region of the stenosis. Subtracted and nonsubtracted digital images underwent gray-scale inversion to produce white-on-black pictures comparable to the gray scale of negative film images. All images were subjected to a gray-scale modification to linearly expand their individual scene dynamic range to fill the full 8 bit dynamic range of the digital radiographic system. This preprocessing step is fully automated. All directly acquired digital images were then subjected to digital magnification by a factor of four and the digitized film images were digitally magnified by a factor of two. This was achieved by bilinear pixel interpolation using the system's array processor. Although this digital magnification does not improve the density of the spatial sampling of the electronic imaging methods, it does provide additional precision in the analysis techniques of the quantitation program. The final overall magnifications of the digital images and the digitized film images were ×4 and ×4.8, respectively. These magnifications were determined experimentally to optimize the quantitative analyses of both film and digital images. The analyzed effective pixel resolution was thus 2048 × 2048 for the on-line digital images and 2458 × 2458 for the digitized film images.

All images were analyzed with a previously described automatic coronary quantitation program.3 The operator chooses a circular region for analysis by first positioning a light-pen cursor over the arterial lesion and then adjusting the size of the circular region to encompass the desired segment of artery to be analyzed. The software then proceeds without further operator intervention. The centerline of the arterial segment within the analysis region is determined by analyzing circular pixel density profiles of decreasing radii, with use of simple signal processing techniques to locate the angular positions of the proximal and distal portions of the arterial segment at each radius. When the radius approaches zero, the entire arterial centerline has been calculated. Linear density profiles perpendicular to the arterial centerline are extracted over the entire length of the arterial segment. Edge points are found by analyzing the linear density profiles in two passes. Initial edge points are found by noting the density of points at the first and second derivatives of each perpendicular density profile and then determining the location of the points that fall at a value of 75% of the difference between the densities at these derivative extrema (i.e., weighted toward the first derivative extrema). This method was found to give best accuracy and precision of measurement of radiographic phantoms in the 0.5 to 5 mm diameter range.3 These initial gradient-determined edge points are then examined for spatial continuity and outliers are discarded. The gray-scale densities of initial edge points are then used to determine final edge points with local thresholding. The set of accepted threshold densities for either edge (independently) is smoothed and any threshold values discarded during the first pass are replaced by linear interpolation from neighboring valid edge points. Each perpendicular profile is reanalyzed and the locations of the final edge points are determined by this locally adaptive threshold method. The geometric diameter at any point along the centerline is the distance along each perpendicular profile between edge points on opposite sides of the artery. Calibration is achieved by measuring a magnification factor based on the known size of the angiographic catheter. Calibrations were obtained from the non-
subtracted images and film images. The catheter in the subtracted images was not used for calibration because of the routine occurrence of spatial misregistration. The computer program determines videodensitometric cross-sectional area at each point along the centerline by integrating the densities across the perpendicular profile from edge to edge. These areas are corrected for background by subtracting a linearly interpolated background determined by the density values at the edge points. The final computer output consists of the arterial image with arterial edges and centerline and plots of geometric diameter (calibrated with reference to the known diameter of the angiographic catheter), densitometric relative cross-sectional area, maximal percent diameter stenosis, and maximal area (densitometric) percent stenosis (figure 1). Approximately 1 min is required to complete the analysis of each view of a single lesion.

This process was repeated for the digitally acquired images after applying a geometric image transformation that removes pincushion distortion, according to a previously described method.4 Film images were not corrected for pincushion distortion.

Of the 16 animals studied, three experienced fibrillation immediately after placement of the stenotic cylinder and postmortem examination revealed thrombosis of the lumina. Three animals had fibrillation during contrast injection and one animal died after coronary dissection. In the nine remaining dogs there were eight cylinders in circumflex arteries and five cylinders in left anterior descending arteries. One stenosis was excluded from analysis because it had slipped from its suture and contrast streaming around the cylinder could not be excluded. One stenosis could not be optimally separated from small, adjacent, perforating branches. Two stenoses could not be analyzed because calibration of the angiographic catheter was not reproducible due to poor contrast density between it and the background. One stenosis required editing of the automatically determined edges to preclude spurious tracking of adjacent rib and soft-tissue shadows in the nonsubtracted image and therefore was excluded from analysis. Finally, one dog died during the final contrast injection and images could not be analyzed in the subtracted mode. Thus eight nonsubtracted and eight subtracted online digital images and nine film images could be analyzed and these ranged in minimal diameter between 0.83 and 1.83 mm. In one of these regions, the corresponding reactive hyperemia could not be determined accurately because of instability of the electromagnetic flow probe after insertion of the cylinder. Postmortem examination in all dogs from which data were analyzed showed absence of any intraluminal clot.

Morphologic characteristics of the stenosis were used to calculate a predicted flow reserve as proposed by Kirkeide et al.5 and simplified by Herrold and Borer6 by the following equation:

\[
0 = \frac{{(-\rho(Q_{\text{r}})^2)}^2 \cdot ((A_n - A_0)/A_n)^2}{{(P_n - P_r)/\text{CFR}_n}} + (8\pi \mu L Q_{\text{r}})/A_n^2 X
\]

where \(X\) = predicted coronary flow reserve, \(\rho\) = blood density (assumed to be 1.06 g/ml), \(\mu\) = absolute blood viscosity (assumed to be 0.05 Poise), \(A_n\) = cross-sectional area of the normal segment, \(A_s\) = cross-sectional area of the stenotic segment, \(L\) = length of stenosis (2 mm), \(P_n\) = perfusion pressure (assumed to be 100 mm Hg), \(P_r\) = critical closing pressure (assumed to be 10 mm Hg), \(\text{CFR}_n\) = measured, normal coronary flow reserve before insertion of the cylinder, and \(Q_{\text{r}}, r\) = normal, resting flow (assumed to represent a velocity of 15 cm/sec in the cross-sectional area of the normal segment).

All hemodynamic variables were averaged from 5 to 10 beats recorded at 100 mm/sec paper speed during steady rates. Reactive hyperemia was determined in triplicate and averaged by determining the ratio of maximal flow after a 20 sec occlusion to basal flow. Each image set was analyzed by an independent observer to obtain minimum diameter, percent diameter stenosis, and relative area stenosis. Results from each orthogonal view were averaged. Intraobserver and interobserver variability were established by a repeated analysis performed at least 3

**FIGURE 1.** Images from a study with a stenosing cylinder in the circumflex artery of a dog. The upper and lower panels show the subtracted and nonsubtracted images, respectively. The right-hand panels show the magnified views. The lower right-hand panel shows the screen overlay with the quantitative variables, stylized arterial segment, and the plots of geometric diameter (diamonds), densitometric relative cross-sectional area (solid line), and the approximation of cross-sectional area as calculated from the geometric diameter data, assuming circular cross-section (dashed line). The automatically determined edge is shown on this image.
weeks later by the original observer and by a second independent observer.

Results were analyzed by standard linear, polynomial, and logarithmic regression analyses: however, no statistically significant improvements were noted when polynomial and logarithmic regressions were compared with linear regressions. Thus all regression results referred to below represent the linear regression results. Standard errors of the estimate were tested by the standard F statistic derived from the ratio of the mean square errors. Subsequently, an analysis of covariance was used to determine significant differences in the slope and intercept values of the regression results.7 Correlation coefficients were tested by a Fisher's Z transformation.8 Hemodynamic data were compared with a paired Students' t test. Results were considered significant at p < .05.

**Results**

Hemodynamics measured before and after placement of the cylinders showed no significant changes (table 1).

Pincushion correction of the small-field-of-view images with centrally located stenoses and catheters did not affect the results and therefore only uncorrected data are presented. Figure 2 shows the results of the measured minimum diameter as assessed by the automated technique compared with the known lumen diameters. A high correlation was obtained for both the subtracted and nonsubtracted on-line digital acquisitions. Automated analysis of film acquisitions showed a poorer overall correlation and almost a tripling of the standard error of the estimate. Table 2 summarizes the full regression results. Statistical analyses showed no significant differences among modalities with regard to slope, intercept, and r values. The standard error of the estimate was significantly greater with the use of film (p < .03 vs subtracted and unsubtracted images).

Figures 3 and 4 show the relationships between percent diameter stenosis and reactive hyperemia, and percent area (videodensitometric) stenosis and reactive hyperemia, respectively. All image modalities were highly correlated with the measured reactive hyperemia and no significant differences were noted among the different image modalities. Moreover, no significant differences in the precision of correlation with reactive hyperemia was found between percent area and percent diameter measurements. All methods showed r values between -.78 and -.85.

Figures 5 and 6 show the relationship between stenotic segment area, measured both geometrically and videodensitometrically, and reactive hyperemia. As in the prior analyses, all image modalities yielded quantitative variables that were highly correlated with reactive hyperemia (r = .77 to .83) and no statistical differences among modalities were noted.

Figure 7 shows the relationship between measured flow reserve and predicted flow reserve. A significant correlation was noted when the subtracted images were analyzed and a nearly significant correlation was seen with the nonsubtracted images (p = .0567). In con-

**TABLE 1**

<table>
<thead>
<tr>
<th>Summary of hemodynamic findings before and after insertion of stenosis cylinders</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Peak positive dP/dt (mm Hg/sec)</td>
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<tr>
<td>Peak negative dP/dt (mm Hg/sec)</td>
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<td>Mean basal coronary blood flow (ml/min)</td>
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^A Value based on only eight dogs because of flow probe instability in one dog after insertion of cylinder.

**TABLE 2**

<table>
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<tr>
<th>Regression results for analyses of different image modalities in determining minimum diameter</th>
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<tbody>
<tr>
<td>Image</td>
</tr>
<tr>
<td>Nonsubtracted</td>
</tr>
<tr>
<td>Subtracted</td>
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<tr>
<td>Film</td>
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^A p < .03 vs SEE of film analysis.
contrast, predictions made from film measurements did not approach statistical significance and demonstrated a very low r value (.49). Despite these major differences, statistical analysis of the regression results failed to demonstrate any significant differences, likely because of the small number of points and the wide variability of results.

Figure 3 shows the results of interobserver and intraobserver variability for measurement of the minimum stenosis diameter and geometric cross-sectional areas. All r values ranged from .90 to .97, with the best results occurring in nonsubtracted, on-line digital images (r = .97, SEE = 0.12 mm). No statistical differences were noted among r values, slopes, intercepts, or standard errors of the diameter measurements. However, in both the intraobserver and interobserver analyses, the standard error of the estimate for cross-sectional area measurements was greater for the film analyses than for the nonsubtracted on-line digital image results (intraobserver variability): 0.56 mm² for film vs 0.20 mm² for nonsubtracted images, p < .02; interobserver results: 0.50 mm² for film vs 0.15 mm² for nonsubtracted images, p < .005). Although the standard error of the estimate for cross-sectional area was smaller for

FIGURE 3. Regression analysis between quantitative percent diameter stenosis, determined from each image type, and reactive hyperemia. Regression lines are shown. No significant differences among these analyses were found.

FIGURE 4. Relationship between reactive hyperemia and videometrically determined percent area stenosis. No statistically significant differences in these regressions were found.

FIGURE 5. Relationship between relative hyperemia and stenotic segment area. No statistically significant differences were noted among results from different image modalities.

FIGURE 6. Relationship between reactive hyperemia and stenotic segment area determined from a combination of the videodensitometric data and the catheter calibration. No statistical differences among the regressions were noted.
FIGURE 7. Relationship between measured and predicted reactive hyperemia (RH).

the subtracted compared with film images, this difference was not statistically significant.

Discussion

This study represents the first time that a fully automated, coronary quantification algorithm has been validated on both morphologic and physiologic grounds in a preparation in vivo. Particular care was exercised to mimic clinical imaging conditions by using known stenotic luminal diameters in ranges approaching those likely to be encountered in patients with significant coronary stenoses. Our findings demonstrate that minimal luminal diameter can be measured rapidly and accurately with this technique and that on-line digital images allow greater morphologic precision than routinely processed cineangiograms. The study demonstrates that the clinically used indexes of coronary stenosis assessed by the current technique bear significant relation to reactive hyperemia, a physiologic measure of the importance of a coronary stenosis. Finally, the study demonstrates that hydraulic equations designed to predict reactive hyperemia solely from morphologic features may provide a useful conceptual approach to predicting the potential significance of a stenosis in a component analysis scheme but that substantial differences between measured and observed reactive hyperemia can occur, even in a relatively uniform animal preparation. These differences are expected to be more pronounced in patients.

Morphometric precision. Many methods have been proposed for the quantitation of coronary lesions, and the precision of most of these methods has been determined in radiographic phantom models, in arterial strips harvested from cadavers, or in noncardiac preparations in vivo. No prior method has been validated in a cardiac preparation in vivo. The proposed method demonstrates very accurate measurements of precision-drilled stenosis cylinders that were imaged in a closed-chest preparation in the coronary arteries of a beating heart. This preparation very closely mimics clinical conditions. The results suggest that clinical implementation should provide a highly accurate method for morphologic quantitation of coronary stenoses. Several conditions, however, must be met. First, adequate separation of the lesion from adjacent structures is required to minimize the likelihood of inaccurate edge detection. Although the program has been designed to allow operator editing of edges, this procedure may increase interobserver and intraobserver variability. One stenosis in this study required such editing and was therefore excluded from analysis. It is anticipated that diverse clinical conditions and variations in imaging characteristics of different x-ray systems will mandate use of such editing features, particularly in designation of "normal" segments and in analysis of stenoses at branch points. Second, the accuracy of the absolute measurements is heavily dependent on the reliability of the calibration system used. The angiographic catheter was used for this purpose in preference to more elaborate methods that might be more difficult to implement clinically. Inaccuracies of this approach have been shown to arise from several factors, including catheter material, manufacturing variabilities in lumen size, and the differential magnification that occurs when the stenosis and the catheter tip are at different distances from the x-ray source. Nevertheless, this remains the most con-

| Table 3 |
| Results of intraobserver and interobserver variability analyses |
| | Nonsubtracted (n = 8) | Subtracted (n = 8) | Film (n = 9) |
| Intraobserver | | | |
| r | .97 | .90 | .92 |
| SEE (mm) | 0.12 | 0.21 | 0.23 |
| SEE (mm²) | 0.20 | 0.29 | 0.56 |
| p value | <.0001 | <.003 | <.0005 |
| Interobserver | | | |
| r | .97 | .90 | .92 |
| SEE (mm) | 0.12 | 0.19 | 0.21 |
| SEE (mm²) | 0.15 | 0.25 | 0.50 |
| p value | <.0001 | <.003 | <.0006 |

*p < .02; #p < .005 for film vs nonsubtracted results.
venient approach and the results from this study and others suggest that it yields values of sufficient accuracy. The importance of the calibration is underscored by two instances in this study that precluded accurate calibration because of poor image contrast between the catheter and background. Under such circumstances only relative measures of stenosis severity are feasible. Finally, calibration of the nonsubtracted digital images was also used for the analysis of the subtracted digital images because of the frequent occurrence of spatial misregistration, which often resulted in spurious edges in the area of the catheter shaft.

Overestimation of diameters less than 1 mm has been previously reported for several automated techniques. Subtracted images yield measures from images. No caliper hand-held obtained calibration because of poor image contrast between the catheter and background. Under such circumstances only relative measures of stenosis severity are feasible. Finally, calibration of the nonsubtracted digital images was also used for the analysis of the subtracted digital images because of the frequent occurrence of spatial misregistration, which often resulted in spurious edges in the area of the catheter shaft.

Overestimation of diameters less than 1 mm has been previously reported for several automated techniques. The diameters studied in this investigation ranged from 0.71 to 1.83 mm and the smallest diameter imaged successfully was 0.83 mm. The regression analyses do not suggest overestimation of sizes within this range. Figure 2 and table 2 show regression slopes that were actually less than unity. It is postulated that this is due to measurement of only the minimal stenosis diameter, not average diameters over the entire length of the stenosis. Phenomena such as motion blurring, limited spatial resolution, oblique orientation of the vessel with respect to the x-ray beam, and geometric magnification would all lead to overestimation, not underestimation, thus providing the rationale for use of this approach. For example, in the experience of this laboratory, quantitation of a 0.4 mm diameter cylindrical phantom (D. Skorton, University of Iowa) yielded a mean diameter of nearly twice the actual size and a minimum diameter of 0.5 mm. Thus accurate results even in very small lumina can be anticipated with minimum diameter measurements. It is unknown whether lumina of smaller caliber could also be measured as accurately in vivo, but physical limitations in maintaining patency and antegrade flow precluded a direct assessment of much smaller lumina in the canine preparation.

Digital vs film images. Few direct comparisons of digital coronary arteriographic and film-based arteriographic results are available. Tobis et al. compared hand-held caliper determinations of coronary stenoses from standard cineangiograms and digital angiograms obtained with fluoroscopic and radiographic exposure levels that were processed by either a blurred-mask or a single-mask frame. In addition, the latter digital images were assessed from edge-enhanced and magnified images. No significant difference in mean percent diameter stenosis measurements or in variability of measurements from any of the three different images were reported. Vas et al. assessed visual estimation from both cine film and digital caliper measurements from magnified digital images and concluded that no differences existed between the two methods and that the use of digital calipers could substantially reduce interobserver and intraobserver variability. Bray et al. compared cineangiograms to digital angiograms processed by the high-pass temporal filtration technique. Using hand-held caliper methods, this group showed a modest correlation between percent stenosis measurements from the two image types and no difference in interobserver variability. Absolute diameters and their accuracy could not be evaluated in these studies nor were automated approaches used.

In contrast, our technique allows a direct comparison of digital and cine images for absolute quantifiability with a fully automated approach. The results showed some deterioration in accuracy and reproducibility when film is used for quantitative coronary arteriography. In addition, the findings suggest that analysis of subtracted images yields results of equivalent precision but with slightly higher interobserver and intraobserver variability. This increased interobserver and intraobserver variability was not significantly different from the higher variability seen in the film analyses. We believe this increase is caused by higher image noise and the potential presence of subtraction artifacts.

Factors limiting precise stenosis measurement have been recently reviewed. Although film-based radiography has a very high theoretical resolution, several factors prevent attainment of this maximal resolution in clinical circumstances. The difference in attenuation coefficients between iodinated contrast medium and tissues is not great and may perturb edge detection in areas with significant variations in background density. The usual measurement of the resolving power of a system by use of tungsten wires or lead stripes does not truly reflect this much poorer object contrast in coronary angiograms. Moreover, the usable spatial resolution of film, considering the physical properties of cesium iodide image intensifiers, the effects of the main objective lens in the image distributor, and the cine camera optics, is markedly deteriorated from the theoretical intrinsic resolution of cine film and is approached by that of a high-quality video pickup tube. A second major factor is that the automated edge-detection scheme used in this investigation was optimized for the noise frequency of digital images. Finally, this investigation was performed on a routinely used clinical imaging system with only one film type and one processing method. Different processing systems and film types may show a different relative accu-
racy when compared with digital images. Thus the small differences shown in this study may not apply under all circumstances and in all laboratories. Moreover, in spite of these findings, the relationship between commonly measured variables of coronary stenosis and reactive hyperemia could not be shown to be significantly different among modalities, suggesting that no major differences are likely to be found in clinical applications.

The slight improvement in accuracy of nonsubtract-ed over subtracted images is likely related to small degrees of misregistration artifact and increased noise of subtracted images in the region of the stenosis that affected the edge-detection algorithm. Such problems might be improved with the use of blurred masks or electrocardiogram-gated masks. Of practical importance, however, is that the acquisition of nonsubtract-ed images is faster and less technically demanding than the acquisition of subtracted images because patient and cardiac motion will not affect the images as severely. Despite great advances in other aspects of digital imaging, misregistration artifact caused by patient motion remains one of the commonest causes of image degradation, and therefore the demonstrated accuracy of nonsubtract quantative digital angiography should enhance clinical implementation and acceptability of the proposed techniques.

Comparison of flow reserve measurements. Very accurate coronary quantitation has been shown to be useful in both reflecting and predicting coronary flow reserve. Thus was important to substantiate that the proposed computer-generated results bore some relation to the physiologic importance of the stenoses. As demonstrated in figures 3 to 6, this was indeed the case. This establishes the potential usefulness of this specific automatic program for studies designed to assess the relationship between morphologic variables and physiologic aspects of coronary flow. It should be emphasized, however, that in this canine preparation there were no ambiguities in designation of the normal segment and that there was relative uniformity in hemodynamics and other factors that might significantly affect flow reserve measurements. Despite this, only moderate correlations with flow reserve were obtained with all indexes and this is in keeping with the finding that such relationships in heterogeneous patients are even less well correlated.

The analysis shown in figure 7 serves to underscore the fact that isolated component analysis of coronary dynamics can be performed with this algorithm. The technique, however, will require further modification to automatically determine stenosis length as well as entrance and exit angles to be more applicable and comprehensive when used to analyze the complex coronary configurations seen in patients. The imperfect prediction of flow reserve is likely related to sever-al factors, including anesthesia and acute surgery, changes in variables such as actual perfusion pressure, presence of collateral flow, and state of vascular tone. These factors are not considered in a component analysis as emphasized by Kirkeeide et al. The analysis, however, does demonstrate that apparently small differences in morphologic accuracy can lead to major differences in the accuracy of predicted measurements, as was the case for the film images in this study.

The component analysis approach is useful because it defines the theoretical flow reserve attributable solely to morphologic features and allows interpatient comparison purely on anatomic grounds. The concept would likely be most useful, however, in conjunction with an actual measure of flow reserve. The difference between theoretical flow reserve as calculated from morphologic features and the actual flow reserve would then reflect the extent to which other physiologic variables such as presence of collaterals, differences in regional muscle mass, and amount of viable myocardium are affecting the flow reserve measurement. This would alert the clinician to consider the presence of these other, less easily measured, factors and would allow direct evaluations of the importance of their effects as well as those of nonmechanical interventions that do not work solely by altering the morphologic appearance of lesions. This approach may aid in drug selection, for example, and in monitoring of therapeut-
tracted images even in ill patients, and the availability of the proposed program that requires only a short time for analysis of a single view are expected to overcome the major obstacles to wider clinical application of coronary quantitation. This physiologically meaningful and prognostically important information will be useful in both refining the therapy of patients and understanding the complex anatomic-physiologic relationships that determine their prognosis.

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