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Variable Morphology of Coronary Atherosclerosis: Characterization of Atherosclerotic Plaque and Residual Arterial Lumen Size and Shape By Epicardial Echocardiography

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The purpose of this study was to evaluate the in vivo characteristics of coronary atherosclerosis by using high frequency epicardial echocardiography. High frequency epicardial echocardiography was used to evaluate residual lumen and wall morphology at the sites of maximal coronary atherosclerosis in 26 patients undergoing coronary artery bypass grafting.

The maximal/minimal wall thickness ratio was 3.1 ± 0.2 (mean ± SEM) with a large range (1.3 to 7.5). Portions of the wall were normal in 16 of 31 lesions; the percent normal circumference ranged from 9% to 85%. Maximal/minimal lumen diameter ratio was 1.5 ± 0.1 (range 1.1 to 2.9). The shape of the residual coronary lumen was noncircular in 16 lesions: oval in 13 and complex in 3. The residual coronary lumen was eccentrically placed within six arteries. These data emphasize the variability of residual lumen and wall geometry in atherosclerosis.

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High frequency epicardial echocardiography is a technique that can directly evaluate coronary artery wall and lumen geometry in vivo at the time of cardiac surgery (Fig. 1). Measurements obtained with this technique have been validated by in vivo animal studies and histologic postmortem studies (1).

We (2) have previously shown by utilizing high frequency echocardiography that in vivo coronary atherosclerosis is more widespread than the coronary angiogram predicts. Details of the coronary artery morphology cannot be visualized by angiography (3,4). Other methods are needed for more precise in vivo assessment and delineation of atherosclerotic disease, complementing ex vivo pathologic studies that have shown that atherosclerosis has variable effects on lumen morphology, causing varying residual lumen shapes from circular to oval to complex (5,6).

The purpose of our study was to provide a detailed description of the morphology of atherosclerotic coronary arteries, in vivo, using high frequency epicardial echocardiography.

Methods

Human Postmortem Hearts

Within 12 h of death and immediately after removal from the cadaver, 10 hearts were washed in a normal saline solution. Polyethylene cannulas were inserted into the proximal left anterior descending, left circumflex and right coronary arteries and connected to a perfusion pump. The heart was suspended in a water tank and a normal saline solution was infused through the cannulas at a mean distending pressure of 90 to 120 mm Hg. After high frequency echocardiographic scanning of the coronary arteries, the heart was removed and the vessels were perfused with 5 to 10 ml of a barium sulfate, formalin, gelatin mixture (barium sulfate 1.2 g/ml, gelatin 0.2 g/ml, potassium iodide 0.3 g/ml, dissolved in a solution of distilled water with 1% octanol and 10% sodium biphosphate, and sodium phosphate dibasic with 0.5 to 2 ml of 10% formalin as an activating agent) (7), at the mean distending pressure that had been recorded in the water tank. The heart was then pressure fixed before coronary artery samples were taken for microscopic evaluation and morphometric analysis (see later).

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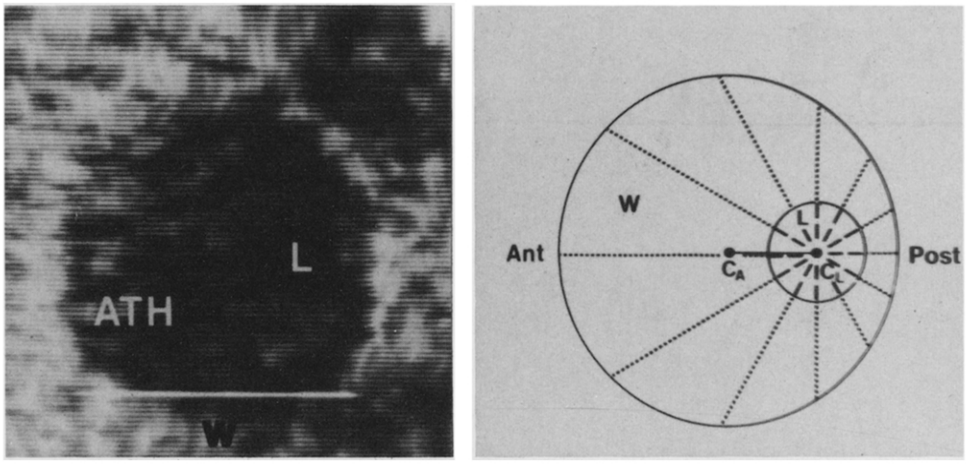

Figure 1. A stop frame high frequency epicardial echocardiographic image of a coronary artery segment in cross section. The lumen (L), atherosclerotic plaque (ATH) and arterial wall (W) are labeled. On the right of this image is the tracing convention used for all lumen, wall and eccentricity measurements of the residual lumen. Ant = anterior; C_A = original lumen; C_L = residual lumen; Post = posterior. Horizontal calibration bar = 3 mm.

Intraoperative Patient Studies

Our in vivo study was approved by the Human Use Committee at the University of Iowa. All patients gave written informed consent. Patients with known coronary artery disease undergoing open heart surgery for placement of coronary artery bypass grafts or undergoing other intracardiac procedures (valve replacement or atrial septal defect repair) were asked to participate.

Coronary bypass operations were performed with use of a median sternotomy and standard operating procedure. Patients who had undergone previous coronary surgery were excluded.

High Frequency Echocardiography

Imaging. A Biosound Surgiscan unit (Biosound Inc.) with a 12 MHz probe was used. The probe has dimensions of 20 × 2.6 × 2.4 cm. The imaging surface, 1.4 cm in diameter, is placed directly over the coronary artery at the time of imaging. The probe has a nominal axial resolution of 0.15 mm and a lateral resolution of 0.25 mm for two-point structural resolution in a fixed system. For the intraoperative studies, the high frequency echocardiographic probe was sterilized with a standard 130°C ethylene oxide sterilizing procedure for an 18-h cycle before use. Images were recorded onto videotape for subsequent playback and analysis. Our analysis emphasized cross-sectional images.

Human postmortem heart studies. The location along the coronary artery from which the echocardiographic images were obtained was marked with a suture placed through the superficial connective tissue. In the in vitro specimens, the right coronary artery from the ostium to the crux of the heart, the left anterior descending coronary artery to the apex and the proximal portion of the left circumflex coronary artery could be imaged. The only factors that decreased imaging ability were total occlusions and diffuse epicardial fat with epicardial coronary arteries diving into the myocardium. This occurred in a minority of cases and from each postmortem heart at least two of the arteries could always be imaged and analyzed (2).

In vivo patient studies. These studies were performed before cardiopulmonary bypass was initiated, while the heart was still beating and the coronary arteries were still distended by normal perfusion pressure. Probe contact was accomplished with a small amount of sterile saline solution. The probe was moved slowly along the coronary artery to scan it and then held stationary during the recording of each image for each arterial segment. The size of the hand-held probe (20 cm in length and 2.6 cm in width) and the posterior location of the left circumflex and distal right coronary arteries were the chief limiting factors in our ability to obtain images. In the absence of gross right ventricular hypertrophy, the left anterior descending coronary artery could be visualized, along with its bifurcating branches, down to its distal portion. The right coronary artery could be visualized throughout its course to the origin of the posterior descending coronary artery. The left circumflex coronary artery, on the posterior side of the heart, could not be examined because of the narrow depth of field (1.5 to 2 cm) and the requirement that imaging in that location be done through the pulmonary artery trunk.

The location of each discrete segment of artery visualized by high frequency echocardiography in the operating room was described by the surgeon, who noted the relation of the segment to major arterial branching points and estimated the distance from other landmarks such as the aortic root and cardiac apex. Each segment was also distinguished from other segments by major arterial branching points and morphologic landmarks. If the location of the echocardiographic image with regard to anatomic landmarks was uncertain, the image was not analyzed.

Measurements. The high frequency epicardial echocardiographic images were digitized with an IREX Digitizing System (IREX Medical Systems). Only images with good wall, lumen and atherosclerotic plaque definition were used for analysis. Whenever possible, we avoided images from arterial segments containing extensive amounts of calcium as these images often display "shadowing" (image loss posterior to the highly ultrasound-reflective calcification). In any image, if border definition (lumen and wall) was not

distinct for the total 360° circumference on the video frame, the tape was played forward and back to more adequately identify the indistinct sections of arterial border. If inadequate border definition exceeded 30% of the arterial circumference, all the data from that image were excluded. Each image was displayed in cross section at that part of the cardiac cycle where the arterial diameter was largest. The inner and outer borders of each arterial segment were outlined. The lumen border was defined as the inner black-white interface, and the lumen area was subsequently calculated. The outer arterial border was identified as the border between the bright specular reflector and the outer gray interface, which represents the loose connective tissue surrounding the artery (Fig. 1).

The identified borders were subsequently entered into a PDP 11/44 computer for determination of wall thickness, lumen diameter, lumen wall area, and eccentricity ratio. (For the corrected estimate of residual lumen position, see later.)

Histologic and Histometric Evaluation

To prepare coronary arteries in the postmortem heart for histologic analysis, vessels were infused under pressure with the gelatin-barium mixture already described. The heart was then fixed in a 2.5% formalin-distilled water solution for a minimum of 24 h. After fixation, coronary artery specimens were taken for tissue preparation for microscopic study. If extensive calcification was present, decalcification procedures were performed before slide preparation. Transverse arterial sections of 8 μm thickness were cut from paraffin-embedded specimens and stained with Verhoeff-van Gieson stain for microscopy. The arterial images were projected through a Leitz microscope (Ernest Leitz and Company) onto a screen at ×58 magnification. The internal and external circumferences and point distances were traced and measured with a light pen and digitizer (Carl Zeiss Incorporated). As with the high frequency echocardiographic images, the measurements of the histologic images were entered into a PDP 11/44 computer.

Protocols

Validation of high frequency echocardiographic shape measurements. In 10 postmortem hearts (8 male, 2 female), 27 coronary artery lesions (10 left anterior descending, 10 right coronary, 4 left circumflex) having various degrees of atherosclerosis were examined by high frequency epicardial echocardiography and the results compared with histologic findings. Segments were compared for mean, maximal and minimal wall thickness and lumen diameters (across 12 radii at equiangles for wall thickness and 6 diameters at equiangles for lumen diameters using the residual lumen centroid). We measured the distance between the centroids of the residual and the presumed original lumens (lumen eccentricity) and derived an eccentricity ratio. This lumen eccentricity ratio was an estimate derived to describe the residual lumen position with respect to its original position normalized for vessel size. This estimate takes the distance from the center of the residual lumen (CL) to the original lumen (CA) and divides the result by the mean residual lumen radius (RL) to correct for the size of the residual lumen:

$$\text{Lumen eccentricity ratio} = (CL - CA)/RL$$

(see Fig. 1).

A lumen eccentricity ratio >1.5 was considered to describe an eccentrically placed residual lumen (eccentric atherosclerosis). A ratio ≥1.5 was considered to describe a concentrically placed residual lumen (concentric atherosclerosis). Thus, we measured both absolute distance between the lumens (lumen eccentricities) and an eccentricity ratio that factors in the radius of the residual lumen. By factoring in the residual lumen, this ratio allows recognition of small lumens that are eccentrically placed but have a small absolute interluminal distance in contrast to large lumens that, because of vessel size, may have large absolute eccentricity but a small eccentricity ratio. When combined, lumen eccentricity and eccentricity ratio provide good descriptors of the position of the residual lumen with respect to the original lumen. A mean of four to six high frequency echocardiographic images and two to five histologic sections were analyzed for each segment.

In vivo characterization of lesion residual lumen morphology by high frequency epicardial echocardiography. In this protocol 31 high frequency echocardiographic segments, obtained from patients undergoing cardiac surgery, were used. They were all judged by angiography to have >50% lumen narrowing as assessed by caliper-measured percent stenosis. For each coronary artery segment, 4 to 10 cross-sectional high frequency epicardial echocardiographic images were evaluated. The cross-sectional image with the smallest residual lumen area was identified as the lesion and digitized for further analysis.

Four geometric measures were quantitated. The first, wall thickness, was measured across 12 radii at equiangles using the residual lumen center. The second was maximal/minimal wall thickness ratio and the number of segments having a wall thickness <0.7 mm (normal). In a previous intraoperative study, we found that the maximal wall thickness for those coronary artery segments of patients with no angiographic evidence of coronary disease was 0.6 ± 0.19 mm (mean ± SD) (2). All but three maximal wall thickness measurements in the "normal" group were ≤0.7 mm (2). We therefore chose 0.7 mm as the maximal normal in vivo wall thickness measurement for the purpose of this study.

The third measurement was an evaluation of area and shape. Maximal/minimal lumen diameter was used for the classification of residual lumen shape. Circular lumens were defined as having a maximal/minimal diameter ≤1.5:1. Oval lumens were defined as having a maximal/minimal diameter >1.5:1. Complex lumens had markedly irregular lumen

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Table 1. Comparison of High Frequency Echocardiographic and Histologic Measurements In Vitro in 27 Coronary Artery Segments

	HFE	Histo	Correlation (r)
Wall thickness (mm)			
Mean	0.9	0.8	0.94
SD	0.38	0.4	
Lumen diameter (mm)			
Mean	2.5	2.8	0.84
SD	0.67	0.64	
Lumen eccentricity ratio			
Mean	0.25	0.25	0.90
SD	0.24	0.24	
Lumen area (mm^2)			
Mean	5.4	6.5	0.84
SD	2.9	2.86	
Wall area (mm^2)			
Mean	9.8	9	0.91
SD	4.69	5.21	

HFE = high frequency epicardial echocardiography; Histo = histologic study.

geometry. The fourth measurements of lumen eccentricity and the lumen eccentricity ratio were calculated as previously described.

Statistical analysis. Paired or unpaired *t* tests were used as appropriate to evaluate two groups of paired data sets. Differences were considered significant when confidence limits exceeded 95% ($p < 0.05$). All results are expressed as mean values ± SD.

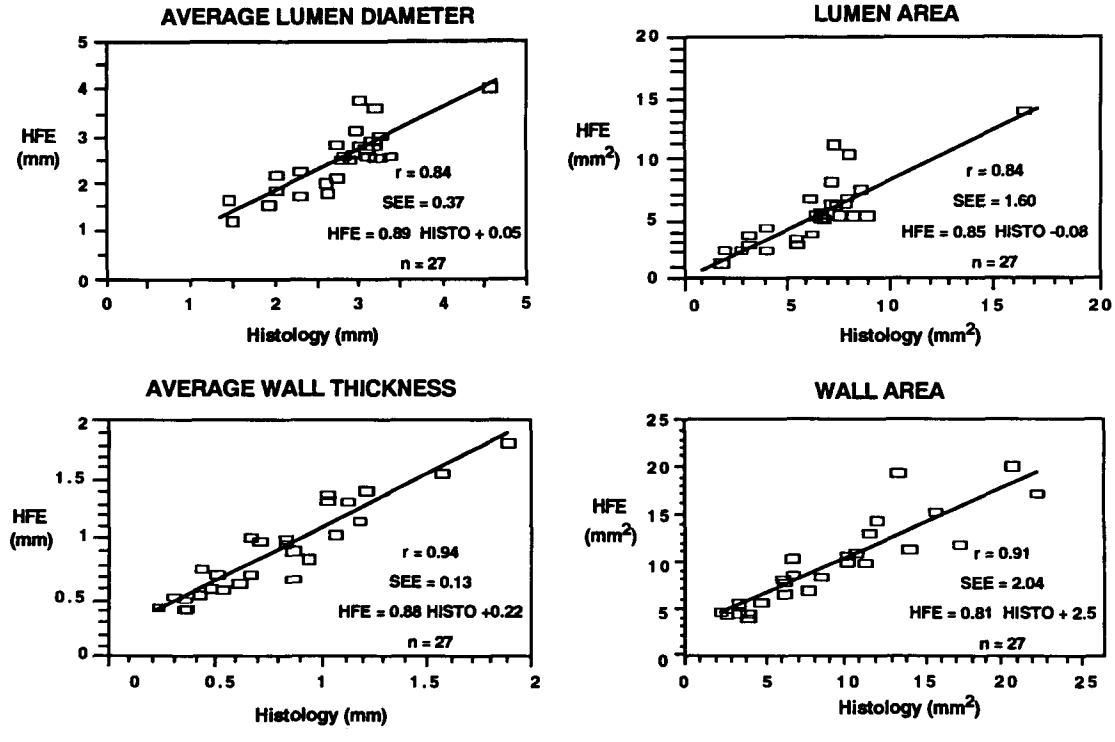
Results

Validation of high frequency echocardiographic shape measurements (Table 1). The mean histologic wall thickness of the segments was 0.8 mm (range 0.2 to 1.9). Figures 2 and 3 illustrate the comparisons between high frequency epicardial echocardiographic and histologic assessment of mean wall thickness, lumen diameter, lumen area, mean wall area and lumen eccentricity ratio. There was an excellent correlation between the two assessments for wall and lumen measurements over the wide range of normal to atherosclerotic vessel segments in the postmortem coronary artery segments. There was a wide range of lumen eccentricity ratios.

In vivo characterization of lesion residual lumen morphology by high frequency epicardial echocardiography. A total of 31 lesions were evaluated, including 25 right coronary and 6 left anterior descending coronary arteries in 26 patients: 19 men, 7 women with a mean age of 59 ± 11.7 years (range 36 to 76). Classifying shape by using maximal/minimal lumen diameter ratios, 15 of the lesions were circular, 13 oval and 3 complex. Twenty of the 28 noncomplex lesions had a concentrically placed lumen, and 8 (29%) had an eccentrically placed residual lumen.

The relation of maximal to minimal wall thicknesses in the lesions and the percent total arterial circumference with normal wall thickness is depicted in Figure 4. Eleven of 31 lesions had a maximal to minimal wall thickness ratio ≥3 with a range up to 7. In 15 segments, some portion of the total arterial circumference displayed normal wall thickness

Figure 2. Data from postmortem specimens: high frequency echocardiographic (HFE) versus histologic (HISTO) measurements of lumen diameter, lumen area, wall thickness and wall area. There was a good correlation between measurements by the two methods.



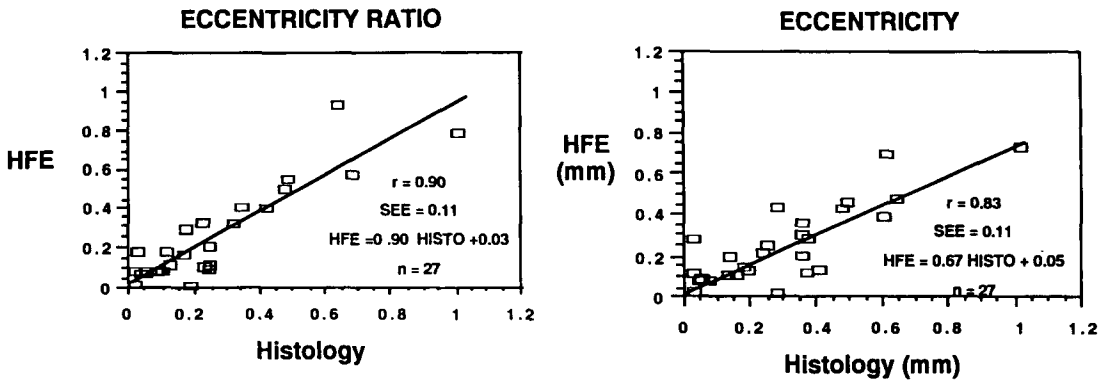


Figure 3. Data from postmortem specimens: high frequency echocardiographic (HFE) versus histologic (HISTO) measurements of eccentricity ratio and eccentricity. There was a good correlation between measurements by the two methods.

(<0.7 mm): in three segments, >60% of the arterial circumference had normal thickness.

Figure 5 illustrates the relation of residual lumen shape to lumen area in those vessels having noncomplex residual lumen geometry. No definite trend was demonstrated; that is, the smaller residual lumens were approximately equally distributed between oval and circular shapes.

Figure 6 illustrates the distance between the original and residual lumens (lumen eccentricity) and the distance corrected for the size of the residual lumen (lumen eccentricity ratio). Although there was a large actual distance between lumens (residual lumen minus original lumen), only six lesions had a relatively large corrected distance between lumens (i.e., >1.5 radians), indicating a very eccentric position of the residual lumen.

Figure 7 illustrates the relation of residual lumen position to lumen area in the eccentric and concentric residual lumens. As lumen area decreased, the distance between the center of the outer arterial area and the residual lumen increased. Thus, the eccentrically positioned residual lumens tended to occur in the most severely diseased arteries.

Discussion

Variability of lumen size and shape. Our study demonstrates the marked variability of residual lumen size and shape in coronary atherosclerosis. Nearly half of the lumens were not circular; the majority of these were oval but there were also a few complex residual lumens for which normal descriptors of lumen geometry using one- or two-dimensional angiographic techniques would be grossly inaccurate. There was marked variability in the atherosclerotic plaque, indicated not only by the residual lumen position but also by the maximal/minimal wall thickness ratios and the percent of the total arterial circumference that retained normal wall thickness.

Wall thickness. About half of the atherosclerotic segments examined had normal wall thickness in at least a portion of the arterial circumference. These in vivo data

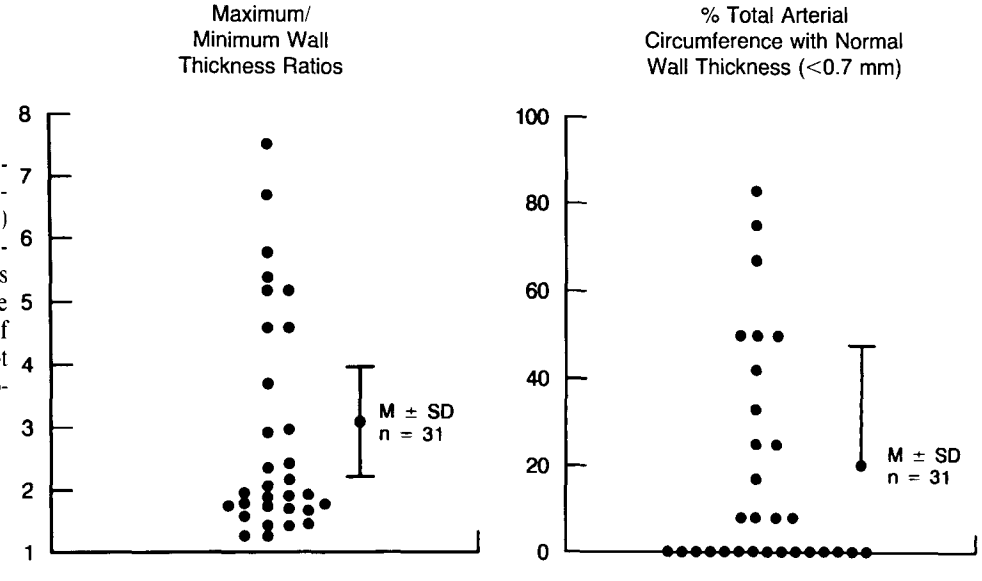


Figure 4. Intraoperative echocardiographic recordings: maximal to minimal wall thickness ratio (**left panel**) and the percent total arterial circumference with normal wall thickness (<0.7 mm) (**right panel**). In 16 of the 31 arteries examined, some portion of the arterial circumference was not involved in the atherosclerotic process.

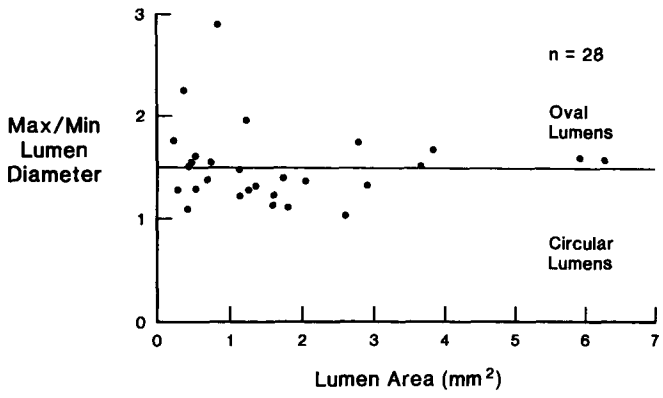


Figure 5. Intraoperative echocardiographic recordings in the 28 patients: lumen shape versus residual lumen area in the oval and circular lumens. There is no clear relation between lumen area and shape. Max/Min = maximal/minimal.

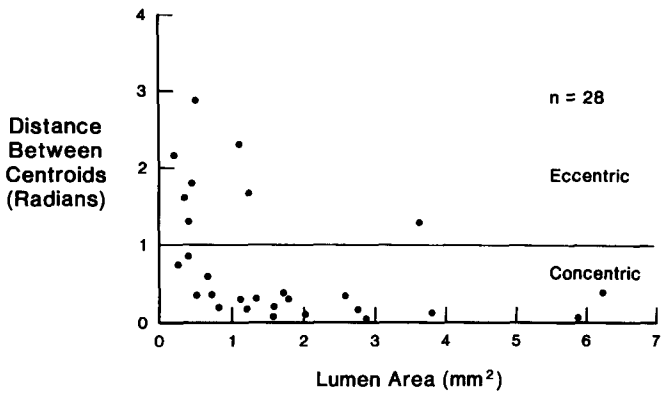
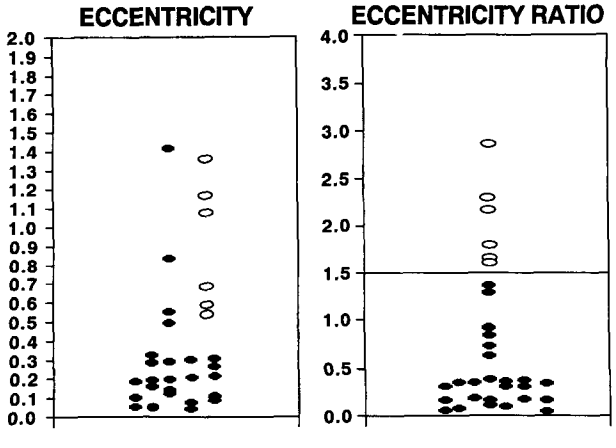


Figure 7. Intraoperative echocardiographic recordings in 28 patients: relation of residual lumen position to lumen area. The eccentrically positioned lumens tended to be small.

support the histologic data of others demonstrating that coronary atherosclerosis does not uniformly affect all portions of the arterial wall (8). This may have considerable clinical significance. Preliminary data show that atherosclerotic lesions have the ability to react to vasodilator substances (8–10). The degree of reactivity may well depend on the extent of normal wall thickness at the site of the atherosclerotic lesion and the components of the atherosclerotic plaque. Lesions with areas of normal wall may be more vasoactive than arterial walls that are concentrically diseased (5,6,11).

Eccentric residual lumens versus percent stenosis. Our data show that eccentrically placed residual lumens tend to occur in the most severely diseased arteries. Although this phenomenon has been described in in vitro specimens, its occurrence in the in vivo state has not been demonstrated (8). Many pathologic studies indicate that most lesions are eccentric. Two factors may explain the lesser degree of eccentricity in this study. The first is due to our strict definition of eccentricity having a ratio of the distance between the original and residual lumen/lumen radius >1.5 mm. If eccentricity ratio were defined as a ratio >1, then 35% of the lesions would be eccentric. Also in our study, we analyzed lesions ranging from 50% stenosis (mild) to >90% stenosis (severe). If we restricted the analysis to severe lesions only, more lesions would be eccentric. Because of this variable deposition of atherosclerosis with the resultant eccentrically positioned and geometrically diverse lumen shapes, it is not surprising that angiographic estimations of lumen obstruction based on "percent stenosis" may be inaccurate and often do not predict the physiologic or functional severity degree of lumen obstruction (12,13). Newer, more sophisticated techniques (quantitative coronary angiography and videodensitometry) may predict residual lumen area at the site of coronary lesions more accurately than can standard angiography (14,15). However, the ultrasound technique directly measures the lumen and atheromatous plaque cross-sectional area, as opposed to the indirect radiographic measurements.

Figure 6. Intraoperative echocardiographic recordings: Eccentricity is the distance between the residual lumen and the center of the arterial segment (**left panel**); eccentricity ratio uses the mean lumen diameter to correct for residual lumen size (**right panel**). A lumen eccentricity ratio >1.5 indicates an eccentrically positioned lumen, which occurred in six cases (**open symbols**).



Echocardiographic versus histologic measurements. Our epicardial echocardiographic measurements were found to be accurate when compared with histologic findings. Sources of small but well documented errors in the histologic preparations are fixation artifacts. Even when arterial shrinkage is carefully controlled, it cannot be completely avoided and has been shown to alter measurements by up to 10% (16,17).

Defining the optimal site for graft implantation and adequacy of anastomosis. High frequency epicardial echocardiography could potentially allow the surgeon to define the optimal site for graft implantation by visualizing the morphology of the recipient artery. It is also potentially useful for evaluating the technical adequacy of the graft-native artery anastomosis when this is completed (18). In practice, however, the present probe is too large and bulky to allow full scanning of the entire heart; the posterolateral surfaces are especially difficult. In the present study, we did not

attempt to modify the operative procedure on the basis of our imaging findings. Miniaturization of the probe should facilitate its clinical use.

Conclusions. The new technique of intravascular ultrasound offers further potential for evaluation of lumen and plaque shape, area and position. The higher frequencies (20 to 40 MHz) at which the intravascular transducers operate should allow superior resolution. Initial comparison of the intravascular technology with high frequency epicardial echocardiography has suggested that they offer comparable data (19,20). However, high frequency epicardial echocardiography offers an easier, noninvasive approach to the evaluation of coronary geometry at the time of cardiac operation.

We have demonstrated that there is marked variability in residual lumen geometry and atherosclerotic plaque morphology at the site of significant coronary lesions. Traditional angiographic techniques do not reflect the complexity and variability of coronary atherosclerosis.

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