Intravascular Ultrasound Assessment of Lumen Size and Wall Morphology in Normal Subjects and Patients With Coronary Artery Disease

Steven E. Nissen, MD; John C. Gurley, MD; Cindy L. Grines, MD; David C. Booth, MD; Rick McClure, MD; Martin Berk, MD; Charles Fischer; and Anthony N. DeMaria, MD

Background. Necropsy studies demonstrate that coronary artery disease (CAD) is frequently complex and eccentric. However, angiography provides only a silhouette of the vessel lumen. Intravascular ultrasound is a new tomographic imaging method for evaluation of coronary dimensions and wall morphology. Few data exist regarding intravascular ultrasound in patients with CAD, and no data exist for subjects with normal coronaries.

Methods and Results. We used a multielement 5.5F, 20-MHz ultrasound catheter to examine eight normal subjects and 43 patients with CAD. We assessed the safety of coronary ultrasound and the effect of vessel eccentricity on comparison of minimum luminal diameter by angiography and ultrasound. Normal and atherosclerotic wall morphology and stenosis severity were also evaluated by intravascular ultrasound. The only untoward effect was transient coronary spasm in five patients. At 33 sites in normal subjects, the lumen was nearly circular, yielding a close correlation between angiographic and ultrasonic minimum diameter \( r=0.92 \). At 90 sites in patients with CAD, ultrasound demonstrated a concentric cross section; correlation was also close \( r=0.93 \). However, at 72 eccentric sites, correlation was not as close \( r=0.77 \). For 41 stenoses, correlation between angiography and ultrasound for area reduction was moderate \( r=0.63 \). In normal subjects, wall morphology revealed a thin (0.30 mm or less) intimal leading edge and subadjacent sonolucent zone (0.20 mm or less). Patients with CAD exhibited increased thickness and echogenicity of the leading edge, thickened sonolucent zones, and/or attenuation of ultrasound transmission.

Conclusions. These data establish that intravascular ultrasound is feasible and safe and yields luminal measurements that correlate generally with angiography. Differences between angiographic and ultrasonic measures of lumen size in eccentric vessels probably reflect the dissimilar perspectives of tomographic and silhouette imaging techniques. Intravascular ultrasound provides detailed images of normal and abnormal wall morphology not previously possible in vivo. (Circulation 1991;84:1087–1099)

Although arteriography is the standard method by which to assess the extent and severity of coronary artery disease, radiographic evaluation of coronary anatomy has many limitations. Necropsy studies have demonstrated that coronary cross-sectional anatomy is frequently complex and eccentric.\(^1\)–\(^4\) Because angiography records only a silhouette of the vessel lumen, radiography will often misrepresent the extent of luminal narrowing. Not surprisingly, several studies have shown considerable intraobserver and interobserver variability in the interpretation of cineangiography and discrepancy between coronary angiograms and postmortem examination.\(^5\)–\(^8\)

The angiographic severity of coronary lesions is most often expressed as percent luminal reduction, a practice that imposes additional limitations. Because coronary disease is often diffuse, there may not be a “normal segment” with which to compare a focal narrowing; percent stenosis may therefore underestimate disease severity.\(^2\)–\(^3\) Accordingly, studies have
documented a poor correlation between percent stenosis and the physiological consequences of coronary obstructions.9

Recent developments in microelectronic and piezoelectric technology have permitted fabrication of miniature ultrasound transducers small enough to be placed within an angiographic catheter, thus enabling real-time tomographic imaging of vascular structures.10–22 Initial experimental studies in our laboratory have documented the ability of intravascular ultrasound to measure luminal dimensions in normal, nonatherosclerotic peripheral vessels and artificially induced concentric stenoses in animals.16 However, few data exist regarding the application of intravascular ultrasound in the evaluation of coronary artery disease in humans, and no data exist for subjects with normal coronary arteries.21,22

Therefore, we performed this study to determine the feasibility and safety of coronary intravascular ultrasound imaging performed during cardiac catheterization. We sought to evaluate both quantitative and qualitative aspects of coronary anatomy using intravascular ultrasound compared with the current standard for assessment of coronary disease, cineangiography.

Methods

Patient Population

Intravascular ultrasound was performed during cardiac catheterization in 51 subjects. In 33 patients, diagnostic left heart catheterization and coronary arteriography were performed to evaluate chest pain. An additional 18 patients were examined after percutaneous transluminal balloon angioplasty. Eight of the 33 patients studied at the time of diagnostic catheterization described atypical chest pain and were determined to have normal coronaries by angiography (agreement of three observers). This normal cohort ranged in age from 37 to 51 years (mean, 44 years). None of the normal subjects had a history of myocardial infarction, hypertension, claudication, cerebral vascular events, or valvular or congenital heart disease. None of the normal subjects had any physical findings of atherosclerosis.

The patients with coronary artery disease were representative of a typical coronary disease population and ranged in age from 35 to 77 years (mean, 57 years). Duration of chest pain ranged from 1 day to 14 years (mean, 3 years). Mean cholesterol value was 223±30 mg/dl. Systemic hypertension was present in 24 patients, and glucose intolerance was present in 11 patients. Sixteen patients exhibited symptoms of unstable angina defined as prolonged pain, sudden increase in frequency or severity of angina, or recent abrupt onset of chest pain syndrome. Prior myocardial infarction was present in 18 of the 43 patients.

Ultrasound Imaging Device

The intravascular ultrasound imaging device consisted of a 64-element transducer mounted at the tip of a 125-cm polyethylene catheter (Endosonics Corp., Rancho Cordova, Calif.). The transducer measured 5.5F (1.83 mm), and the shaft of the catheter was 4.5F (1.5 mm) in size. A 4-mm-long rigid section at the catheter tip contained the transducer and several ultraminiaturized integrated circuits. Thus, digital signal processing and multiplexing were performed within the catheter so that only four conductive wires were required to transmit information from the transducer to the image reconstruction computer. The transducer operated with a center frequency of 20 MHz and a bandwidth of 10 MHz. The catheter contained a coaxially located central lumen that accommodated a 0.014-in. angioplasty guide wire to facilitate safe intracoronary placement.

Ultrasound energy was individually transmitted and received from each of the 64 transducer elements and was processed using a customized high-speed array processor. The computer used distance and amplitude information derived from multiple elements to synthesize more than 1,000 radial scan lines for each image. This dynamic computerized reconstruction generated 10 frames/sec of real-time ultrasound images. For each picture element (pixel) in the image, the number of elements contributing to the gray scale value depended on the distance between the transducer and the pixel. This approach, known as a synthetic aperture array, theoretically provides constant imaging focus independent of the distance from the transducer. Axial resolution is 80 μm, whereas lateral resolution depends on depth, averaging 200 μm.

Ultrasound images were synthesized and displayed using a 512×512-pixel matrix with an eight-bit gray scale (256 levels). Controls permitted adjustment of overall system gain as well as gray scale level and window. Framing rate could be reduced by real-time averaging of two or more sequential frames. Images were recorded on Super-VHS videotape for subsequent playback, review, and analysis.

Imaging Protocol

Informed consent was obtained before the procedure. Patients who had left main coronary disease or were clinically unstable during catheterization were excluded from the study. Patients with an estimated proximal coronary diameter that was too small to safely accommodate the 1.83-mm catheter were also excluded. Forty-eight of the 51 patients were receiving long-acting nitrates or calcium channel blockers at the time of study. All 51 patients received heparin during angiography in doses ranging from 3,000 to 8,000 units at the discretion of the operator. The 18 patients undergoing balloon angioplasty received a total of 10,000 units heparin at the beginning of the procedure.

After diagnostic angiography, the radiographic view was selected that optimally depicted the greatest degree of luminal diameter reduction of the coronary vessel to be examined. The criteria for choice of optimal angle of view included elimination of vessel overlap and minimization of segment foreshortening.
This view was subsequently used to guide intravascular ultrasound imaging and to obtain cineangiograms for comparative purposes. In all cases, cineangiography was performed at a rate of 30 frames/sec using a 12- or 15-cm field of view.

An 8F or 9F sheath was placed in the femoral artery, and an 8F or 9F right or left Judkins large-lumen angioplasty guiding catheter was advanced into the coronary ostium. Initial studies (14 patients) required a 9F guiding catheter (Interventional Medical Inc., Davers, Mass.) to accommodate the ultrasound device. Subsequent improvements permitted use of a large-lumen 8F design (Schneider Inc., Minneapolis, Minn.) with an inside diameter of 0.082 in. (37 patients).

Before cannulation of the coronary, the intravascular ultrasound device was advanced through the lumen of the guiding catheter and positioned in a large vessel (aorta or left main coronary) where an averaged image of from four to 32 frames was stored in digital memory. A central 3.5-mm circular section of this reference image was digitally subtracted from all subsequent images to remove transducer ring-down artifacts. The subtraction process effectively removed ring-down artifacts from the image for the zone 2.2–3.5 mm in diameter. For the zone from the surface of the catheter (1.83 mm) to 2.2 mm in diameter, the artifact could not be completely removed because the ring-down signal saturated the microcircuit amplifiers at the tip of the catheter. Therefore, an image-blanking circle 2.2 mm in diameter was superimposed over the image to obscure any structures within this nonlinear zone.

A 0.14-in. angioplasty guide wire was advanced through the ultrasound catheter and fluoroscopically guided into the distal coronary artery or saphenous bypass graft. The ultrasound imaging catheter was then advanced over the guide wire into the vessel. The catheter was advanced or withdrawn during continuous ultrasound imaging until an apparent change in luminal dimensions (increase or decrease) was noted. For each such site, the ultrasound catheter was maneuvered to as central and coaxial a position in the coronary as feasible, primarily by catheter rotation and guide wire movement. At each of these sites, intravascular ultrasound images were recorded, and cineangiography was performed by hand injection of iodinated contrast through the guiding catheter. A representative pair of angiographic and ultrasound images is given in Figure 1.

For sites at which coronary luminal narrowing was observed by angio- graphic, the intravascular probe was positioned both at the location of smallest diameter and at the nearest angiographically normal segment. Residual stenoses after angioplasty were excluded from this analysis. For patients examined after balloon angioplasty, a guide wire remained in place, and the ultrasound probe was exchanged over the wire for the balloon device.

Angiographic Measurements

For each coronary site examined, the cineangiogram was magnified twofold and projected onto a 40-cm back-projection screen. The diameter of the guiding catheter was measured with manual calipers at a location adjacent to the coronary ostium, and
this measurement was compared with the known external diameter of the catheter (2.67 or 3.0 mm) to correct for radiographic magnification. For each vascular site, the projection demonstrating minimum coronary diameter was measured with calipers at the location of the radiopaque ultrasound imaging catheter (Figure 1). At stenosis sites, angiographic cross-sectional area reduction was calculated from diameter measurements.

**Ultrasound Measurements**

Videotaped ultrasound studies were digitized into a 612×480-pixel matrix using an image processing computer (Mipron, Kontron Electronics, Canton, Mass.) that enabled digitization of a series of 102 ultrasound images (10.2 seconds). These digitized sequences were reviewed, and the frame with optimal delineation of the blood-intimal border was selected for subsequent measurement. Although a single frame was used for measurement, review of the dynamic imaging sequence was routinely used to confirm the location of the interface between the lumen and the vessel wall. In addition, injection of iodinated contrast media during imaging produced luminal opacification that assisted in the identification of the intimal leading edge (Figure 2).

The smallest axis of the vessel lumen was identified by visual inspection, and distance was measured by placing an electronic cursor at the acoustic interface between the lumen and the intimal leading edge at two opposite sides of the artery. This procedure was repeated until the minimum diameter was empirically determined. Adjustment for magnification was performed using a distance scale automatically recorded within each ultrasound image. Lumen cross-sectional area and perimeter were determined by planimetry of the ultrasound leading-edge interface. Because not all frames showed a continuous border between the lumen and the leading edge, each 102-image (10.2 seconds) sequence was replayed at varying speeds to facilitate accurate cursor placement. Diameter, perimeter, and cross-sectional area measurements for a representative ultrasound image are shown in Figure 3.

**Analysis of Eccentricity**

Vessels were analyzed separately in two groups segregated by degree of lumen eccentricity as determined by intravascular ultrasound. A standardized index of eccentricity—the circular shape factor—was used to determine the degree of deviation of the lumen cross section from a perfect circle. The planimetered cross-sectional area was used to calculate mean vessel diameter:

\[
d = 2\sqrt{\frac{\text{CSA}}{\pi}}
\]

where CSA is cross-sectional area. The perimeter for a perfect circle with this diameter was determined from \(P = \pi d\), where \(P\) is perimeter. This calculated perimeter was compared with the actual planimetered perimeter of the vessel lumen. This calculation yielded an index of eccentricity, the circular shape factor, defined as:
FIGURE 3. Intravascular ultrasound images of left anterior descending coronary artery showing luminal eccentricity. Measurement of minimum and maximum luminal diameters is illustrated in panel A, and planimetry of cross-sectional area (CSA) is shown in panel B. Gray arrow points to area of increased intimal thickness and echogenicity with ultrasound attenuation.

\[
\text{CSF} = \left( \frac{\text{Calculated perimeter}}{\text{Observed perimeter}} \right)^2
\]

where CSF is circular shape factor (Figure 4).

Analysis of Wall Morphology

Coronary wall morphology in normal subjects and patients with coronary disease was evaluated by measuring the maximal thickness of several characteristic features of the vessel wall and assessing the echogenicity of these structures. Two distinct vessel wall layers were identified at most sites—an echogenic intimal leading edge and a sonolucent subintimal zone (Figure 5). In the normal cohort, the maximal thicknesses of these two structures were measured with an electronic cursor, and mean and

FIGURE 4. Intravascular ultrasound image of a coronary artery showing severe eccentricity (left panel) and calculation of circular shape factor (right panel). CSF, circular shape factor (see text).
SD values were computed. In the patients with coronary disease, a wall layer was classified as abnormal if the thickness of the structure was more than 2 SDs greater than the normal value. Echogenicity of a wall layer was considered abnormal if the structure impeded transmission of ultrasound, thus blocking visualization of underlying anatomic features.

Results

Feasibility and Safety

Coronary intravascular ultrasound was successfully performed in all 51 subjects. No untoward effects were noted in any of the subjects, although five patients demonstrated transient coronary spasm as evidenced by a focal narrowing by angiography, which responded to withdrawal of the probe or intracoronary nitroglycerin. All subjects were free of catheter-induced spasm on the final angiogram of the study.

The coaxial central lumen guide wire facilitated placement in more distal coronary locations and provided some limited ability to position the catheter at a more central location in the vessel. Gray scale manipulation provided little or no improvement in image quality; therefore, all studies were analyzed using the entire 256 gray levels. Overall system gain was adjusted over a range of 4 db to compensate for small differences in catheter sensitivity secondary to manufacturing variance.

Coronary Eccentricity and Dimensions

In the normal cohort, ultrasound assessment of vessel eccentricity yielded a mean circular shape factor index averaging 0.96±0.02 with 95% confidence limits of 0.92 and 1.0. Thus, normal vessels demonstrated a nearly circular cross-sectional profile. These normal values served as the basis for characterization of eccentricity in patients with coronary disease.

In the eight subjects with normal coronaries, minimum diameter by cineangiography and intravascular ultrasound was compared for 33 sites, including five in the left main artery, 13 in the left anterior descending coronary artery, 10 in the right coronary artery, and five in the left circumflex artery. Minimum diameter was 2.88±0.57 mm by cineangiography and 2.83±0.52 mm by ultrasound (p=NS). Linear regression analysis revealed a close correlation between cineangiography and ultrasound for these normal vessels (r=0.92) (Figure 6). The regression equation (least-squares fit) was close to the line of identity (y=0.91x+0.23), and SEE was small (0.21).

In the 43 patients with coronary disease, cineangiography and intravascular ultrasound were performed for 202 sites. In an additional two patients, no ultrasound images were obtained because of electronic failure of the probe. Forty sites were excluded from analysis because of technical problems related to ultrasound (23 sites) or angiography (17 sites). Ultrasound technical problems included extreme off-axis probe position with resultant poor image quality (20 sites) and videotape problems (three sites). Angiographic technical difficulties included inadequate image contrast to measure luminal size (13 sites) or catheter calibration (four sites).
For the remaining 162 sites in the patients with coronary disease, minimum vessel diameter by angiography was similar to minimum ultrasound diameter (3.17±0.83 mm) (p=NS). However, linear regression analysis revealed a lower correlation coefficient than that observed for normal vessels, (r=0.86), and the regression equation deviated further from the line of identity (y=0.32x+0.42). The SEE was also larger (0.43 mm).

These 162 sites in patients with coronary disease were analyzed in two subgroups segregated by extent of lumen eccentricity. A concentric lumen was defined as a circular shape factor within the 95% confidence limits for normal vessels (0.92 and 1.0). A concentric vessel was present at 90 of the 162 sites in patients with coronary disease. Representative ultrasound images showing a concentric lumen are illustrated in Figure 7. At these concentrically diseased sites, angiographic vessel diameter was similar to minimum ultrasound diameter (3.21±0.80 versus 3.29±0.87 mm, p=NS) with a close correlation (r=0.93) (Figure 8). The least-squares fit revealed a regression equation close to the line of identity (y=1.02x+0.03) with a small SEE (0.32 mm).

An eccentric vessel lumen, defined as a circular shape factor of less than 0.92, was present at 72 of the 162 sites. For these eccentric segments, minimum angiographic diameter was 3.17±0.83 mm, and minimum ultrasound diameter was 3.11±0.76 mm (p=NS). For the eccentric arteries, correlation was not so close between cineangiography and ultrasound (r=0.77). The regression equation was more divergent from the line of identity (y=0.70x+0.88), and the SEE for eccentric arteries was larger (0.49 mm) (Figure 8).

Cross-sectional Area Reduction

Of the 162 vessel segments selected for examination, focal luminal cross-sectional area reduction of 25% or more was identified at 41 sites by cineangiography and at 47 sites by ultrasound. For the lesions identified by both techniques, mean stenosis severity, expressed as percent luminal area reduction, was similar by cineangiography (48.9±13.8%) and by intravascular ultrasound (52.3±16.3%) (p=0.10). However, the correlation between percent stenosis by cineangiography and ultrasound was moderate (r=0.63). The regression equation demonstrated considerable diversion from the line of identity (y=0.54x+20.7). SEE was moderately large (10.9%) (Figure 9).

Analysis of Wall Morphology

Subjects with normal coronaries exhibited characteristic wall morphology by intravascular ultrasound.

**Figure 6.** Scatterplot comparing angiographic and ultrasound minimum diameters for normal vessels. Correlation is close, and regression equation is close to line of identity.

**Figure 7.** Representative intravascular ultrasound images showing concentric disease of vessel wall. For both vessels, circular shape factor indicates a nearly circular lumen. CSF, circular shape factor.
A discrete ultrasonic reflectance was typically observed at the acoustic interface between the lumen and the intima (Figure 5). This layer was evident at 25 of 33 sites in the normal subjects and exhibited a maximum thickness averaging 0.18 ± 0.06 mm, yielding 95% confidence limits of 0.06 and 0.30 mm. At eight of the normal sites, ultrasound failed to reveal distinct laminations of the vessel wall despite continuous imaging and catheter manipulation. A distinct subintimal sonolucent layer was also evident at these 25 sites with a maximal thickness averaging 0.11 ± 0.04 mm, yielding a normal range of 0.03–0.20 mm. These normal values for maximal thickness served as the basis for classification of diseased vessels with an upper limit of 0.30 mm for the echogenic leading edge and 0.20 mm for the subintimal sonolucent zone.

The laminar structure of the vessel wall was evident for only a portion of the circumference of the vessel in any individual frame at each of the normal sites. The acoustic reflectance of the leading-edge structure was minimal, and “dropout” of endothelial targets was frequently evident. Manipulation of the catheter and careful review of the dynamic imaging sequences were required to obtain optimal measurement of vessel wall structures.

Patients with coronary artery disease exhibited considerable diversity in vessel morphology by intravascular ultrasound. At 131 of 162 coronary sites, a distinct echogenic leading-edge structure was evident and could be measured (Figures 1–4, 7, and 10–13). Maximal thickness of this leading-edge interface was normal (0.30 mm or less) at 56 sites, including 69% of angiographically normal segments and 34% of sites with an angiographic luminal irregularity. Increased thickness of this leading-edge echo was observed at the other 75 sites, including 31% of angiographically normal sites and 66% of segments located at an angiographic luminal irregularity. In the most striking examples, the leading-edge echo demonstrated such prominent acoustic reflectance that little or no ultrasound energy penetrated the intimal layer, yielding a “shadow” effect with complete attenuation of the ultrasound transmission (Figures 3, 4, 7, and 11). Along the circumference of a single coronary site, the leading-edge echo often demonstrated a wide variety of ultrasound characteristics (Figures 7 and 11).

In the patients with coronary disease, a distinct subintimal sonolucent zone was evident at 123 of the 162 sites. The maximal thickness of this sonolucent structure was normal (0.20 mm or less) at 36 sites, including 56% of angiographically normal segments and 28% of sites located at an angiographic luminal irregularity. The sonolucent zone was increased at 87 sites, including 44% of angiographically normal segments and 72% of sites with a luminal irregularity. This sonolucent layer often appeared as a character-

---

**FIGURE 8.** Scatterplots comparing angiographic diameter with minimal ultrasound diameter for concentric sites (left panel) and eccentric sites (right panel). Correlation between angiographic and ultrasound diameters was closer for concentric sites than for eccentric sites, and regression equation was closer to line of identity. CSF, circular shape factor.

**FIGURE 9.** Scatterplot comparing cross-sectional area (CSA) reduction by angiography and intravascular ultrasound at stenotic sites. Correlation is moderate (r = 0.63).
Figure 10. Images showing sonolucent crescents in left anterior descending coronary artery (panel A) and right coronary artery (panel B). In both panels, arrows point to crescent-shaped zone of ultrasonic lucency that encroaches on lumen.

Characteristic crescent-shaped structure occupying a portion of the circumference of the vessel (Figure 10). These sonolucent crescents were often associated with an angiographic luminal irregularity. At some locations, the sonolucent band was thickened but symmetrical, lending a distinctive triple-layer appearance to the vessel (Figure 12). The increased thickness of the sonolucent zone and exaggerated trilaminar appearance were not evident in any of the normal subjects.

Ultrasound abnormalities in the thickness of the leading edge or sonolucent zones were often observed at angiographically normal sites (Figures 1 and 11). In patients with any luminal irregularity by angiography, ultrasound abnormalities in intramural...
FIGURE 12. Intravascular ultrasound and cineangiographic images of vessel exhibiting exaggerated trilaminar appearance. Left panel: Ultrasound probe is located in an ectatic area (black arrow), whereas in right panel, ultrasound probe is located at a site with a smaller diameter. In both panels, intimal leading edge is thickened, but there is no asymmetric luminal encroachment.

thickness were observed at nearly all other coronary sites.

A third, deeper layer of the arterial wall was present at most coronary vascular sites and varied widely in appearance. A distinct interface at the trailing edge of this third layer was not apparent except within bypass grafts (Figure 7, right panel). Because this deeper layer probably represents the adventitia and other tissues encasing the vessel, the ambiguity of the trailing edge precluded measurement of total vessel wall thickness.

Balloon angioplasty sites were the most heterogeneous in appearance. Distortion of anatomic landmarks was often present, the lumen was frequently eccentric, and apparent fractures of the intimal leading edge were often evident as a focal discontinuity in the leading edge (Figure 13).

Discussion

Multiple studies have established the limitations of angiography in the assessment of atherosclerotic disease of the coronary arteries.1-9 Cineangiography portrays the vessel lumen as a silhouette, a perspective that cannot reflect the complex eccentric nature of coronary artery disease. A tomographic technique such as intravascular ultrasound has many potential benefits, including precise measurement of luminal cross-sectional area and delineation of intramural anatomy.

The present study demonstrates that coronary intravascular ultrasound is feasible and safe and provides measures of the coronary lumen that correlate with cineangiography. The only untoward effect noted in the current investigation was transient coronary spasm, which occurred in five of 51 patients studied. This technique enabled visualization of wall morphology, not just the lumen, and provided images of coronary atherosclerosis not previously attainable in vivo by any method. The ability to evaluate intramural anatomy offers the opportunity for significant new insights into the pathophysiology and natural history of coronary disease.

Several approaches to intravascular ultrasound have been attempted. Most devices have used a single ultrasonic element that is mechanically rotated by a drive shaft running the length of the catheter.10 The present study used an alternative approach in which scan lines are generated electronically by sequential operation of multiple transducer elements.11 This approach provides a mechanically flexible catheter and the ability to accommodate a central lumen guide wire, both of which are valuable in
facilitating safe intracoronary instrumentation. The multielement transducer lacks moving parts and thus eliminates distortion of the image produced by non-uniform transducer rotation. In addition, the electronic approach uses a principle known as “synthetic aperture array” to permit constant focus of an ultrasound beam from the near to the far field.

A potential disadvantage of the multielement approach is the proximity of the transducer to the catheter surface with resultant vulnerability to ring-down artifacts. In the present study, this limitation was minimized by digital subtraction of the ring-down signal from the central portion of the image. The current multielement design provides less inherent acoustic power and requires complex electronic hardware for image reconstruction. The reduced acoustic power may influence image quality, and the electronic complexity may increase the cost of the system.

Because of the complex, eccentric nature of coronary disease, we felt that precision measurements of coronary dimensions represented an important potential application of intravascular ultrasound. In a previous study in experimental animals, we demonstrated that intravascular ultrasound correlated closely with cineangiography in the measurements of diameter and cross-sectional area of normal, nonatherosclerotic vessels. The close concordance between a planar technique, such as angiography, and a tomographic imaging method, such as ultrasound, was not surprising for vessels with a circular cross section.

In the present study, similar results were observed for normal vessels in patients without angiographic coronary disease. However, the correlation for normal vessels in patients was not as close as that observed in the experimental animals (Figure 6). This finding probably reflects the increased luminal complexity and greater curvature of human coronaries compared with straight peripheral vessels in young animals. The inability to pursue exhaustive manipulation of the ultrasound probe to optimize images in human studies may also contribute to the lesser correlation for clinical studies.

In patients with coronary disease who have a relatively concentric vessel cross section by ultrasound (circular shape factor, 0.92 or more), we also observed a moderately close correlation between cineangiography and intravascular ultrasound for minimum luminal diameter (Figure 7). Thus, our study confirmed the expected concordance between tomographic and silhouette techniques for vessels with a relatively circular cross-sectional profile. However, when eccentric human coronaries (circular shape factor, less than 0.92) were analyzed, vessel diameter by angiography and ultrasound correlated much less closely (Figure 8). We interpret these data as demonstrating the advantage of ultrasound, which provides a full circumference image of the vessel, over angiography, which portrays only two surfaces of the artery.

Although mean values for vessel diameter were similar by angiography and ultrasound, SEE values were moderately large (0.32-0.49 mm). Several factors probably contribute to the differences between angiography and ultrasound. Not all angiographic coronary projections are feasible, and it is likely that true minimum angiographic diameter was not always visualized. Ultrasound imaging sequences occasion-

**Figure 13.** Intravascular ultrasound images after percutaneous balloon angioplasty of left anterior descending coronary artery in two different patients. Left panel: Multiple fissures are evident in intimal leading edge echo, the largest of which is identified with arrow. Right panel: Origin of septal side branch is seen at 4 o'clock, fracture of intimal leading edge is present at 1 o'clock, and large false lumen is apparent at site marked by arrow.
ally demonstrate dropout of endothelial targets, and diameter measurements may have failed to identify the blood-intima border in these cases. We found that catheter manipulation and opacification of the lumen by contrast injection significantly enhanced identification of the blood-intima interface.

Transducer angulation resulting in an imaging plane oblique to the long axis of the vessel represents an additional confounding variable in ultrasound measurements. Nonorthogonal imaging would be expected to substantially increase measurements of maximum vessel diameter by ultrasound but produce a lesser effect on minimum diameter. In the present study, we compared minimum diameters because this measurement has been shown to correlate most closely with clinical outcome in quantitative angiographic studies. Catheter manipulation was used to obtain minimum ultrasound diameters and thus reduce the impact of off-axis imaging.

Assessment of percent stenosis revealed a weak correlation between intravascular ultrasound and cineangiography (Figure 9). Tobis et al\(^2\) found a poor correlation between angiography and intravascular ultrasound for residual stenoses after balloon angioplasty. However, the cross-sectional anatomy after angioplasty is particularly complex, and poor correlation between a silhouette and tomographic imaging technique is not unexpected. Because we excluded postangioplasty lesions from analysis, the limited correlation between ultrasound and angiography for percent stenosis is particularly striking. These findings are consistent with observations performed using intraoperative high-frequency epicardial ultrasound and support the concept that there are important differences between tomographic and planar vascular anatomy.\(^2\) Because percent stenosis is often used to determine therapy, the results of this study suggest that intravascular ultrasound has the potential to significantly alter clinical decision making in management of coronary artery disease.

These initial human coronary ultrasound examinations provide detailed images of vessel wall structures. However, there is no accepted standard on which to base interpretation of these images. Several investigators have studied excised vessel specimens using intravascular ultrasound and described a correspondence between in vitro microscopic and ultrasonic anatomy.\(^17\)-\(^19\) A triple-layered ultrasound appearance of muscular arteries has been reported with the layers proposed to represent the intima, media, and adventitia. However, such investigations are limited by potential alterations in vessel anatomy produced by postmortem changes and fixation techniques. The coronary artery in vivo is distended by pulsatile physiological pressure, which strongly influences vessel size, tissue thickness, and acoustic properties. Because of these phenomena, anatomy visualized by ultrasound may have a different appearance in vivo than that observed in the collapsed, chemically fixed arteries encountered in the pathology laboratory.

Therefore, in the present study, we used coronary images obtained from subjects with normal coronary arteries as the basis from which to evaluate atherosclerotic changes in wall morphology. This approach yielded normal values for the maximal thicknesses of the echogenic intimal leading edge and sonolucent subintimal zone usually evident in coronary ultrasound images. In normal coronary segments, the intimal leading-edge echo was thin and of low amplitude (Figure 5). This finding corresponds to the histological observation that the intima of normal vessels is quite thin and discrete in the absence of atherosclerosis.

A spectrum of abnormal findings was identified in coronary disease patients. At sites of angiographic luminal irregularity, the ultrasound image characteristically revealed a crescentic sonolucent band encroaching on the lumen, usually with an overlying area of variably echogenic and thickened intimal leading edge (Figure 10). In vitro studies have suggested that these sonolucent crescents represent lipid-laden plaques with or without a fibrous cap.\(^15\)-\(^20\) In extreme cases, the intimal leading-edge echo was very thick and highly reflective, preventing transmission of ultrasound energy to subjacent structures (Figures 3 and 11). The structures that produce acoustic shadowing are reported to represent lesions with sufficient fibrosis or calcification to markedly attenuate ultrasound transmission.\(^15\)-\(^20\)

An important finding of this study was the presence of ultrasonic abnormalities of coronary anatomy in many segments without accompanying angiographic abnormalities. Patients with minimal coronary disease by arteriography demonstrated a thickened intimal leading edge or sonolucent crescents in multiple “angiographically normal” segments. In fact, in patients with angiographic disease at any site, it was difficult to locate any segments with an ultrasound appearance similar to those of normal subjects. These findings are consistent with necropsy observations that human coronary disease is diffuse and frequently underestimated by contrast angiography. Furthermore, these observations demonstrate that angiographically uninvolved vessel segments in patients with coronary disease cannot be used to define normal vessel anatomy by ultrasound.

The ultrasound appearance at sites of balloon angioplasty was highly variable. The vessel wall was often severely distorted, demonstrated fracture of the continuity of the intimal leading edge, or occasionally yielded evidence of dissected tissue planes (Figure 13). Precise interpretation of anatomy after percutaneous transluminal coronary angioplasty was made difficult by distortion, thickening, and shadowing produced by atherosclerosis. Nevertheless, our preliminary experience supports the potential of intravascular ultrasound to augment angiography in the evaluation of balloon angioplasty results.

For routine clinical application in measurement of the coronary lumen, several limitations of intravascular ultrasound must be addressed. The sizes of the
current catheter and ring-down artifact limited imaging to vessels more than 2.2 mm in diameter. Evaluation of smaller vessels and severe stenoses will require further miniaturization of the intravascular ultrasound device. We are currently testing a prototype 3.5F (1.15-mm) version of this multielement catheter with both increased acoustic power and transducer sensitivity. Catheters combining ultrasound imaging with Doppler flow or a balloon angioplasty device are also undergoing development and testing. Potential distortion of luminal measurements by oblique imaging planes must also be addressed. The data in the current study were generated using a particular multielement imaging system. Differences between this approach and mechanical intravascular ultrasound devices have not been explored.

Application of intravascular ultrasound to routine evaluation of wall morphology will also require further improvements. Drop-out of structures with minimal echogenicity and shadowing by dense atherosclerotic plaques, accentuated by high-frequency ultrasound, prevented measurement of every vessel wall structure in each ultrasound image. It should also be emphasized that intravascular ultrasound is capable of classifying structures as echogenic or sonolucent but does not provide precise histological information. For example, some investigators have reported a sonolucent appearance to both vessel media and lipid-laden plaques. Because both normal structures (media) and pathological structures (lipid-laden plaque) may have similar ultrasonic appearances, this ambiguity precludes precise quantitation of ultrasonic plaque area. Further delineation of the relation between ultrasound characteristics and wall morphology will need to be elucidated.

The results of this initial study of coronary imaging by intravascular ultrasound are highly encouraging. The technique yielded striking new images of coronary atherosclerosis in vivo and permitted precise measurement of cross-sectional luminal dimensions from a tomographic perspective. Further studies in a broad spectrum of patients will be required to define the exact role of this new imaging modality in the evaluation of coronary artery disease in the clinical setting.

References


Key WORDs: ultrasound, intravascular, coronary artery disease, atherosclerosis
Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease.
S E Nissen, J C Gurley, C L Grines, D C Booth, R McClure, M Berk, C Fischer and A N DeMaria

Circulation. 1991;84:1087-1099
doi: 10.1161/01.CIR.84.3.1087

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/3/1087

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/