Update on Atherosclerosis

Intravascular Ultrasonic Imaging

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Because conventional imaging methods are inadequate for evaluating human coronary arteries in vivo, an intravascular ultrasonic imaging catheter was developed that allows the arterial wall to be studied in cross-section from within the artery. The catheter incorporates a mechanically rotating 20-MHz transducer, which is designed so that the ringdown occurs within the catheter and imaging is permitted up to the catheter's surface. The device rotates at 1800-rpm within a plastic sleeve and provides real-time cross-sectional images at 30 frames/sec. Preliminary experimental and clinical studies indicate that the intravascular ultrasonic imaging catheter could play a valuable role in providing preoperative information concerning arterial wall thickness and tissue characteristics, in distinguishing normal from diseased arterial wall structures during therapeutic intervention, and in assessing the results of intervention. ***(Texas Heart Institute Journal 1990; 17:181-9)***

Key words: *Angioplasty, transluminal; balloon dilatation; catheterization; coronary arteriosclerosis; coronary disease; echocardiography; ultrasonic diagnosis*

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Presented at the 19th annual symposium of the Texas Heart Institute, titled "Atherosclerosis: Etiology, Diagnosis, and Treatment," held 11-14 October 1989, at the Westin Galleria Hotel, Houston, Texas

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A wide variety of therapeutic interventions has been developed to treat coronary artery disease. Whether the goal is to enlarge the arterial lumen by balloon dilation or to reduce the atheromatous mass by means of laser ablation or mechanical atherectomy, it is important that the volume of atherosclerotic plaque be assessed before and after treatment. Current methods of doing this include angiography, which allows assessment only of the degree of luminal narrowing caused by the atheroma, and intravascular angioscopy, which reveals information about the appearance and topography of the luminal surface.[1,2] Although angioscopy can distinguish ulcerated plaques and thrombus, it cannot provide quantitative information concerning the extent of atheromatous involvement in the arterial wall.[3] Neither angiography nor angioscopy provides much data on the size, location, or composition of the atheroma. Although ultrasound could potentially provide such data,[4] ultrasonic imaging of coronary arteries has been limited because of difficulty in visualizing the coronary tree via a transcutaneous approach. Coronary images have been obtained either in vitro with conventional 12-MHz external ultrasonic imaging devices or in exposed epicardial coronary arteries at the time of open-heart surgery.[5-7] Such external ultrasonic devices are obviously limited when it comes to evaluating human coronary arteries in vivo. To circumvent this limitation, an intravascular ultrasonic transducer, positioned on the end of a catheter, has been used to image coronary and peripheral arteries in vitro and in animal studies.[8-11] This approach, which allows the arterial wall to be imaged in cross-section from within the artery, opens up the possibility of imaging human coronary arteries in the catheterization laboratory both as a routine complement to diagnostic angiography and before, during, and after therapeutic intervention.

Several research groups have been working on the development of ultrasonic imaging catheters. In 1971, Bom and coworkers,[12] in Rotterdam, developed an early prototype, 32-element, phased-array catheter. More recently, Yock and colleagues,[9] in association with Cardiovascular Imaging Systems, Inc., have used a mechanically rotating crystal to generate intravascular images during atherectomy. Hodgson's group[13] has been testing a phased-array system by Endosonics: because this system has no rotational motion, the catheter can be passed over a central guidewire, but the system offers less spatial resolution than do the mechanical devices. At Boston Scientific Corporation, Crowley and associates[14] have developed a mechanically rotating catheter whose transducer revolves within a plastic polymer acoustic window. Finally, our group has developed a mechanically rotating 20-MHz transducer, which is designed so that the ringdown occurs within the catheter and imaging begins at the catheter's surface. The present article describes our experience with this intravascular ultrasonic imaging device.

General Description of the Catheter

The catheter incorporates a single 20-MHz ultrasound transducer, located at its distal end. The transducer is oriented so that the ultrasonic beam is aimed parallel to the long axis of the catheter (Fig. 1). The beam strikes a metal mirror and is refracted at a 90° angle, so that it exits the catheter perpendicular to the device's long axis. This design permits imaging to begin at the surface of the catheter, since the initial ringdown oscillations occur in the space between the transducer and the mirror, not between the catheter and the arterial wall. If the transducer were directly on the catheter's surface, the ringdown oscillation artifact would prevent imaging within 0.3 mm of the catheter's surface. The present catheter measures 1.2 mm in diameter; future models will probably be even smaller in diameter. In the preliminary in vitro studies, the catheter was hand-rotated a full 360° within the lumen of the arterial specimen. During rotation, the B-mode ultrasonic image appeared on the video screen as a circle composed from positional data transmitted by an angular potentiometer attached to the catheter's proximal end. More recently, the catheter has been adapted to an 1800-rpm motor drive, which now provides real-time cross-sectional images at 30 frames per second. For the in vitro studies reported here, a precision positioning device was used to control the catheter's height, angle, and speed of rotation during imaging.

Measurement of Arterial Wall Thickness

Human atherosclerotic arterial specimens were obtained at autopsy. Specimens were available from coronary, splenic, iliac, femoral, and tibial distributions. On gross examination, most of the arteries were severely atherosclerotic. The arteries were divided into 2-cm segments and placed in saline. The ultrasonic imaging catheter was then used to image each segment in 1-mm increments. Accurate intraarterial positioning was assured by placing a surgical needle through the arterial wall to provide an acoustic reference point. The resulting images, which appeared on a video monitor, were stored on a Sony video image transcriber and archived onto a computer disk. Extreme care was taken to prevent air bubbles from adhering to the catheter's tip, which would have compromised the images' quality severely. Moreover, misalignment of the long axis of the catheter by more than 15° away from the coaxial plane of the artery would have caused a dropout of reflected ultrasound and consequent image degradation.

The arteries were marked with a suture at the level of the reference needle, and sectioned at 1-mm intervals for histologic analysis. These sections were stained with hematoxylin and eosin, and measurements were made from photographs of the sections. After each artery had been studied, the computer images were retrieved from the disk. The luminal cross-sectional area of these images was then measured along the length of each artery. Table I compares the mean ultrasonic and histologic measurements.

Three distinct arterial wall components were visualized ultrasonically: a highly reflective intima, an echolucent media, and a moderately reflective adventitia. Figure 2A reveals an ultrasonic cross-sectional image from a normal human carotid artery, and Figure 2B shows a histologic section of the same artery. On the luminal side of the ultrasonic image, the echolucent media is defined by its contrast with a strong echo that is believed to originate from the internal elastic lamina. This belief is based upon the observation that, in arteries with small-to-moderate eccentric atheroma, a bright echo extends behind the base of the atheroma, medial to the echolucent muscular layer, which corresponds to the internal elastic lamina on histologic section (Fig. 2B). If this bright echo were produced by the tissue-fluid inter-

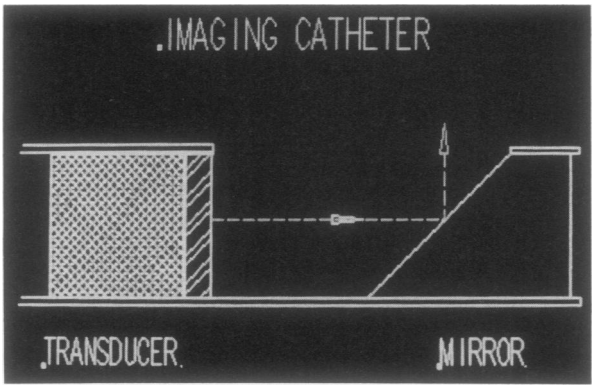

Fig. 1 *Schematic representation of the catheter's distal end, showing the single 20-MHz ultrasound transducer and the mirror. When ultrasonic energy is transmitted against the mirror, the sound waves are deflected perpendicular to the long axis of the catheter.*

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TABLE I. Comparison of Arterial Wall Thicknesses (Mean ± Standard Deviation) as Measured in Vitro at Identical Longitudinal Points, by Ultrasonic and Histologic Techniques

	Histologic Measurements (mm)	**Ultrasonic Measurements** (mm)
Intima	0.9 ± 0.8	1.2 ± 0.8
Media	0.4 ± 0.2	0.5 ± 0.2
Total Wall Thickness	1.7 ± 0.8	2.4 ± 0.8

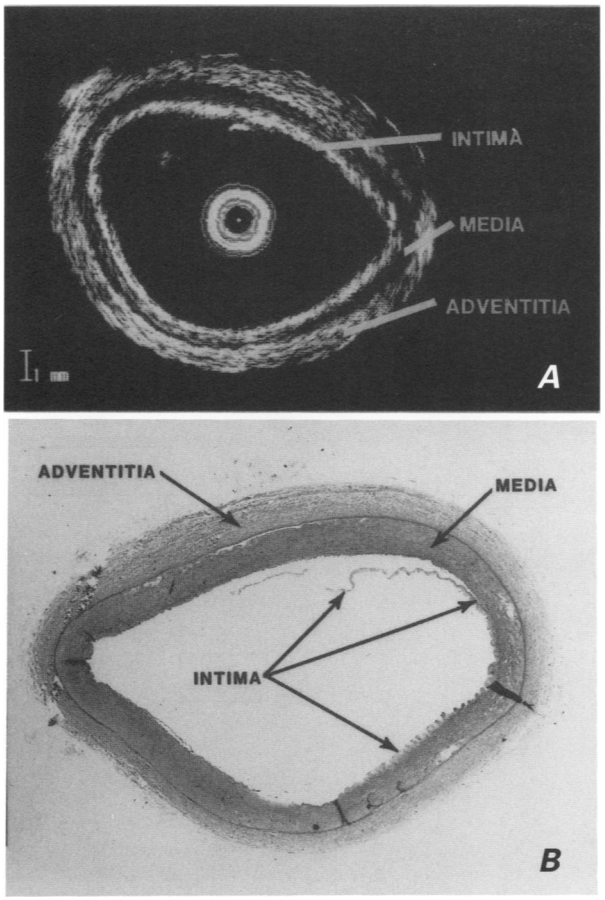

***Fig. 2 A**) Ultrasonic cross-sectional image from a normal human carotid artery. The central echodensity is due to the presence of the intravascular catheter. The catheter is surrounded by a black echolucent area, which is the arterial lumen. The next bright echo-reflectant structure is the intima, which is exaggerated in comparison with the thin intimal layer seen in the accompanying histologic section (**B**). The increased echo reflectivity from the intima extends into the media, which is echolucent. The outermost echo-reflective structure is the adventitia.*

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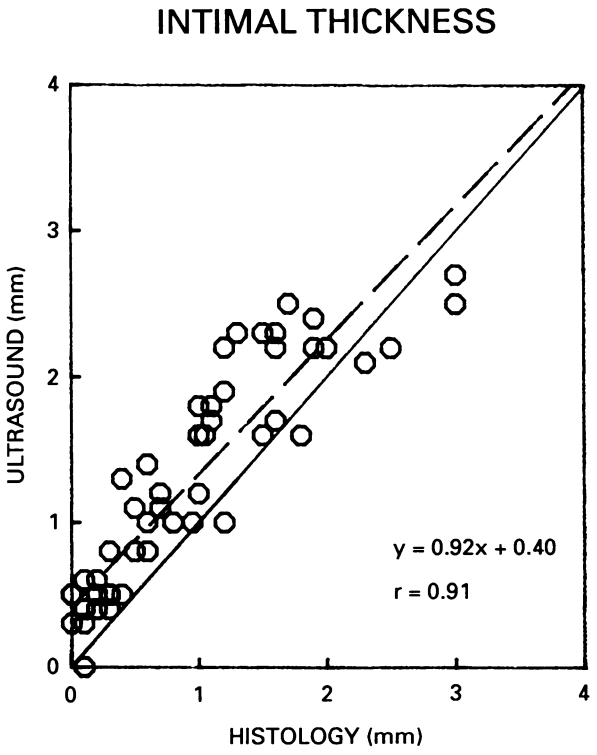

***Fig. 3** The intimal thickness measured by ultrasound correlated well with the intimal thickness measured directly from the histologic sections (r = 0.91). The ultrasonic measurements exaggerated the histologic measurements by 0.3 mm (33%; p < 0.001).*

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face, it would be expected to appear in front of the plaque, where the tissue-fluid interface is located. Therefore, this bright echo in normal arteries appears to be caused by reflections from the internal elastic lamina, not by the tissue-fluid interface.

The results of this study suggest that, for measuring the thickness of the intima, the media, and the total arterial wall, intravascular ultrasonic imaging is an accurate method compared with direct histologic evaluation (Fig. 3). However, the study revealed several factors that can limit one's ability to use ultrasound to measure the thickness of arterial layers. For example, ultrasonic images caused the media, as it passed behind certain atheromata, to appear markedly thinner than it actually was, or to disappear altogether, a phenomenon due partly to a dropout of ultrasonic information behind areas exhibiting dense fibrosis or calcification. (In other instances, however, there was actual thinning of the media behind thick, eccentric plaques, a phenomenon observed first on ultrasonography and then confirmed by histologic study, which revealed destruction of the media behind thick atheromata.) Compared to the histologic samples, the ultrasonic images exaggerated the mean thicknesses of intima and total arterial wall by 33% and 41%, respectively. The most likely explanation for this exaggeration is that strong echoes from the highly reflective internal elastic lamina and fibrous adventitia extended into the region where the media and lumen were visualized, artifactually increasing intimal and total wall thicknesses.

Tissue Characterization

In another study, 20 refrigerated human arterial segments were obtained from coronary, carotid, iliac, and femoral arteries less than 1 week after necropsy and were imaged at room temperature in a saline bath. Intimal, medial, and adventitial structures from the ultrasonic images were examined, and distinctions in echo reflectivity were correlated with the corresponding histologic findings.[15]

Twenty-three high-quality images from the 20 arteries were selected and paired with their histologic counterparts. Five trained observers then viewed the ultrasonic images without benefit of seeing the histologic specimens, and answered the following questions:

1) Is the artery normal or abnormal (i.e., does it contain atheroma)?
2) Is calcification present?
3) Can the muscular media be seen well enough for the thickness of the atheroma to be measured?
4) Are regions of liquid necrotic material present within the intimal plaque?

The observers' answers were pooled, and differences were resolved by consensus. The criteria used to identify calcification included very intense ultrasonic echo reflections accompanied by shadowing of the distal wall. Figure 4A shows an ultrasonic image from a diseased human carotid artery. At the base of the eccentric intimal plaque is a small region of calcification that causes shadowing or dropout of the echo information. The echolucent media is seen circumferentially. The corresponding histologic section (Fig. 4B) shows the small area of dense calcium. The thin internal elastic membrane generates a highly echogenic signal that, on the ultrasonic image, exaggerates the true thickness of this echo-reflective structure. Fibrous, noncalcified intimal plaques are demonstrated in ultrasonic images by an echogenic structure of at least 0.25 mm, without echo shadowing. Shadowing is seldom seen because fibrous plaque, although a good echo reflector, is not as brightly reflective as calcium. Regions of necrotic liquid appear as large echolucent areas within the plaque and are distinguishable from calcium-induced dropout because the area is surrounded by tissue reflections.

Figure 5A, an ultrasonic image from a severely diseased iliac artery, features a large echolucent region that was found on gross examination to contain liquid necrotic material. In the companion gross specimen (Fig. 5B), a large space to the right of the lumen contains liquid necrotic material.

Twenty of the 23 arterial images evaluated in this study had intimal thickening on histologic section, whereas 3 did not. The observers correctly categorized all 23 specimens either as "normal" or as having a "thickened intima." Regions of necrotic liquid ("lakes") were correctly identified by all the observers, and there were no false positives. Eleven of the arterial sections were calcified, and all 11 were correctly categorized by means of ultrasound. In this instance, however, there was 1 false positive, a noncalcified artery with highly fibrotic plaque that resembled calcification with shadowing. All of the calcified arteries were correctly interpreted as calcified.

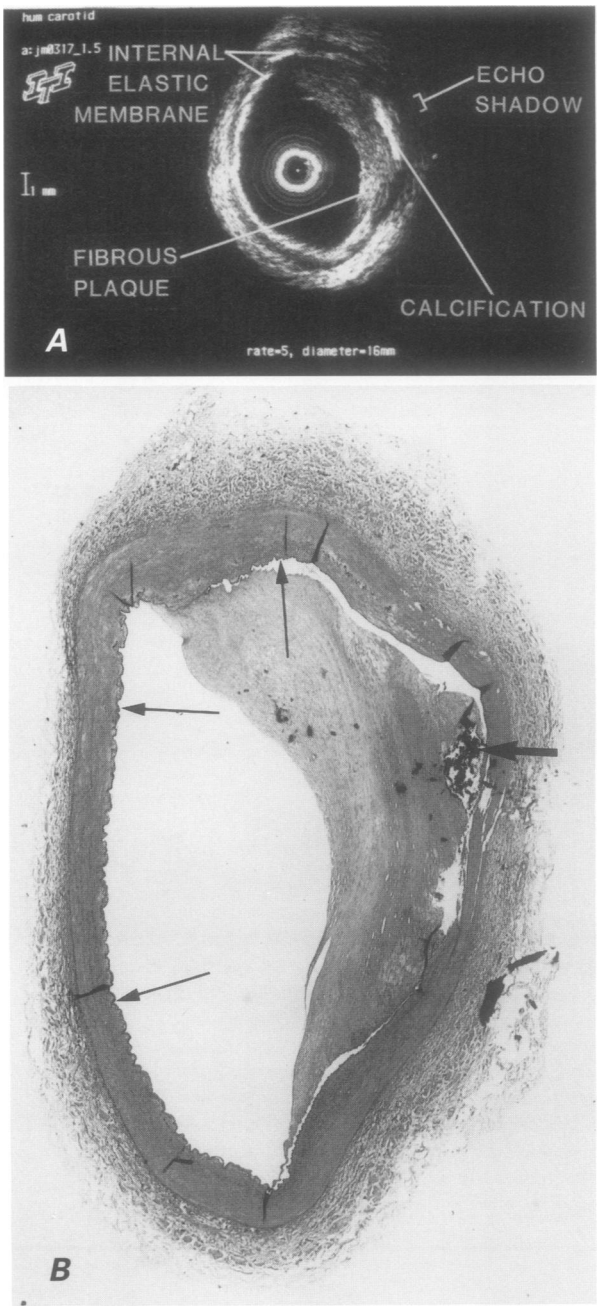

Fig. 4 *Both the ultrasonic image (**A**) and the histologic cross-section (**B**) show calcium as a very echo-dense reflector, with dropout of the echo signal behind the calcium at the base of the plaque. In the histologic section, the thick arrow points to the small area of dense calcification, whereas the thin arrows designate the internal elastic membrane.*

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The observers' ability to identify the echolucent media was also evaluated. In their judgment, [14] (61%) of the 23 ultrasonic images contained enough circumference of an identifiable echolucent media to permit the measurement of intimal plaque thickness. We believe that this capacity to identify the echolucent media is important, because it allows intimal plaque

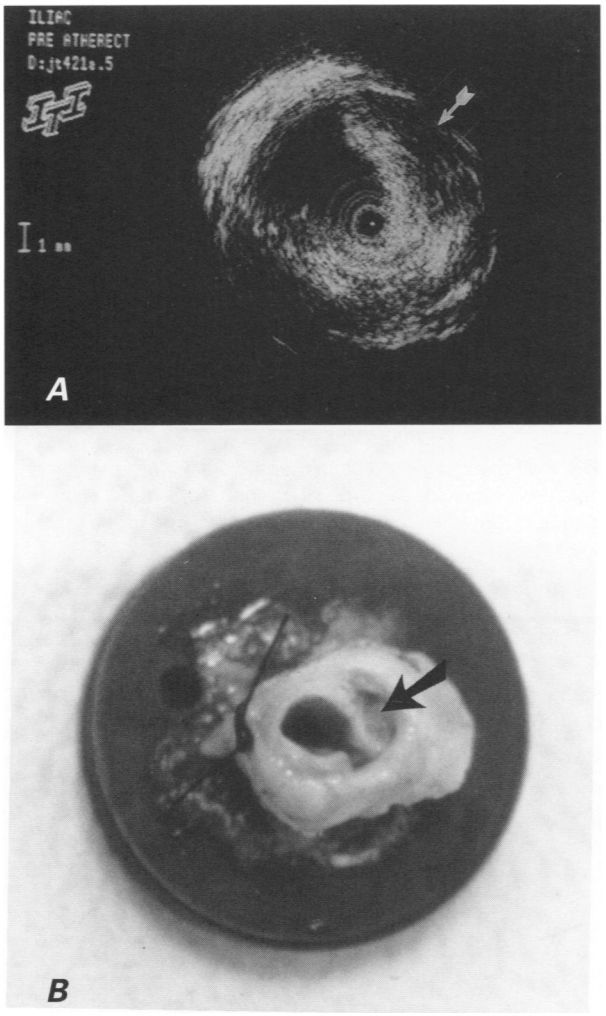

Fig. 5 ***A****) Adjacent to the echolucent lumen of a severely diseased human iliac artery segment, another echolucent area (arrow), bounded by echoes from the fibrotic plaque and from the adventitia, contains necrotic liquid.* ***B****) The gross specimen reveals the location of this material (arrow), which remained liquid even at room temperature.*

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thickness to be measured separately from total wall thickness, thus permitting determination of atherosclerotic depth. The results of this initial study support the hypothesis that intravascular imaging with high-resolution ultrasound allows close characterization of the tissue type within the arterial wall structure.

Ultrasonic Imaging Before and After Balloon Angioplasty

The ultrasonic imaging catheter was evaluated before and after balloon dilation in human atherosclerotic arterial segments that had been mounted on plastic bases and immersed in saline.[16] Before dilation, 17 arterial segments were imaged at 1-mm longitudinal intervals. Each segment was then dilated with a coronary or peripheral artery balloon whose inflated diameter was 1.0 to 1.3 times the diameter of the artery. After dilation, the arterial sections were remounted onto their plastic bases and replaced in the beaker of saline. Care was taken to orient each artery in a manner similar to that used to obtain the images before dilation. A 2nd set of ultrasonic images was then obtained at 1-mm intervals, at the same levels imaged before dilation; a surgical needle served as an acoustic reference point. After each artery had been studied, the computer images were retrieved from the disk. The pre- and postdilation cross-sectional luminal areas were measured along the length of the artery and were compared by means of Student's paired *t* test. Corresponding histologic sections were then prepared, and measurements were taken from photographs of these sections. Linear regression analysis was used to compare the postdilation histologic cross-sectional measurements to the postdilation ultrasonic-image measurements. Figure 6 shows a representative pair of ultrasonic images, obtained before (A) and after (B) balloon dilation, in an arterial section that was only moderately diseased. In all 15 of the specimens in which adequate images were obtained, the echo-free lumen was clearly delineated; the fibrous plaque and the adventitia were seen as regions of high echo reflectance, while the muscular media appeared as an area of low echogenicity.

Both ultrasonic and histologic images were analyzed after dilation, for evidence of plaque tearing and dissection. Diagnosis of a plaque tear was based

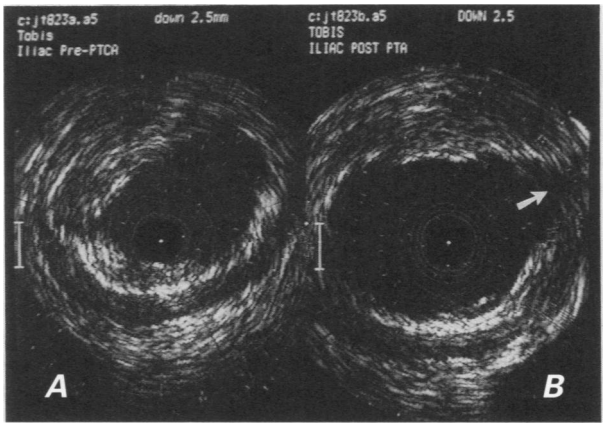

Fig. 6 *A pair of ultrasonic images obtained before (****A****) and after (****B****) dilation of a moderately diseased artery. The images were obtained 2.5 mm below the needle reference line. The central black area marks the site of the transducer. In* ***A****), the echo-free lumen is clearly delineated from the fibrous, atheromatous plaque, which has high echo reflectance. The muscular media has low echogenicity, and the surrounding adventitia shows high echo reflectance. After balloon dilation (****B****), the cross-sectional area was increased and there was a minor tear in the plaque (arrow).*

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on observation of a fracture of the intimal plaque, showing separation of the torn ends. Moreover, separation of the intimal plaque from the media appeared to result in a new echolucent area. Figure 7 shows ultrasonic images of a densely calcified, fibrotic human iliac artery before (A) and after (B) balloon angioplasty. Note that the plaque tear is characterized both by separation of the plaque from the media and by separation of the torn ends. Plaque tears were present in most of the arterial specimens and were typically located either in the thinnest portion of the atheroma or at the junction of the plaque and the normal arterial wall. The tears also produced a dissection plane between the plaque and the internal elastic membrane. Stretching of the artery in this region resulted in enlargement of the true lumen. In several instances, the ultrasonic images also disclosed an intimal flap (Fig. 8). In 11 of the 13 cases in which matched ultrasonic and histologic sections were available, the ultrasonic images accurately indicated the histologic presence or absence of tears. To determine the accuracy of the intravascular ultrasonic measurements, multiple luminal cross-sectional images derived from ultrasound were compared with those derived from the histologic sections at the same sites along the length of each arterial segment. In the case of 39 paired, postdilation

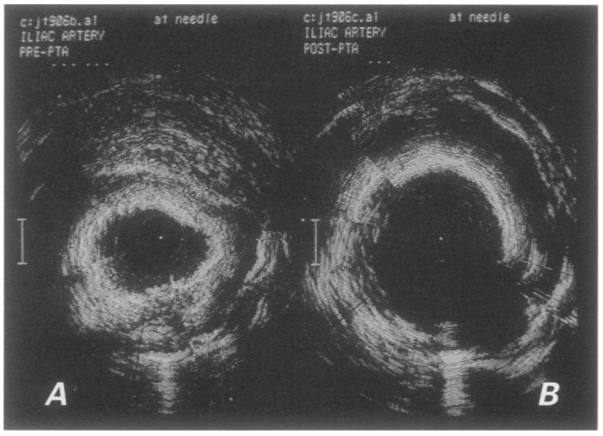

Fig. 7 *Results of balloon angioplasty in a densely calcified, fibrotic human iliac artery. The predilation ultrasonic image (**A**) shows dense fibrocalcific plaque, with a dropout of echo information distal to the atheroma. At the base of each ultrasonic image, there is an artifact corresponding to the acoustic reference needle, which was placed in the outside wall of the artery. The postdilation ultrasonic image (**B**) shows dilation of the lumen, with tearing of the plaque's edges and separation of the torn edges (at 4 o'clock). In the top right-hand quadrant, a new echolucent area may be seen behind the dense fibrocalcific plaque. This dissection plane was observed to extend behind the atheromatous plaque on the histologic cross-section as well. The torn portion of the atheroma was the thinnest section of the plaque; on the ultrasonic image, it appears at approximately 3 to 4 o'clock.*

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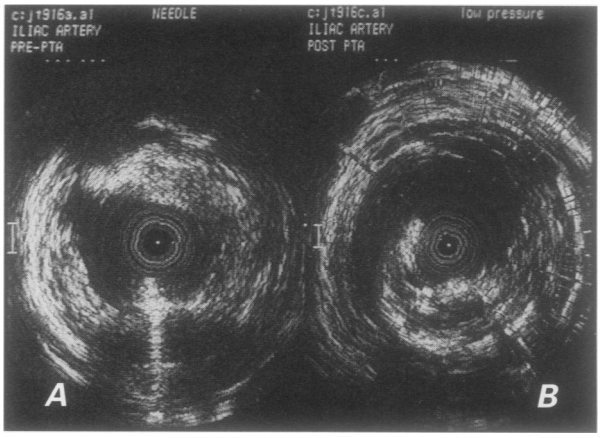

Fig. 8 *In this composite photograph of ultrasonic images obtained before (**A**) and after (**B**) balloon dilation, the arterial plaque is torn after dilation, and an intimal flap protrudes into the lumen at 7 to 10 o'clock.*

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sections, the 2 cross-sectional areas correlated closely (Fig. 9). The correlation coefficient was 0.88, and the standard error of the estimate was 3.2 mm^2. The measurements were related by means of the following equation:

Luminal area (ultrasonic) = 0.94 x luminal area (histologic) + 0.52 mm^2

To assess the increase in luminal area produced by balloon dilation, the pre- and postdilation ultrasonic cross-sectional areas were then compared. In

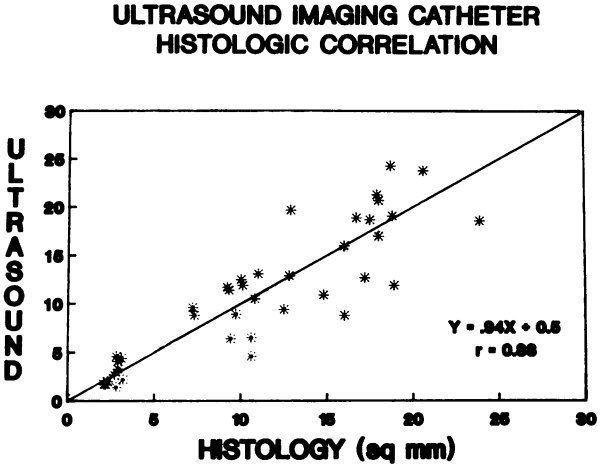

Fig. 9 *To determine the accuracy of the measurements, the ultrasonic luminal cross-sectional area was compared with the histologic luminal area at multiple sites along the length of each arterial segment. The correlation coefficient was 0.88 for the measurements obtained with the intravascular ultrasound catheter (y-axis), when compared with measurements derived from the histologic sections (x-axis).*

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the 15 arterial segments in which adequate ultrasonic images were obtained, the cross-section that showed the greatest percentage of postdilational change in luminal area was determined. On the average, these maximal luminal areas increased from 8.7 mm^2 before dilation to 15.1 mm^2 after dilation ($p < 0.01$).

In comparing the ultrasonic cross-sectional areas with those of the histologic sections, we encountered several sources of error. First, the preparation of histologic specimens may cause artifactual compression and distortion, especially after balloon angioplasty, when the integrity of the arterial wall may be compromised. Second, fixation in formalin may cause the tissue to shrink. Ultrasonic images obtained before and after formalin fixation revealed a 4% difference between the 2 measurements; this difference may account for some of the variations in area between corresponding ultrasonic and histologic sections. Therefore, in determining the true size of anatomic structures, ultrasonic calculations in vivo may be more accurate than measurements derived from histologic specimens. The results of our studies suggest that ultrasonic energy can be used intravascularly to evaluate human atherosclerosis before and after therapeutic interventions.

Clinical Trials

Several clinical trials of the motor-driven ultrasonic imaging catheter are currently in progress. These trials involve imaging of peripheral artery disease at the time of balloon angioplasty or mechanical atherectomy; intracoronary imaging during bypass surgery; and intracoronary imaging during angioplasty. To protect the arterial wall during mechanical rotation, a plastic introducing sheath 1.6 mm in diameter is advanced through a 9-Fr guiding catheter, over a standard angioplasty guidewire. After the sheath is in position across the target stenosis, the guidewire is removed, and the ultrasound subassembly is inserted into the sheath's proximal end through a hemostatic 0-ring. While the sheath remains stationary across the stenosis, the subassembly is advanced and retracted under fluoroscopic control, obtaining images of the stenosis at multiple positions without damage to the arterial wall.

The preliminary results of these clinical studies indicate that the ultrasonic imaging catheter yields high-quality images of the arterial wall and lumen, which can provide information about the eccentricity of the plaque and the type of tissue present (fibrotic, calcified, or thrombotic). Interestingly, we observed that arterial contraction occurs only in the portion of the wall that is free of atheroma. If the artery is affected by thick atheroma or if calcium is present, the affected segment will not expand with each heartbeat; in contrast, a normal segment will dilate appropriately during the cardiac cycle.

The potential benefit of the ultrasonic imaging device is revealed by an angioplasty case in which an eccentric obstruction of the mid left anterior descending artery was dilated with a 4.0-mm balloon.[17] After dilation, a hazy density appeared on angiography (Fig. 10A). On sequential angiograms, the lumen continued to diminish. Therefore, multiple repeat dilations were performed, at increasing pressures and for longer durations. When the ultrasonic imaging catheter was inserted, it revealed dense calcification and local dissection at the dilation site. The luminal area was sharply delineated along the length of the artery, until the dilation site was reached, at which point the lumen became filled with a mildly echo-reflective density (Fig. 10B). This density continued for ap-

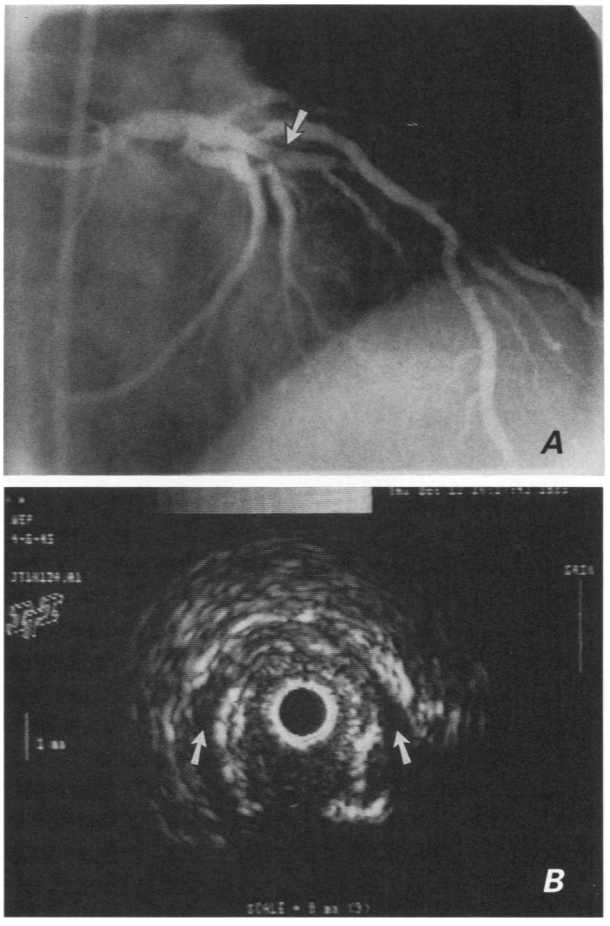

Fig. 10 *After initial balloon dilation, this left anterior descending coronary artery at angiography (**A**) exhibits a residual haziness at the level of the dilation (arrow), despite complete inflation with a 4.0-mm balloon. Subsequent unsuccessful dilations led to ultrasonic investigation (**B**), which revealed dissection and separation between the internal elastic membrane and the media (arrows). The portion of the lumen just below the central catheter circle is not completely echolucent because it is filled with a large residual atheroma or thrombus which corresponded to the hazy section on angiography.*

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proximately 0.5 cm and almost occluded the residual lumen. On the basis of our in vitro tissue characterization studies, we believe that this intraluminal echogenic source was probably thrombus, which could have formed as a consequence of angioplasty. The information derived from this intravascular evaluation influenced our decision to repeat the balloon dilation instead of terminating the procedure. In the same patient, ultrasonography revealed both atheroma and calcification (neither of which had been detected by angiography) in a segment of the mid left anterior descending artery that had not been dilated (Fig. 11).

Future Applications

An intravascular ultrasonic catheter such as the one described above can provide information about the distribution and quality of an atheroma before and after therapeutic intervention. Preoperative characterization of the atheromatous tissue may suggest which of several alternative therapies would be most effective. In the future, incorporation of an ultrasound transducer within an angioplasty balloon will likely allow the arterial wall to be visualized in cross-section during dilation. An intravascular imaging catheter could also allow the differentiation of normal and diseased arterial wall segments along the circumference of the lumen. During laser therapy of eccentric plaques, this ability to distinguish eccentric plaque from normal arterial wall is crucial to prevent exposure of the uninvolved wall (Fig. 12). Moreover, a method that can assess the degree to which an atheromatous plaque has been disrupted by a percutaneous intervention is of considerable potential benefit.

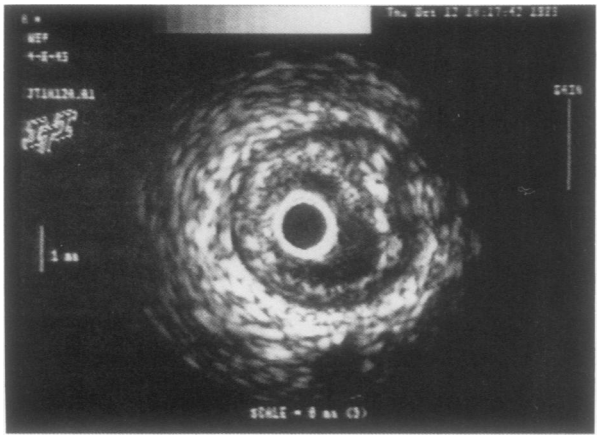

Fig. 11 *In the same case demonstrated by Figure 10, the mid left anterior descending artery (which was not dilated) has a 2.0 x 1.5-mm residual lumen narrowed by a large amount of atheroma with minimal calcification with shadowing (at 3 o'clock), neither of which was revealed by angiography.*

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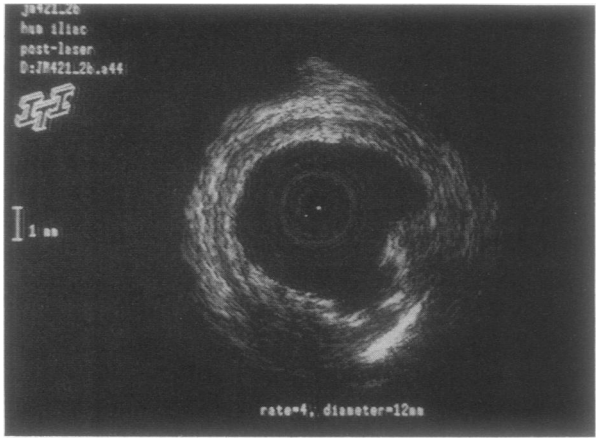

Fig. 12 *In this human iliac artery, destruction of the atherosclerotic plaque at 5 o'clock was due to photo-ablation with a bare Argon laser fiber. This in vitro feasibility study was performed with direct visual guidance, but it does show the ability of the ultrasonic imaging catheter to identify the portion of the arterial wall affected by atheroma. The potential benefit of this will be to guide a laser beam towards an atheromatous mass and away from a thin intima.*

(From: Mallery JA, Tobis JM, Gessert JM, Griffith JM, Henry WL. Intravascular ultrasound imaging. In: Abela GM, ed. Lasers in cardiology. Boston: Kluwer Academic Publishers, 1990, with permission of the publisher.)

The intravascular ultrasonic technique, performed percutaneously in the catheterization laboratory, appears to be a fundamental and important departure from traditional angiographic methods for assessing the severity of coronary, carotid, and peripheral vascular disease.

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