## Title

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## Journal

American heart journal, 119(6)

## ISSN

0002-8703

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## Publication Date

1990-06-01

## DOI

10.1016/s0002-8703(05)80190-5

# Assessment of normal and atherosclerotic arterial wall thickness with an intravascular ultrasound imaging catheter

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Atherosclerosis is a diffuse disease process that produces thickening of the vascular wall because of intimal deposition of lipid, fibrous tissue, and calcific material.[1] No presently available diagnostic method allows this thickening to be accurately measured in human coronary arteries in vivo, except ultrasound imaging during direct exposure of the heart at the time of surgery.[2-4] Contrast coronary angiography provides an image of the contour of the lumen but gives no information about either the volume or composition of the atheroma present.[5] A mild degree of luminal narrowing on the angiogram may in reality represent a large atheroma volume.[6]

Interventions designed to reduce atheroma volume, such as laser angioplasty and aggressive pharmacologic serum cholesterol reduction, require a technique that allows accurate measurement of arterial wall thickness and atheroma volume to properly judge their effects. Acute interventional procedures such as balloon angioplasty might also benefit from a technique that continuously monitors the atheroma thickness in real time.[7]

Extravascular ultrasound imaging provides a method for evaluating arterial wall thickness.[2, 3] For instance, carotid arteries have been extensively studied with external real-time B mode ultrasound imaging.[8] A high degree of accuracy in measurement of luminal dimension compared to results achieved with angiography has been established. In addition, there is reasonable reproducibility in the measurement of the extent of atherosclerosis over 6 months.[8] Coronary images have also been obtained with conventional 12 MHz external ultrasound imaging devices in vitro or at the time of open-heart surgery on exposed epicardial coronary arteries.[2, 4]

An alternate method for using ultrasound to evaluate wall thickness involves placing a miniaturized ultrasound transducer on the end of a catheter.[7, 9-11] This approach would allow the arterial wall to be imaged from inside the artery and might open the possibility of imaging human coronary arteries in the catheterization laboratory as a routine complement to diagnostic angiography, as well as before, during, and after percutaneous transluminal coronary angioplasty, laser, or atherectomy intervention. The purpose of this study was to evaluate a prototype intravascular ultrasound imaging catheter. The hypothesis tested in this study is that high-frequency intravascular ultrasound imaging provides a method for accurate measurement of arterial wall thickness in normal and atherosclerotic human arteries.

## METHODOLOGY

This study used an imaging catheter with a single 20 MHz ultrasound transducer oriented so that the ultrasound beam was aimed parallel to the long axis of the catheter (Fig. 1). The ultrasound beam was reflected from a metal mirror so that the beam exited the catheter perpendicular to the long axis of the catheter. This design permitted imaging up to the surface of the catheter, since the initial transducer oscillations occurred in the space between the transducer and the mirror. The imaging catheter and display were developed by Intertherapy Inc, Costa Mesa, Calif. The diameter of the catheter was 1.2 mm. To construct an image, the catheter was rotated by hand through 360 degrees inside an artery. Dur-

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Received for publication Dec. 8, 1989; accepted Jan. 16, 1990.

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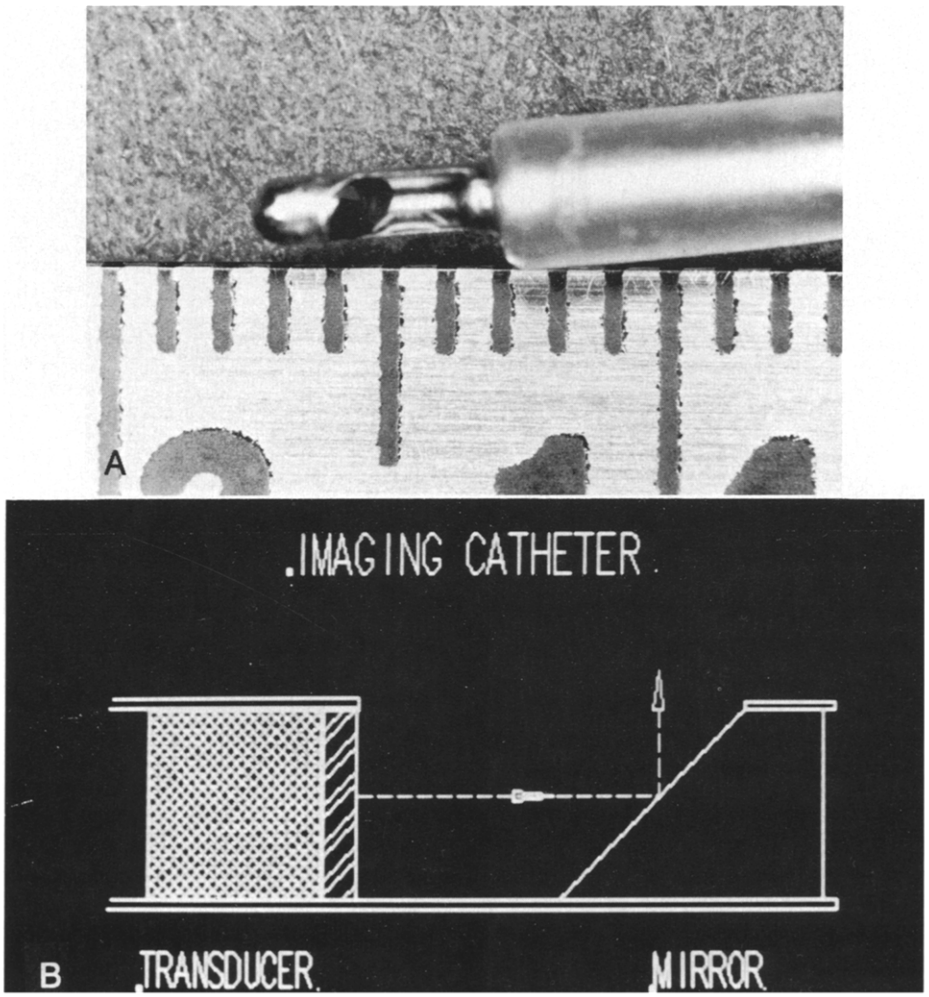


**Fig. 1. A,** Prototype ultrasound imaging catheter transducer and mirror. **B,** Schematic representation of tip of one prototype device. Single 20 MHz ultrasound transducer is located at distal end of catheter so that ultrasound energy is transmitted again a mirror, which deflects ultrasound perpendicular to long axis of catheter.

ing rotation the B mode ultrasound representation was painted as a circle on the screen with the use of position information provided by an angular potentiometer attached to the proximal end of the catheter. The resulting image was a cross section of the artery.

In the present study the catheter was mounted in a precision positioning device, which was used during imaging to control the height, angle, and rotation of the catheter (Fig. 2). Segments of human arteries were positioned vertically in a beaker filled with saline solution. By means of the positioning device, the catheter was advanced along the course of the artery. At each 1 mm increment the catheter was rotated 360 degrees to construct a cross-sectional image. Thus a series of cross-sectional images along the course of the artery segment were obtained.

To assess the ability of this catheter to accurately measure wall thickness, fresh (less than 1 week old) arterial segments from human coronary, carotid, and femoral arteries were imaged at room temperature in a saline bath. Only arteries preserved by refrigeration in saline solution were used in this study, in as much as we have observed changes in ultrasound reflectivity in formalin-preserved specimens. Measurements were made of intimal, medial, and total arterial wall thickness from ultrasound images in four orthogonal quadrants, and these measurements were compared to those from the corresponding quadrants from hematoxylin and eosin–or trichrome-stained histologic

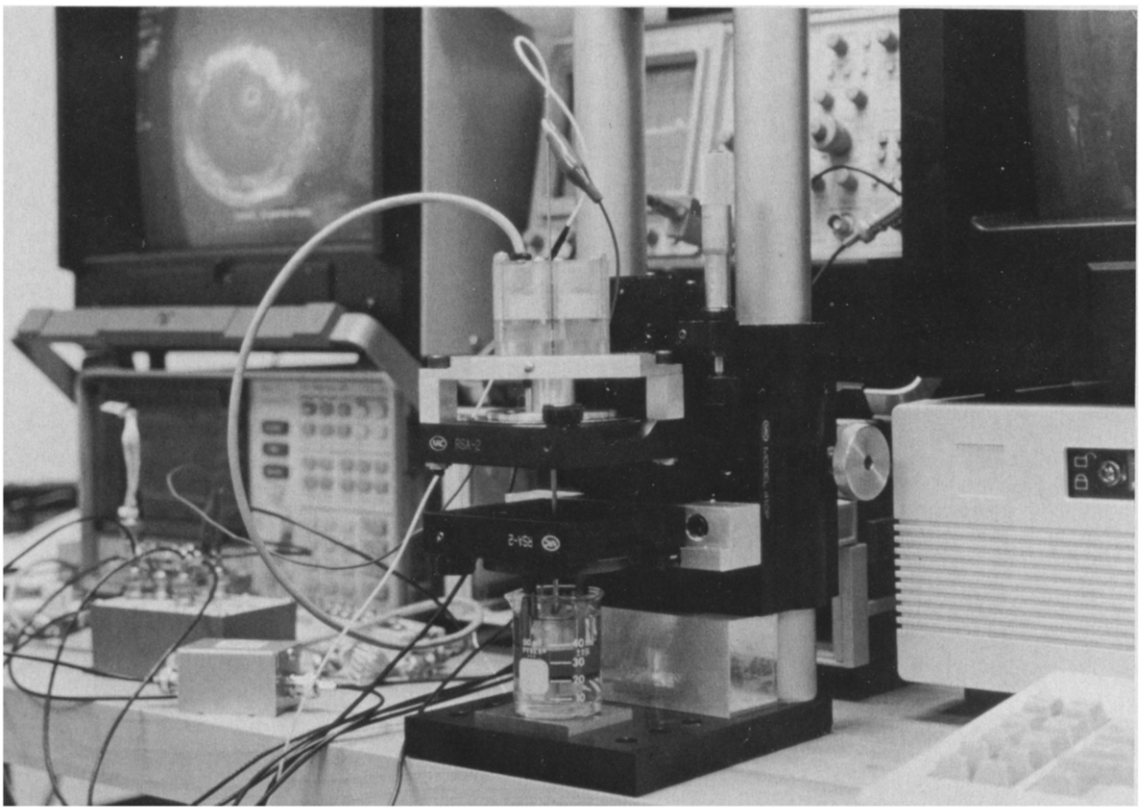

**Fig. 2.** Mounting apparatus and recording equipment. Imaging catheter has been placed through mounting apparatus to hold it in place. Distal end of transducer was passed through artery segment, which is immersed in beaker of saline solution. As catheter was rotated, cross-sectional image was generated on video monitor *(upper left-hand corner).*

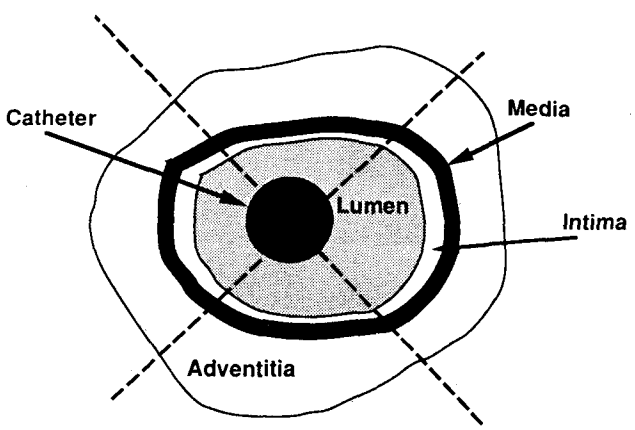


**Fig. 3.** Diagram showing how wall thickness measurements were made in four different quadrants. Photographs of arterial histology slides were made at known magnification. Each layer of artery was measured along quadrant line. If calcification obscured the wall, no measurement was obtained in that quadrant. Muscular media is dark (echolucent) and separated intima (and plaque if present) from adventitia (outside portion of artery).

sections of the same arteries (Fig. 3). To facilitate measurement of histologic sections, all histologic specimens were photographed at known magnification such that the resultant photograph was similar in size to the ultrasound image. To maintain proper radial alignment of ultrasound and histologic images, the thickest part of the arterial wall from the ultrasound image was rotated to align with the thickest wall of the histologic images. In five instances where there was fairly uniform arterial wall thickness, an eccentric piece of calcium in the arterial wall was used to ensure proper radial alignment of images. Arterial specimens were imaged from one end to the other in 1 mm increments with the ultrasound device; histologic sections were likewise made in 1 mm increments from the specimen. Thus a given ultrasound image corresponded within 0.5 mm to the histologic section. In addition, internal markers, such as pieces of calcium were used to check that ultrasound images, and histologic sections were aligned.

The muscular medial layer of the artery, the tunica

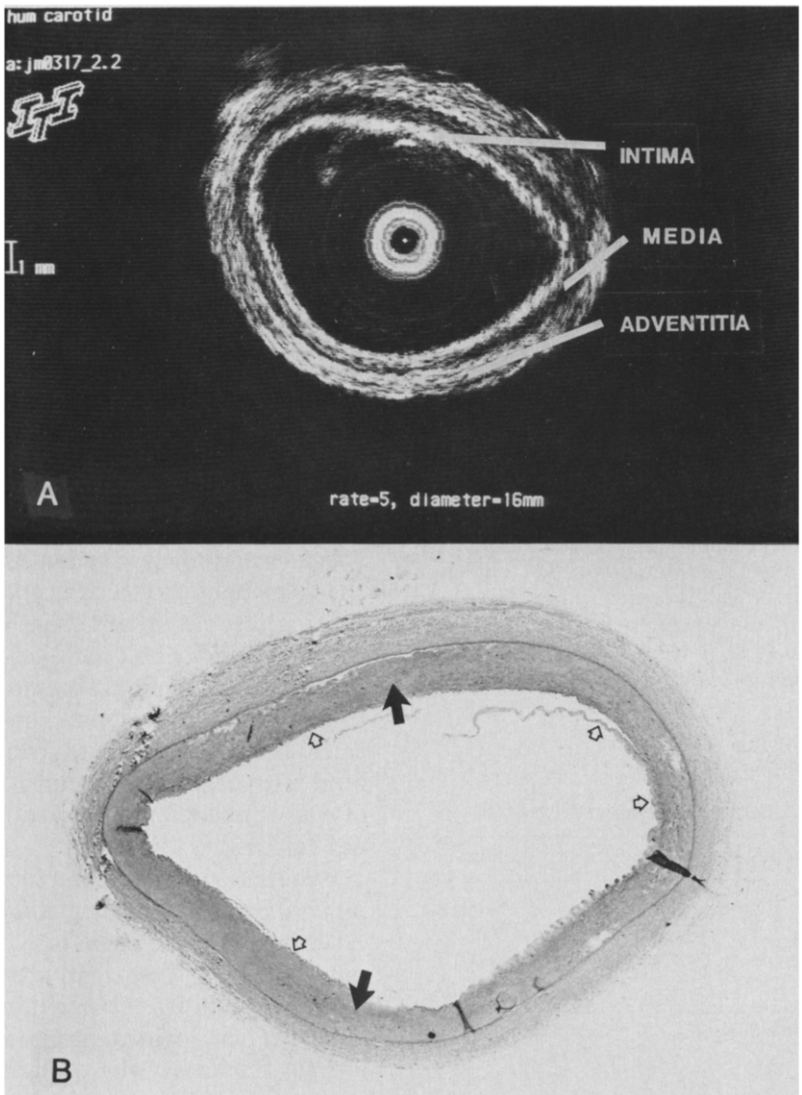


**Fig. 4. A,** Intravascular ultrasound image of normal human carotid artery showing characteristic three-layer appearance. Muscular medial layer of artery is relatively echolucent and provides reference point in arterial cross section separating intima from adventitia. Intima is seen extending from lumen-tissue interface to echolucent media. Adventitia consists of all echoes originating peripherally to media. **B,** Histologic section corresponding to ultrasound image showing thin intima *(open arrows),* which is partially removed from media. Dense echoes on ultrasound image overestimate intimal thickness. Media *(filled arrows)* appears thicker on histologic section than on ultrasound image.

media, was relatively echolucent and provided a reference point in the arterial cross section separating the intima from the adventitia. Because of its echolucency, medial thickness was able to be measured. It was also possible to measure intimal thickness in atherosclerotic arteries. In these arteries the intima was defined as extending from the lumen-tissue interface to the echolucent media on ultrasound images and from the surface of the lumen to the internal elastic lamina on histologic sections. Linear regression analysis was used to compare wall thickness measured by ultrasound with wall thickness measured by histologic examination.

## OBSERVATIONS

A total of 59 segments from 14 different human arteries were imaged. The muscular media of the arteries was seen in all specimens as a zone of relative

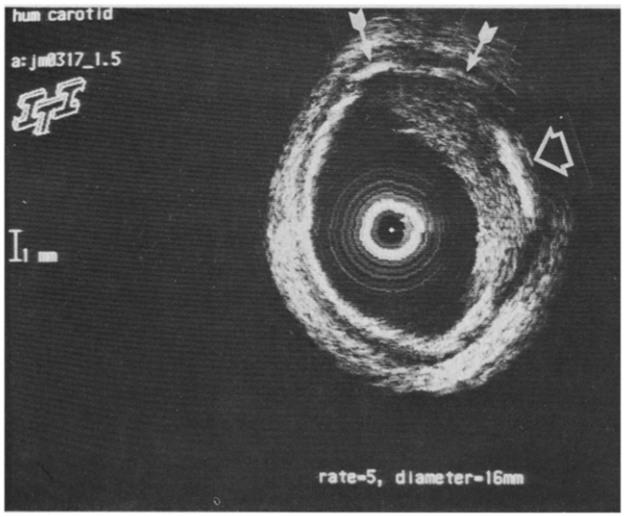


**Fig. 5.** Ultrasound image showing diseased human carotid artery. Eccentric intimal plaque contains small region of calcification at its base, which causes shadowing *(open arrow)*. Echolucent media is seen circumferentially. Echogenic line believed to arise from internal elastic lamina is seen extending behind plaque *(filled arrows)*.

**Table I.** Comparison of arterial wall measurements

| | *Histology* | *Ultrasound* | *p Value* |
|---|---|---|---|
| Intima | 0.9 ± 0.8 | 1.2 ± 0.8 | <0.001 |
| Media | 0.4 ± 0.2 | 0.5 ± 0.2 | NS |
| Total wall thickness | 1.7 ± 0.8 | 2.4 ± 0.8 | <0.001 |

Mean ± standard deviation in millimeters; NS, not significant.

echolucency compared to the more echogenic intima and adventitia. Fig. 4, *A* shows a B mode cross-sectional image of a normal human carotid artery. The luminal surface of this artery is seen as a bright echo. The smooth muscle media is seen within the wall of the artery as an echolucent zone. The adventitia is the bright zone on the outside. The thickness of the adventitia depends on how much connective tissue was left surrounding the artery when it was harvested. Fig. 4, *B* shows a hematoxylin and eosin–stained histologic section of the same artery. Some region of medial echolucency was seen in all specimens, but regions of intimal or medial calcification obscured the lucent appearance of the media in some places such that the lucent ring could not be followed all the way around the circumference of the artery in the most severely diseased segments (41 of 59, 69%).

The lucent media is demarcated on the lumen side by a strong echo, which appears to originate from the internal elastic lamina. The evidence for this bright echo arising from the internal elastic lamina is based on the observation that in arteries with small-to-moderate eccentric atheroma, the bright echo is seen to extend behind the base of the atheroma adjacent to the lucent muscular media, which is also the location of the internal elastic lamina according to results of histologic examination (Fig. 5). If this bright echo were produced by the tissue-fluid interface, it would have been expected to be imaged in front of the plaque where the tissue-fluid interface was present. It follows that this bright echo in normal arteries is caused by reflections from the internal elastic lamina and not the fluid-tissue interface.

Segmental calcification was seen in all diseased specimens studied. Shadowing of the distal wall by the tremendous reflective capability of calcium, preventing insonation of tissue beyond the calcium, is the ultrasonic hallmark of calcification. When present, shadowing prevented measurement of wall thickness in the region of the artery containing the calcium. Intimal thickness could be extrapolated behind most regions of calcification, but measurement of wall thickness was carried out at areas that were not calcified.

By ultrasound the mean intimal thickness was 1.2 mm ±0.8 mm, the mean medial thickness was 0.5 mm ±0.2 mm, and the mean total wall thickness was 2.4 mm ±0.8 mm. The mean ultrasound and histologic measurements are compared in Table I. According to results of histologic examination, in regions of normal intimal thickness, where the intima consists mainly of the endothelial cell layer and internal elastic lamina, the ultrasound images overestimated the intima and showed a band of echoes 0.5 mm thick. Fig. 6 is a graph that shows the correlation of intimal thickness measured by cross-sectional ultrasound intravascular imaging compared to direct measurement of intimal thickness by means of microcalipers from histologic sections. There was a close correlation between intimal thickness measured by the ultrasound catheter and that measured by histologic section ($r = 0.91$). In most measurements intimal thickness was increased because of atherosclerosis, so that intimal thickness corresponded to atheroma thickness. These measurements were related by the regression equation: IPT (ultrasound) = 0.92 × IPT (histology) + 0.40 mm, where IPT is intimal plaque thickness.

Fig. 7 is a graph of total arterial wall thickness determined by ultrasound catheter compared with the total arterial wall thickness measured by histologic

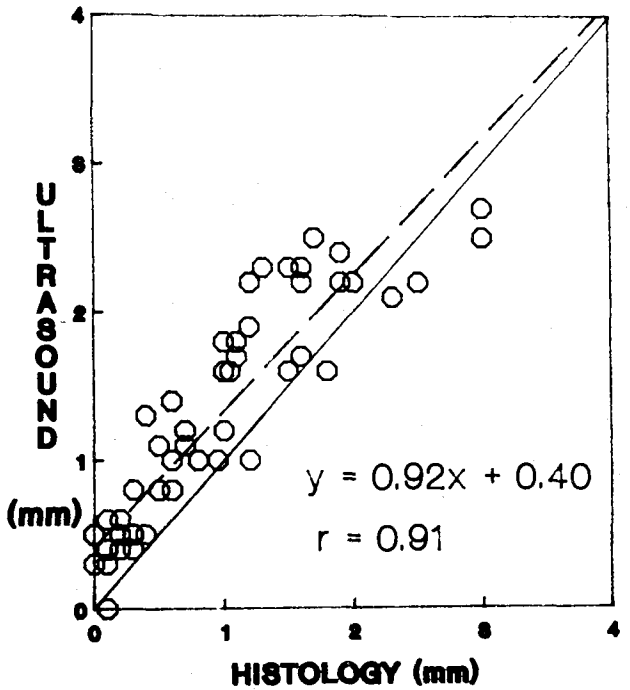


**Fig. 6.** Intimal thickness by ultrasound catheter measurement correlated well with intimal thickness by direct measurement of histologic section ($r = 0.91$). Ultrasound measurement overestimated histologic measurement by 0.3 mm (33%, $p < 0.001$).

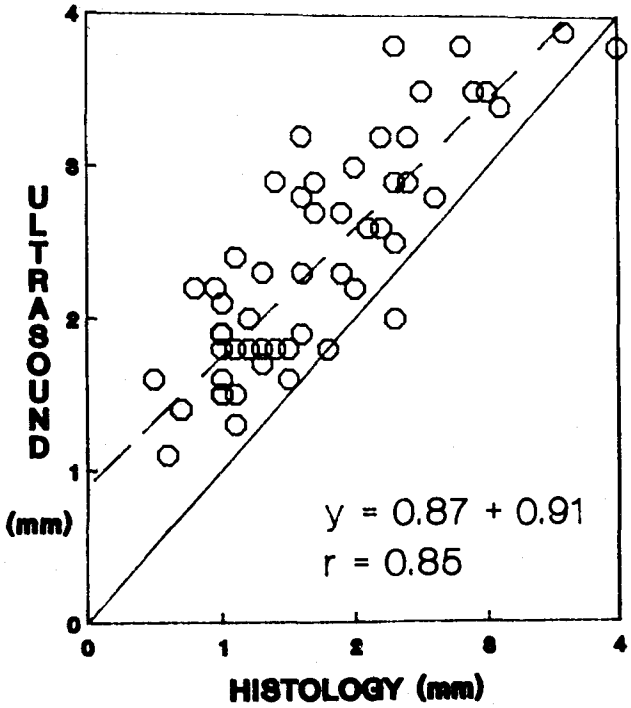


**Fig. 7.** Total wall thickness determined by ultrasound catheter correlated closely with wall thickness measurements from histologic section ($r = 0.85$). Ultrasound images overestimated mean total wall thickness compared to measurements from histologic sections by 0.7 mm (41%, $p < 0.001$).

section ($r = 0.85$). These variables were related by the regression equation: TWT (ultrasound) = 0.87 × TWT (histology) + 0.91 mm, where TWT is total wall thickness.

Fig. 8 shows a graph of medial thickness measured by ultrasound compared to that measured histologically ($r = 0.83$). These variables were related by the regression equation: Media (ultrasound) = 1.1 × Media (histology) + 0.06 mm.

Because calcification induced shadowing in many quadrants, medial thickness could not always be measured; therefore there are fewer data points (n = 18) than with intimal thickness. It is of note that the ultrasound measurements overestimated the mean intimal and mean total wall thickness by 0.3 mm and 0.7 mm, respectively, compared to histologic measurements ($p < 0.001$). The mean medial thickness was not significantly different between ultrasound and histologic measurements.

## COMMENTS

The results of the present study support the hypothesis that intravascular imaging with ultrasound is an accurate method for measuring arterial intima, media, and total wall thickness. In addition,

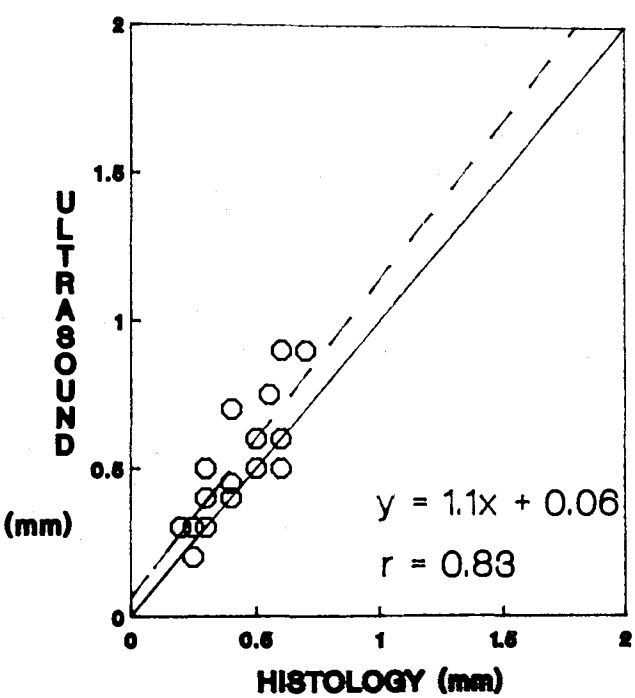


**Fig. 8.** Medial thickness measured by ultrasound catheter correlated well with direct measurement from histologic sections ($r = 0.83$).

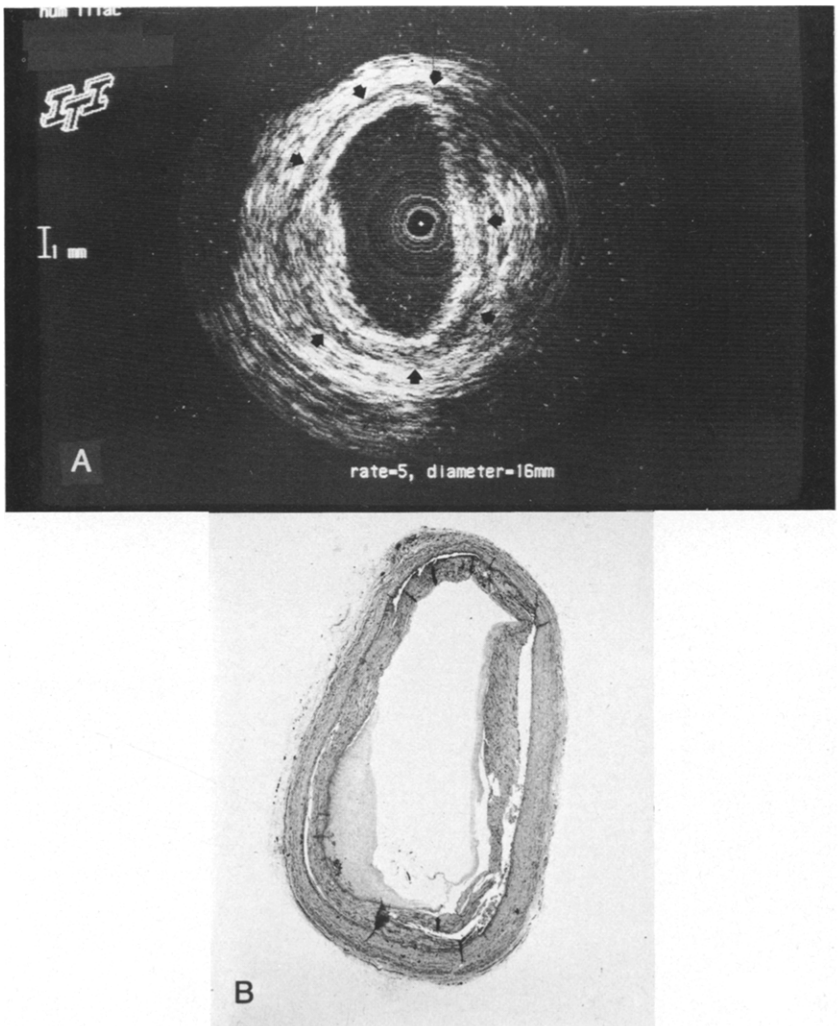


**Fig. 9. A,** Ultrasound image showing artifactually compressed human iliac artery. Area of intimal thickening can be distinguished because echolucent media is visible *(arrows)* and is seen to extend around perimeter of atheroma. **B,** Histologic section corresponding to ultrasound image shows intima to be nonuniformly thickened in left lower quadrant as predicted from ultrasound image. If media had not been visualized, thickness of atheroma would have been overestimated.

results of previous studies have shown this method to yield reproducible results.[12] To obtain these measurements, however, it is necessary to visualize clearly the medial layer of the artery. Because the atheroma develops in the intimal layer, any attempt to measure the thickness of the atheroma requires imaging of not only the innermost boundary of the atheroma (i.e., the lumen) but also its outermost boundary (i.e., the muscular medial layer). It was observed during the course of these studies that the medial layer of the artery could be differentiated from adjacent tissues by its relative echolucency. This lucency has been attributed to the muscular layer having less collagen than the fibrous adventitia or less elastic tissue than the internal elastic lamina.[13, 14]

Fig. 9 shows how ultrasound images may be misinterpreted in the detection of intimal thickness. The intimal thickness in Fig. 9, as delineated by the echolucent media, shows that a thick eccentric plaque contributes substantially to the wall thickness on one side. Opposite the eccentric plaque the wall is also thick. Close inspection of the ultrasound image shows that much of this thickness is due to the width of the adventitia and the medial muscular layer and not to intimal plaque. If the media had not been visualized on the ultrasound image, the thickness of the atheroma in this segment would have been overestimated. Thus the echolucent media is an important landmark in ultrasound arterial microanatomy. Along the circumference of some arteries that had large atheroma

masses, the ultrasound image of the echolucent media became indistinct from the arterial wall echoes. In these instances the histologic sections showed that the dense atheroma had indeed eroded the true media, thus making it impossible to ultrasonically distinguish the intimal atheroma from the adventitia. These observations could have significant implications if intravascular ultrasound images are to be used to guide atheroma ablation with laser or mechanical methods to the limit of the media but not beyond.

Published ultrasound images of arteries that use ultrasound transducers external to the artery do not clearly show the relative lucency of the medial layer of the artery.[2, 4] It may be that the lower ultrasound frequencies used with external probes (12 MHz) are not adequate to resolve the reflective differences among arterial layers. Alternatively, imaging tissue from outside the artery with its consequent high reflectivity from the bright adventitia, results in such diminution of the ultrasound signal that inner arterial detail cannot be resolved. Therefore imaging from within the arteries may offer several advantages over external imaging in evaluating arterial structure.

Several factors were identified during the study, which limited the ability to measure the thickness of some of the arterial layers. For example, the media was seen to thin noticeably or disappear on ultrasound images as it passed behind some of the atheromas. This was especially noticeable behind moderate eccentric atheromas and might be caused by attenuation of the ultrasound signal passing through the thickest portion of the atheroma. An alternate and more likely explanation is that there is actual thinning of the media behind thick eccentric plaques. Support for this latter hypothesis is the observation that thinning of the media was seen on the histologic sections behind thick atheromas. In addition, the presence of calcium prevents measurement of medial thickness and total wall thickness because of ultrasound shadowing. The combination of these factors limited our ability to accurately measure medial thickness in approximately 70% of the quadrant boundaries in the arterial sections.

We observed that ultrasound images overestimated the mean intimal and total arterial wall thickness by 33% and 41%, respectively, compared to histologic sections. There are several possible explanations for this phenomenon. First, the ultrasound imaging system assumes a velocity of sound of 1540 m/sec in tissue, which is the velocity of sound in water at body temperature (37° C). However, the present studies were carried out at room temperature (22 to 25° C). Because the velocity of sound is about 5% slower at room temperature compared to body temperature, one would expect to overestimate arterial dimensions by about 5%. Temperature change is probably only responsible for a small amount of the overestimation observed in this study. A second possible explanation is shrinkage in tissue size during histologic fixation. However, the most likely explanation for the overestimation by ultrasound is that the strong echo reflection from the highly reflective internal elastic lamina and fibrous adventitia extended into the region where the media and lumen were visualized and thereby produced an artifactual increase in total wall and intimal thickness.

It should be noted that the present study was limited to evaluation of arteries in vitro, at room temperature, in saline solution, in an apparatus with carefully controlled and restricted motion of the catheter. The artery sections were not distended under physiologic pressures during the ultrasound imaging. Imaging in pulsatile, mobile, living, blood-filled arteries provides several potential technical obstacles that may degrade image quality. Results of this study underscore the importance of being able to image the echolucent medial layer if the objective is to assess the thickness of the atheroma.

We conclude that intraarterial ultrasound imaging appears to be feasible and shows promise as a method for accurately measuring normal and diseased arterial wall thickness, thereby allowing an assessment of the extent of atheromatous involvement of artery walls. Such an approach, performed percutaneously in the catheterization laboratory, could represent a fundamental and important departure from traditional angiographic methods for assessing the severity of coronary, carotid, or peripheral arterial disease.

## SUMMARY

A prototype intravascular ultrasound imaging catheter with a 20 MHz transducer was used to obtain 59 cross-sectional images in 14 segments of human atherosclerotic arteries. Three distinct components of the arterial wall were visualized on the ultrasound images: a highly reflective intima, an echolucent media, and a moderately reflective adventitia. Images were obtained at 1 mm increments in vitro and were compared with histologic sections at the same levels. Measurements of the arterial layers showed a close correlation between ultrasound images and histologic sections for the thickness of the intimal plaque ($r = 0.91$), the media ($r = 0.83$), and the total wall thickness ($r = 0.85$). The ultrasound images overestimated the mean intimal and total wall thickness by 0.3 mm and 0.7 mm compared to mea-

surements in histologic sections ($p < 0.001$). Intravascular imaging with high-frequency ultrasound is an accurate method for measuring microanatomic arterial dimensions and the extent of atheromatous involvement of the arterial wall. This method could represent an important adjunct to traditional angiographic techniques for assessing the severity of atherosclerosis.

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