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ORIGINAL ARTICLE

Variability in Tissue Characterization of Atherosclerotic Plaque by Intravascular Ultrasound: A Comparison of Four Intravascular Ultrasound Systems

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Different intravascular ultrasound (IVUS) systems vary in their image presentation. The purpose of this study was to compare four IVUS systems in vitro to determine the accuracy of tissue characterization of atherosclerotic plaque compared with histology. Ninety-eight plaque segments from 23 formalin-fixed human iliac arteries were imaged in saline at room temperature with four different IVUS systems. To assess the accuracy of IVUS in describing plaque, three types of analysis were performed: (1) the ability to identify the presence and extent of lumen or plaque boundary; (2) sensitivity, specificity, and interobserver variability of IVUS in qualititatively identifying plaque components compared with histology; and (3) quantification of calcification. The synthetic aperture device had a lower sensitivity in identifying lumen and plaque boundaries (87%, 38% respectively) compared with other machines (96%-100%, 95%-100%). All three mechanically rotating systems had fair to good sensitivities for identifying calcification (57%-73%) or lipid filled areas (50%-83%). The sensitivity of discriminating fibrous tissue from fatty areas was low (39%-52%). The synthetic aperture system had a significantly lower sensitivity for identifying all three tissue types (4%-21%). There was significant interobserver variability (kappa value = 0.47-0.68) as well as machine to machine variability (kappa value = 0.52) for tissue characterization. Calcified areas were underestimated by System 1 ($p < .05$) and System 4 ($p < .01$) because of weaker echo reflections or poor image quality. There are significant differences in image representation among these four IVUS systems in the diagnosis of tissue components of complex atherosclerotic plaque. These variabilities should be considered when interpreting studies performed with different machines.

INTRAVASCULAR ultrasound (IVUS) is a unique method for assessing atherosclerosis because it not only provides accurate morphometric measurements of the arterial lumen and plaque[1-10] but it also can characterize the tissue components of atherosclerosis.[2,3,8,11-14] The major components of atherosclerotic plaque are fibrous tissue, lipids, calcium, and fibromuscular cells.[15] The identification of these components by intravascular ultrasound is based on their characteristic backscatter patterns.[2,3,8,11-14,16,17] However, there are some conflicts in interpretation among previously reported studies for identifying characteristics of plaque composition and morphology from ultrasound images.

The available intravascular ultrasound systems differ in their technology and their representation of the ultrasound backscatter. We hypothesized that the variability of interpretations of intravascular ultrasound images may be caused in part by differences in the imaging systems used. The purpose of the present study

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was to compare four intravascular ultrasound systems in vitro, in terms of the accuracy of tissue characterization of atherosclerotic plaque compared with histology and also to assess the interobserver variability among the devices.

METHODS

Human Artery Specimens

A total of 23 iliac arteries approximately 1 cm in length was excised from seven patients (two male and 5 female) at necropsy in the Orange County Coroner's Office. The arteries were immediately preserved in 10% formaldehyde for at least 24 hours.

Ultrasound Imaging Systems

Four intravascular ultrasound systems and catheters were compared.

1. A mechanical rotating 30MHz transducer and a 2.9F catheter.
2. A mechanical rotating 30MHz transducer with a 3.5F catheter.
3. A mechanical rotating 25MHz transducer with a 3.9F catheter.
4. A nonrotating 3.5F catheter system using a 64 multielement transducer set at 20MHz.

The first three systems use mechanical rotation of the transducer or mirror, whereas System 4 uses a different technology called synthetic aperture in which the ultrasound image is created by computer reconstruction of the input from 64 separate transducers around the circumference of the catheter.[18] The arteries were imaged in August, 1994, with the newest product of each company. Although the investigators had full technical support from the companies to help obtain the best images, there was no financial support from any company and none of the investigators had any financial involvement.

Intravascular Ultrasound Imaging

An acoustic reference point was established by suturing a surgical needle into the wall of the artery perpendicular to the long axis. This technique assured that the same cross section was studied by all four machines and that the ultrasound images corresponded exactly to the cross section chosen for histological analysis. The catheters were inserted into the arteries until the image with the surgical needle echo was visualized. Care was taken to position the catheter centrally and coaxially. Ultrasound imaging was performed in a saline-filled bath maintained at room temperature. The images were optimized under visual inspection by manipulating the system settings provided with each device. The gain and ramp settings were determined by the same observer for all machines with the intent to maximize image morphology without excessive drop-out, to not saturate adventitial intensity, and to minimize noise. When there was a range of gain settings which was considered acceptable, several images with different gains were used for image interpretation. The arterial images were recorded onto a super VHS tape (3M, St. Paul, MN) for at least 10 seconds while moving the catheter back and forth through the plane of the needle echo to obtain images with maximum intensity of the acoustic reference.

Intravascular Ultrasound Image Analysis

Selected video clips (5-10 seconds long) from each artery segment were digitized with a video frame-grabbing board (Mêdia 100, Data Translation, Marlboro, MA). The digitized clips were randomly positioned in an editing storyboard to minimize observer bias from interpretation of the images from the other systems. The images were interpreted prospectively by two independent well-trained observers without any knowledge of the histological information. The two observers were not involved in acquiring the images and had no influence over gain or system settings. If there was disagreement between observers, the image was interpreted by consensus of the two readers to assess sensitivity, specificity, and predictability of each system for tissue characterization. In addition, single frame images of each artery segment were digitized (24STV with software by MediaGrabber, RasterOps Company, Santa Clara, CA) and stored for quantitative measurements. To assess intravascular ultrasound accuracy in describing plaque, three types of analysis were performed on the ultrasound images.

I. Lumen and Plaque Recognition

One measure of image quality was the ability to identify the presence and extent of the lumen boundary as well as plaque boundary (intima-media or media-adventitia interface). The ultrasound images were reviewed and two independent observers were asked if they could determine the majority of the lumen and plaque outlines.

II. Tissue Characterization by Intravascular Ultrasound

To assess the correspondence between the ultrasound image patterns and the histological specimens, tissue characterization was performed for 98 plaque segments using two kinds of classification.

A. Simplified Classification

1. High echogenicity with shadowing: defined as an area of high echo intensity, greater than the adventitia, with acoustic shadowing peripherally.
2. High echogenicity without shadowing: defined as an area of high echo intensity without acoustic shadowing. The intensity was equal to or greater than the adventitia.
3. Low echogenicity: defined as an area of low echo intensity, less than the adventitial reference.

B. Detailed classification

Based on the black and white patterns within the ultrasound images, a set of more detailed descriptors was also defined to determine if the echo patterns corresponded accurately to finer distinctions of tissue types (Fig 1).

1. Bright homogeneous echo with shadowing: large and bright homogeneous areas with echo intensity more

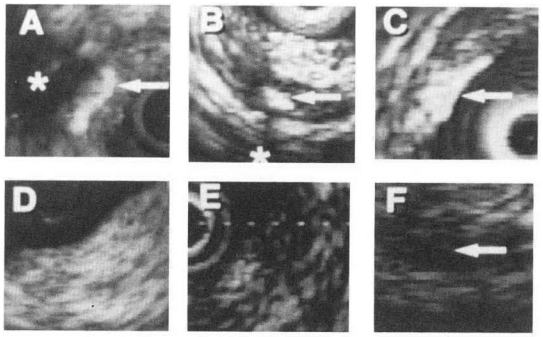


Fig 1. Ultrasound classification of plaque component patterns. (A) Bright homogeneous echoes (Arrow) with shadowing (*acoustic shadow); (B) Small bright homogeneous echoes (Arrow) without shadowing (*acoustic shadow); (C) Bright homogeneous echoes without shadowing (Arrow); (D) Bright speckled echoes; (E) Low-intensity speckled echoes, and (F) Echolucent area (Arrow). For the simplified classification, panel A and B correspond to high echogenicity with shadowing, panel C and D correspond to high echogenicity without shadowing, and panel E and F correspond to low echogenicity.

than the adventitial reference. Acoustic shadowing present. A homogeneous area was defined when the intense echogenic area was continuous and occupied more than 75% of the region of interest.

2. Small bright homogeneous echo with shadowing: small (<0.5 mm^2) but bright homogeneous area with acoustic shadowing. The intensity was more than the adventitial reference.
3. Bright homogeneous echo without shadowing: an area of bright homogeneous echo without shadowing, the intensity of which was more than the adventitial reference.
4. Bright speckled echo: bright speckled echoes in an area without acoustic shadowing. The intensity of the echo signal was equal to or more than the adventitial reference. A speckled echogenic pattern was defined when the intense echoes in the region of interest were discontinuous occupying less than 75% of the region of interest.
5. Low-intensity speckled echo: a low-intensity speckled echogenic area, the intensity of which was less than the adventitial reference.
6. Echolucent area: An echolucent area surrounded by echogenic tissue. These echolucent zones were distinct from areas of technical drop out, shadowing behind calcified areas or the media zone.

III. Quantification of Calcification

When an ultrasound image consistent with calcification was present, the cross-sectional area which showed bright homogeneous echoes with shadowing was outlined by an observer and measured using an on-screen image analysis application (NIH image, public domain software). If the histological specimen revealed a calcified area that was not recognized by ultrasound, that ultrasound area was scored as zero.

Histological Preparation and Analysis

After the arteries were imaged by intravascular ultrasound, the needle was removed, the area was marked by India ink, and then the specimens were decalcified and processed for histology. The specimens were stained with Masson's trichrome and hematoxylin-eosin. In six arteries, an Oil-O red stain was also applied to eccentric plaques which were imaged before formalin fixation to highlight the distribution of fatty tissue.

To compare the histological descriptors with the two types of ultrasound classification, a simplified three-category system as well as a more detailed six-category system was generated.

A. Simplified Histologic Classification

1. Calcified area: Areas with either large calcification or areas of small speckled calcium (microcalcification).
2. Fibrous area: Histological areas of either fibro-acellular, hypo-cellular, or fibro-cellular matrix.
3. Fatty area: Areas of either pure lipid or a mixture of fibro-fatty tissue.

B. Detailed Histologic Classification (Figure 2)

1. Large calcified areas
2. Small speckled calcium (microcalcification): The size was less than 0.05 mm and did not coalesce into a compact deposit.[12]
3. Fibro-acellular or hypo-cellular area: Hypocellularity was defined as an area of fibromuscular cells that occupied less than 25% of the acellular matrix portion.
4. Fibro-cellular area: An area of fibromuscular cells intermixed with connective tissue matrix.
5. Fibro-fatty area: Fibrous tissue interspersed with lipid-containing cells and vacuoles.
6. Lipid area: Contiguous areas of lipid containing foam cells, cholesterol crystals, or a lipid pool.

The histological slides were placed on a low-power microscope (Olympus stereo zoom Model-SZFILLD, Olympus Microscope, Tokyo, Japan), which was connected to a video camera (SONY CCD, Model-DXC 101, Sony, Tokyo, Japan). The histological slides were digitized using the same computer, frame grabbing, and analyzing system as used for the ultrasound video images.

Correspondence Between Ultrasound and Histological Interpretations

The IVUS echo patterns were interpreted as corresponding to the histologic classification as follows:

IVUS ECHO PATTERN	TISSUE DIAGNOSIS
High echogenicity with shadowing	Calcification
High echogenicity without shadowing	Fibrous area
Low echogenicity	Fatty area

A 3 × 3 comparison table was then derived to compare the incidence of correct or incorrect diagnoses using the ultrasound criteria.

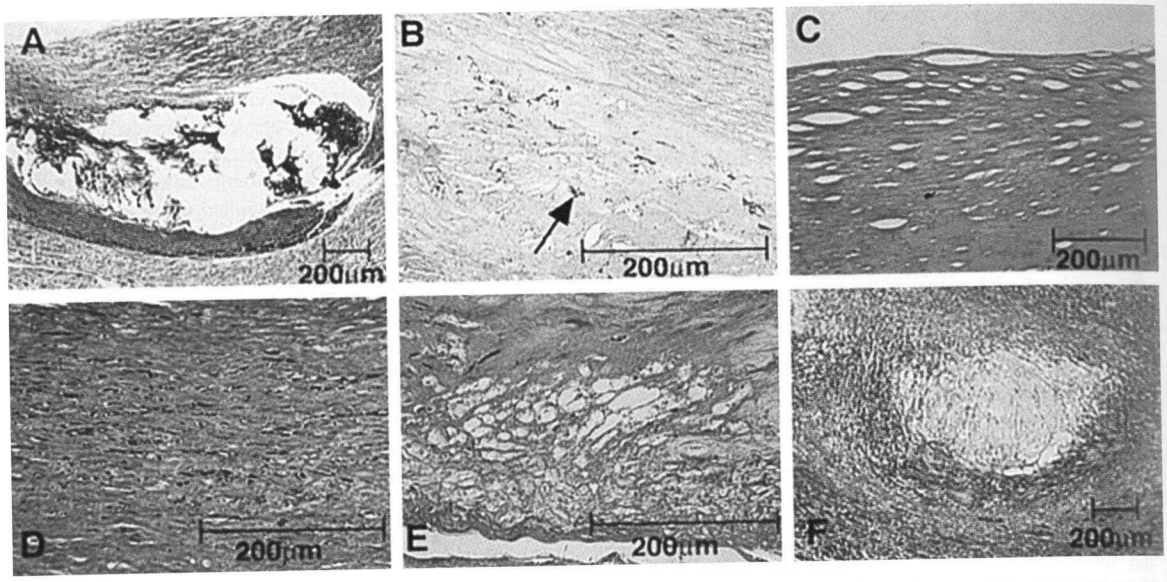


Fig 2. Histological classification of plaque components. (A) large calcified areas (×100), (B) small speckled calcium (arrow, microcalcification: ×400), (C) fibro-acellular or hypo-cellular area (×200), (D) fibro-cellular area (×400), (E) fibro-fatty area (×400), and (F) lipid area (×100) trichrome stain (A, C-F) and hematoxylin-eosin stain (B).

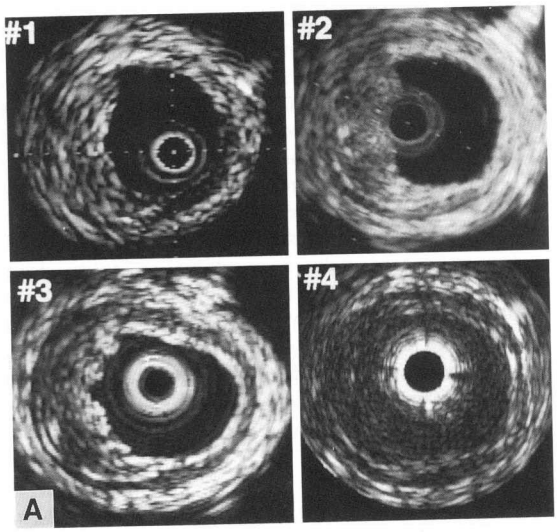
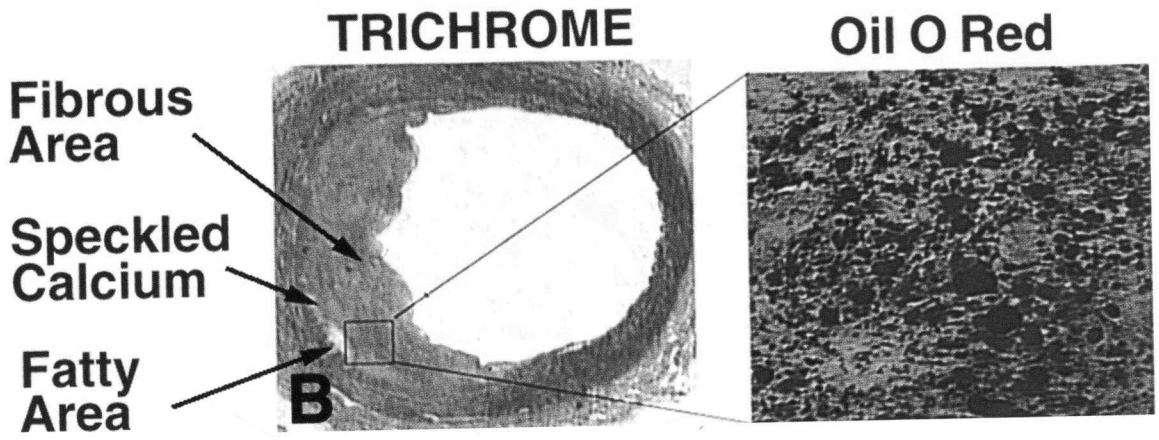


Fig 3. (A) Images of the same arterial plaque in cross section by four intravascular ultrasound systems. The acoustic needle reference is positioned at 2 o'clock. (B) Histological specimen of the corresponding arterial cross section (Masson's trichrome and Oil-O red stains). The histological section consists of three different tissue components: fibro-cellular plaque predominates, but there is a small lipid area at the base associated with a spicule of calcium (seen at higher magnification). Systems 2 and 3 detected the lipid area as a less intense echogenic zone. These systems also showed a small area of high echogenicity corresponding to the spicule of calcium, but there was no shadowing present. The observers did not identify this portion as calcified because of the lack of echo shadowing. Neither the lipid nor calcified area was identified by System 1. On the Oil-O red stain, the lipid area was seen as red droplets in a meshwork of fibrous tissue. This corresponded closely to the less intense echogenic zone which still had some reflections from the fibrous components. System 4 did not accurately reveal the plaque boundary.



In addition, the more detailed classification using six descriptors was compared using the following interpretation of the ultrasound echo patterns.

IVUS ECHO PATTERN	TISSUE DIAGNOSIS
Bright homogeneous with shadowing	Large calcified area
Small bright homogeneous without shadowing	Small speckled calcium
Bright homogeneous without shadowing	Fibro-hypocellular area
Bright speckled	Fibro-cellular area
Low-intensity speckled	Fibro-fatty area
Echolucent	Lipid area

A 6 × 6 comparison table was used to derive the sensitivity and specificity of the ultrasound interpretations. When the plaque was poorly identified on a particular ultrasound image, the diagnosis of each tissue component identified by histology was considered as a false-negative for the ultrasound image. Plaque areas behind calcium were not included in this study because it is impossible to interpret these ultrasound areas because of signal drop-out with any of the systems.

Technological Improvement–A Supplemental Updated Study

By the time this study was completed, two of the catheter systems were upgraded. An improved CVIS system and their Microrail catheter (30MHz/3.2F) (CVIS Corporation, Sunnyvale, CA) and the upgrades to the Endosonics system and catheter (Endosonics, Rancho Cordova, CA) were available in August 1995. Therefore, a supplemental updated study for those systems was performed to determine the ability to identify the lumen and plaque boundary. The sensitivity for tissue characterization with the simplified three category classification was assessed in 49 plaque segments from 20 new iliac arteries. These observations were compared between the new machines and the older versions.

Statistics

Values were expressed as mean ± standard deviation. Analysis of variance with the Bonferroni Post Hoc test was used to compare the mean values between groups. Chi-square analysis was used to compare sensitivity and specificity between machines. In these analyses, $p < .05$ was considered to be significant.

To assess the measure of agreement between observers and among machines, kappa statistics was used.[19] This method does not require any assumption that there is a correct diagnosis. The value of kappa (κ) ranges from -1.0 to $+1.0$. A value of 0 indicates chance agreement, whereas a value of $+1.0$ shows perfect agreement. A negative value indicates that disagreement is predominant among observers. A value ≥ 0.75 implies excellent agreement, values from 0.40 through 0.75 suggest fair to good agreement, and values less than 0.4 imply poor agreement.

RESULTS

Initial Comparison Study

The mean age of the seven donors was 58 ± 25 years (range: 15–86 years). Because the specimens were obtained from the coroner's office, no clinical information was available.

Lumen and Plaque Identification

Intact lumen was identified by histological analysis in 23 (100%) out of 23 iliac arteries (Table 1). There was no significant difference in the ability to identify lumen boundary among the four machines. Eccentric plaque was identified in 21 (91%) out of 23 iliac arteries. Chi-squared analysis indicated that System 4 had a lower sensitivity compared with the other devices in identifying the existence of the plaque. This was caused by drop-out of portions of the image or difficulty in identification of the lumen-intima, intima-media, or media-adventitia boundary.

Tissue Characterization

Fig 3 shows how the four systems differ in the depiction of tissue characterization for the same arterial cross-section. Table 2 compares the sensitivity of characterizing the plaque components for the four machines using the simplified three category classification consisting of calcified, fibrous, or fatty tissue. The percentage of exact correspondence between histology and ultrasound is shown in the diagonal boxes. All three mechanical rotation systems had fair to good sensitivities for identifying calcium (57%-73%), or for identifying lipid (50%-83%). The capability of discriminating fibrous tissue from fatty areas was low (sensitivity 39%-52%) for all three mechanical systems because of significant overlap in interpretation. Fibrous tissue was

Table 1. Identification of Plaque and Lumen Boundary

	System 1	System 2	System 3	System 4
Lumen No. identified by IVUS/by Histology	22/23	22/23	23/23	20/23
Percentage	96%	96%	100%	87%
Plaque No. identified by IVUS/by Histology	20/21	21/21	21/21	8/21
Percentage	95%	100%	100%	38%*

NOTE: *$p < .0001$ *v* System 1, 2, and 3.

Table 2. Sensitivity of Intravascular Ultrasound to Correctly Identify Histological Tissue Characteristics in 98 Plaque Segments With A Simplified Classification

	High-E With Shadowing	High-E Without Shadowing	Low-Echogenicity	Not Identified
System 1				
Calcified area	**57%**	13%	17%	13%
Fibrous area	6%	**39%**	50%	5%
Fatty area	0%	50%	**50%**	0%
System 2				
Calcified area	**68%**	18%	14%	0%
Fibrous area	9%	**51%**	40%	0%
Fatty area	0%	32%	**68%**	0%
System 3				
Calcified area	**73%**	18%	9%	0%
Fibrous area	10%	**52%**	38%	0%
Fatty area	0%	17%	**83%***	0%
System 4				
Calcified area	**13%†**	13%	17%	57%
Fibrous area	4%	**4%‡**	21%	61%
Fatty area	0%	5%	**21%§**	74%

ABBREVIATIONS: High-E, High echogenicity.

NOTE: *$p < .05$ *v* System 1, $p < .005$ *v* System 4.

†$p < .01$ *v* System 1, $p < .0001$ *v* System 2, 3.

‡$p < .001$ *v* System 1, 2, 3.

§$p < .005$ *v* System 2, $p < .0005$ *v* System 3.

The boldface numbers show the percentage of exact correspondence between the tissue diagnosis based on the ultrasound pattern and histology. Sensitivity was calculated as the number of true-positive ultrasound pattern divided by the number of areas with the corresponding histological tissue diagnosis.

misdiagnosed as calcium or as lipid in 48%-56% of cases. Although fatty tissue was never misinterpreted as calcium, it was misdiagnosed as fibrous tissue in 17%-50% of cases. Small areas of calcification were occasionally misrepresented as hypoechoic areas in 9%-17% of cases. By chi-squared analysis, the only statistically significant difference between systems was that System 3 had an improved sensitivity at 83% for identifying fatty areas. The sensitivity of tissue characterization was significantly worse in System 4 for all three tissue components ($p < .01$).

The specificity of the four imaging systems is shown in Table 3. Among the three mechanical rotation systems, a statistically significant difference was observed with System 1, which provided a lower specificity for fatty areas. System 4 had significantly weaker specificity for all three kinds of tissue compared with any of the mechanical systems.

Table 4 compares the sensitivity of characterizing the plaque components by the four machines with use of the more detailed six category classification. When the calcified areas were segregated by size into large or small speckled areas, the sensitivity for identifying large areas of calcium was improved for all three mechanical systems, but not for System 4. Small areas of speckled calcium were very hard to identify for any of the systems. The capability of discriminating fibrous tissue (fibro-acellular, fibrous-hypocellular or fibro-cellular) and fatty tissue (fibrofatty or lipid), was much lower than with the three category classification for all four machines due to significant overlap. System 2 was an exception in that it was able to identify fibrocellular areas as a bright speckled pattern better than the other devices ($p < .05$).

Calcified Plaque

Large calcified areas (excluding areas of speckled calcium) were identified by histology in 17 (74%) of 23 iliac arteries. The sensitivity and specificity for identifying large calcified areas of plaque among the systems are shown in Table 5. The ability to identify calcium with System 4 was significantly lower than the three mechanical rotation systems ($p < .0001$).

A representative example of images with all four systems from a calcified artery is shown in Fig 4. Of 11 calcified areas measurable both by histology and ultrasound, the mean values for the areas of calcification are shown in Figure 5. The area of calcification was underestimated by System 1 ($p < .05$) and System 4 ($p < .01$) because of weaker echo reflections or poor image quality.

Table 3. Specificity of Intravascular Ultrasound for Tissue Characterization in 98 Plaque Segments With the Simplified Histological Classification

	System 1	System 2	System 3	System 4
Calcified area	92%	93%	93%	25%*
Fibrous area	63%	76%	83%	26%†
Fatty area	52%§	68	70%	13%‡

NOTE: *$p < .0001$ *v* System 1, 2, and 3.

†$p < .001$ *v* System 1, $p < .0001$ *v* System 2, 3.

‡$p < .005$ *v* System 1, $p < .0001$ *v* System 2, 3.

§$p < .05$ *v* System 2, 3.

Specificity was calculated as the number of ultrasound areas with true-negative diagnosis divided by the number of corresponding histological areas without presence of that tissue type.

Table 4. Sensitivity of Intravascular Ultrasound to Correctly Identify Histological Tissue Characteristics in 98 Plaque Segments With Detailed Classification

	BH-S	SBH-S	BH-NS	BSp	LSp	E
System 1						
CA	**71%**	0%	0%	12%	6%	0%
SCA	0%	**17%**	0%	17%	50%	0%
Fib	7%	0%	**14%**	24%	38%	7%
FC	4%	0%	4%	**36%**	56%	0%
FF	0%	0%	0%	57%	**36%**	7%
L	0%	0%	0%	25%	50%	**25%**
System 2						
CA	**88%**	0%	4%	0%	0%	0%
SCA	0%	**0%**	17%	33%	33%	17%
Fib	14%	0%	**3%**	31%	38%	14%
FC	4%	0%	4%	**65%***	27%	0%
FF	0%	0%	13%	27%	**47%**	13%
L	0%	0%	0%	0%	50%	**50%**
System 3						
CA	**82%**	0%	6%	6%	0%	0%
SCA	0%	**33%**	17%	17%	33%	0%
Fib	15%	0%	**8%**	38%	23%	15%
FC	4%	0%	8%	**50%**	38%	0%
FF	0%	0%	0%	14%	**57%**	29%
L	0%	0%	0%	25%	25%	**50%**
System 4						
CA	**18%†**	0%	6%	6%	12%	0%
SCA	0%	**0%**	0%	17%	33%	0%
Fib	3%	0%	**0%‡**	3%	24%	0%
FC	4%	0%	0%	**4%§**	19%	0%
FF	0%	0%	0%	7%	**14%‖**	0%
L	0%	0%	0%	0%	40%	**0%**

ABBREVIATIONS: CA, largely calcified area; SCA, speckled calcified area; Fib, fibro-acellular or hypo-cellular area; FC, fibrocellular area; FF, fibro-fatty area; L, fatty area or lipid pool; BH-S, bright homogeneous echo with shadowing; sBH-S, small bright homogeneous echo with shadowing; BH-NS, bright homogeneous echo without shadowing; BSp, bright speckled echo; LSp, low-intensity speckled echo; E, echolucent area.

NOTE: $*p < .05$ *v* System 1.

$\dagger p < .005$ *v* System 1, $p < .0001$ *v* System 2, $p < .0005$ *v* System 3.

$\ddagger p < .05$ *v* System 1.

$\S p < .005$ *v* System 1, $p < .0001$ *v* System 2, $p < .0005$ *v* System 3.

$\| p < .05$ *v* System 2, 3.

The bold number shows the percentage of times when there was an exact correspondence between ultrasound pattern and histology.

Kappa Statistics

The kappa values for the measure of agreement between systems and between observers are shown in Table 6. The table does not include the values from System 4 because the number of images with sufficient quality was too small. There was fair to good, but not excellent agreement between machines and between observers for all comparisons, suggesting significant variability in image interpretation; in addition, the agreement was closer with the simplified tissue characterization scale than with the more detailed six descriptor classification.

Table 5. Calcified Areas of Plaque

	System 1	System 2	System 3	System 4
Sensitivity	71%	88%	82%	18%*
Specificity	88%	93%	88%	27%†

NOTE: $*p < .005$ *v* System 1, $p < .0001$ *v* System 2, $p < .0005$ *v* System 3.

$\dagger p < .0001$ *v* System 1, 2, 3.

Technological Improvements

For the follow-up study, a total of 20 arteries from 10 donors was used (mean age 65 ± 14, range 46-91 yrs). There was a significant improvement in image quality for both System 1 and System 4. The sensitivity for identification of fibrous areas increased in both systems ($p < .0001$). The newer System 4 also improved in its ability to identify calcified areas ($p < .05$), however, identification of lipid was still low for both systems (Table 7).

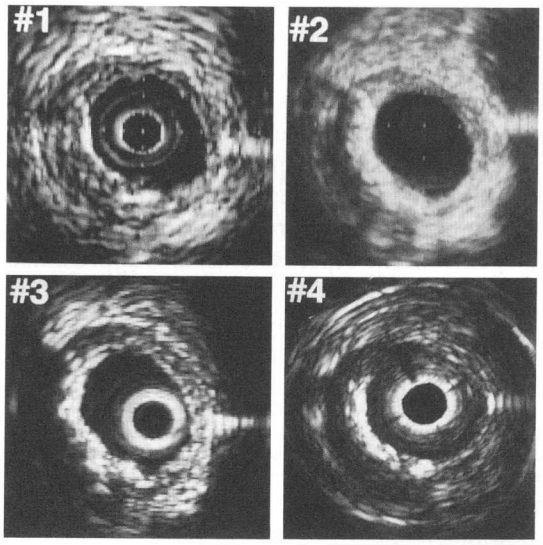


Fig 4. Ultrasound representations from the same arterial cross section of a calcified plaque. Systems 2, 3, and 4 reveal distinct, intense echoes but with differences in the degree of shadowing. In the image from System 1, the lumen-plaque interface is bright, but less intense than portrayed in other systems. This area was not diagnosed as calcified with System 1 because there was no shadowing.

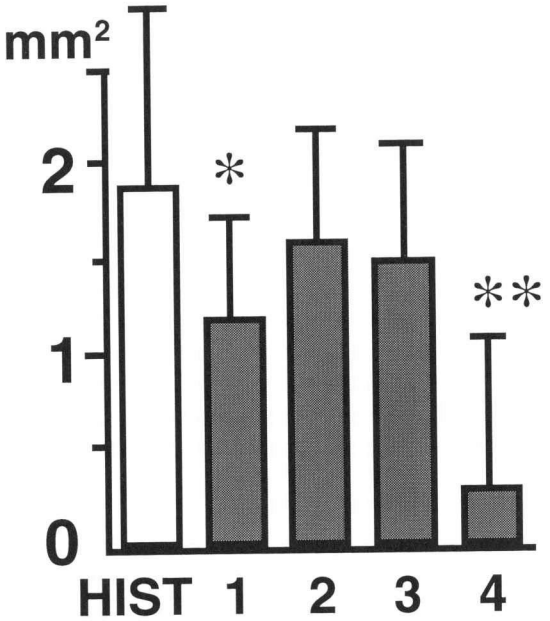


Fig 5. Measurements of calcified plaque area between histology (HIST) and four ultrasound systems (*$p < .05$, **$p < .01$).

DISCUSSION

The major finding of this comparison study is that there is significant variability in the accuracy of identifying plaque morphology and tissue characterization between the four intravascular ultrasound systems. This study is the first prospective analysis to compare four intravascular ultrasound systems using histology as the reference standard. The ultrasound images were interpreted independently in a randomized manner without knowledge of the histological findings and without reference to the ultrasound images from the other systems, thus approximating the conditions under which images are interpreted during clinical cases. Each system has individual benefits and limitations. System 2 has acceptable sensitivity for the major tissue components. System 3 has a significant advantage in identifying fatty tissue. System 1 underestimates calcified areas, and has a low sensitivity for lipid areas. The sensitivity for plaque characterization with the older version of System 4 was statistically inferior because of inadequate image quality for plaque detection.

Table 6. Kappa Statistics

	Simplified Classification	Detailed Classification
Among three Systems	0.52	0.41
System 1 *v* System 2	0.47	0.35
System 1 *v* System 3	0.52	0.40
System 2 *v* System 3	0.57	0.45
System 1 interobserver	0.47	0.41
System 2 interobserver	0.62	0.54
System 3 interobserver	0.68	0.47

Table 7. Technological Improvements

	System 1 1994	System 1 1995	System 4 1994	System 4 1995
Ability to identify lumen boundary	96%	100%	87%	100%
Ability to identify plaque boundary	95%	79%	38%	56%
Sensitivity for large calcification	71%	70%	18%	50%*
Sensitivity for fibrous areas	39%	88%†	4%	79%†
Sensitivity for fatty areas	50%	10%*	21%	20%

NOTE: *$p < .05$ compared with the same company's system in 1994.

†$p < .0001$ compared with the same company's system in 1994.

This study attempted to define the tissue characterization capabilities of these four IVUS systems compared with traditional histological descriptors. When IVUS images are compared unblinded with histological cross-sections, previous research studies with all four machines have reported close comparisons. However, in this blinded, prospective analysis, subtle discrimination of tissue components was difficult compared with a detailed histological analysis. For the simplified distinction between calcium, fibrosis, and lipid, there was still wide variability among the four systems studied as shown by the kappa statistics of $\kappa = 0.52$.

Reasons for the Variability Between Systems

Systems 1, 2, and 3 are mechanically rotating devices, whereas System 4 is a 64-element synthetic aperture device. Even among the mechanically rotating systems, there are significant differences in catheter design, transducer size and composition, and electronic processing of the ultrasound backscatter to produce an image. It was not the purpose of this study to identify which factors were the most likely responsible for the variability in image quality. The four systems were compared as a final

product with different acquisition settings to optimize the final picture.

Calcified Area

Previous studies have stressed the importance of identifying calcified areas by intravascular ultrasound, particularly for guiding interventional strategies[20,21] or predicting the clinical outcome of interventions.[22] The present study provides a comparison among the four systems of the sensitivity for correctly identifying large calcified areas. The sensitivity was lower for all machines in identifying smaller areas of speckled calcium. This result was similar to the study by Friedrich et al.[12] It is interesting to note that the small areas of speckled calcium were frequently identified as punctate islands of high echo intensity; however, these areas were not diagnosed as representing calcium because there was no distinct shadowing. Another reason for the lower sensitivity may be system dependent, as shown in Figure 4. This example suggests that System 1 portrays calcium as less intense reflections than the other systems. These areas may be misdiagnosed as fibrous tissue because the echo intensity is not greater than the adventitia and there is no shadowing. Small dots of speckled calcium were sometimes misdiagnosed as representing fatty areas, because the speckled calcium is often located within fatty regions of complex plaques.[12] With respect to System 4, the low sensitivity for calcified areas was due primarily to poor image quality, which made it difficult to identify the morphology of the plaque, let alone the more subtle diagnosis of plaque composition.

Fibrous and Fatty Areas

All four systems had a weaker correspondence between ultrasound and histology for fibrous areas than for calcium or lipid areas. Fibrous areas were sometimes misdiagnosed as calcium because of shadowing or when the fibrous area was just in front of calcium. Fibrous areas were also misdiagnosed as fatty areas because of the relative echolucency of the area in 21% to 50% of cases. This may be caused by nonperpendicular reflection of the ultrasound beam or unrecognized signal drop out.[11,14,23] Fatty areas were never misdiagnosed as calcium but were misdiagnosed as fibrosis in 17% to 50% of cases.

There may be several reasons why it is difficult to distinguish fibrous tissue from lipid laden areas on intravascular ultrasound images: (1) areas of pure lipid are rarely seen in our histologic samples, the lipid is usually intermingled with loose fibrous tissue. Because the fibrous tissue is echogenic, the resulting ultrasound image produces a mixed pattern of an echogenic and echolucent structure. (2) fatty areas are often located within a complex plaque which may be obscured by a highly echogenic fibrous cap or superficial calcification.

Interobserver Variability

The current study showed a significant variability between observers when using the four devices ($\kappa = 0.47$-0.68). This finding is consistent with the fact that the images were interpreted independently, without knowledge of the histology or the findings from the other devices. Poor interobserver variability may be caused by lower reflectivity of calcium in some systems or a lower ability to discriminate fat from fibrous areas. The training level of each observer is also an important variable. Interobserver variability was also adversely influenced when the more complicated, finer detailed, six category classification system was used.

Synthetic Aperture Device

The synthetic aperture device has an advantage of being an over-the-wire system, which is more user-friendly during interventional procedures and is more readily adaptable to innovative combined imaging and interventional devices.[6] There are several reports that the synthetic aperture array system produces accurate morphometric measurements and tissue characterization compared with histological analysis.[5,6,9,18,24,25] Although the present study was unable to confirm these observations, recent technical advances with the synthetic aperture device using 64 imaging elements and five integrated circuits provide significant improvement in plaque definition.

This study shows the accuracy for the diagnosis of tissue components of complex atherosclerotic plaque with the current level of technology available before 1996. The purpose of the study

was to understand the capability and limitations of each system and to stimulate manufacturers to improve the quality of these intravascular ultrasound devices. By directly comparing these four machines, it is clear that one must be cautious when interpretating studies performed by different devices. With the current technology, the images provided by the different machines do not result in a uniform diagnosis of plaque composition.

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