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ORIGINAL ARTICLE

Variability of a Three-Layered Appearance in Intravascular Ultrasound Coronary Images: A Comparison of Morphometric Measurements With Four Intravascular Ultrasound Systems

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The purpose of the study was to compare four intravascular ultrasound (IVUS) machines in vitro for their image representation of coronary arterial walls. There has been considerable variability among reported studies on the accuracy of morphometric measurements of coronary arteries by IVUS. This variability may be caused in part by the difference in the IVUS system used. A total of 24 formalin-fixed coronary arteries were imaged in saline at 37° with four different IVUS systems. The images were interpreted independently and compared with histology. Each system had benefits and limitations: System 1 overestimated the lumen area and had difficulty in identifying the media; System 2 underestimated the media area, but had a lower positive bias for lumen area; System 3 overestimated the lumen area but more clearly identified tissue characteristics such as internal elastic membrane and the echolucent media zone which improved the likelihood of observing a three-layer appearance; and System 4 showed less distinct separation of the arterial components and had poor correlations with histology for media measurements. The ability to make accurate morphometric measurements from IVUS images depends on the clarity of the separation of plaque and media. Among the four systems studied, there is significant variability in the appearance of the ultrasound images and the accuracy of morphometric measurements. These system differences should be considered when comparing IVUS studies performed by different groups.

INTRAVASCULAR ultrasound produces unique cross-sectional images of arterial walls that provide accurate morphometric measurements of coronary arteries compared with phantom models[1-3] or histology.[1-13] There has been considerable variability among the reported studies with correlation coefficients varying from 0.70 to 0.99. This variability has been explained by differences in (1) the source and type of artery, eg, coronary or iliac;[14] (2) the part of the artery measured, eg, intima, media, or lumen;[11,15] (3) the imaging preparation, eg, saline versus blood, room versus body temperature;[12,16] (4) catheter position;[12] and (5) histological preparation.[4,17]

In addition, the ultrasound image representation of normal coronary arteries as a three-layered structure has been documented by several investigators,[18-22] but has been questioned by others.[23-25] Fitzgerald et al reported that intimal thickening was necessary to obtain a three-layered appearance.[25] This variability in coronary wall appearance may also affect the accuracy of morphometric analysis.

The hypothesis of this study is that the variability of interpretation of intravascular ultrasound images and the differences in morphometric measurements may be caused in part by differences in the imaging systems used. The purpose of this study was to compare four intravascular ultrasound machines in vitro to distinguish if there were differences among the devices which could explain the variability in interpretation of the ultrasound images for a three-layered appearance and the differences in measurement of lumen, intima, media, and total wall area.

METHODS

Human Artery Specimens

A total of 24 coronary arteries with mild intima hyperplasia were excised from 14 patients studied at necropsy in the Orange County, California Coroner's Office. The arteries were immediately preserved in 10% formaldehyde.

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Ultrasound Imaging Systems

Four intravascular ultrasound systems and catheters were compared.

1. A mechanical rotating 30MHz transducer and 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 the fourth system 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.[20,26] The arteries were imaged in August, 1994 with the newest product from 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

A surgical needle was sutured into the arterial wall to serve as an acoustic reference to compare the same cross section among the four machines and between the ultrasound images and histology. Ultrasound imaging was performed in a saline-filled bath maintained at 37° centigrade. Each ultrasound catheter from the four machines was inserted sequentially into an artery to obtain images at the section with the surgical needle reference. Care was taken to position the catheter centrally within the artery and coaxial with the long axis. The ultrasound images were optimized by visual inspection from the same observer for all machines by adjusting the system settings such as the gain and ramp filters. An attempt was made to prevent drop-out of image data, diminish noise, and not saturate adventitial intensity, so that lumen, intima, media, and adventitia boundaries and media echolucency were maximally detected. In cases in which a range of gain settings were considered optimal, several images with different gain settings were used for image interpretation. The arterial images were recorded on Super-VHS tape for at least 10 seconds with the catheter moving slowly back and forth to obtain a cross-sectional image with maximum intensity at the reference needle echo.

Intravascular Ultrasound Image Analysis

The arterial cross-sectional image with the maximum intensity of the reference needle was digitized in a 640 × 480 pixel matrix with a Macintosh IIci computer (Apple Computer, Cupertino, CA) using a video frame-grabbing board (24STV and MediaGrabber software RasterOps Company, Santa Clara, CA). Quantitative measurements were performed with a public domain image analysis application (NIH image). Each of the ultrasound machines provide their own internal calibration of the image scale which is determined by the estimated speed of sound through biological tissue at 37° (1,540 m/sec). The images were interpreted and measured by two independent observers without knowledge of the histological information. The images were randomly sorted in the computer and presented to the observers to prevent a bias of comparing the image of the same artery serially by the four machines. The two observers were not involved in data acquisition or gain and system settings. Interobserver variability of the measurements was performed by linear regression analysis and by a measure of agreement using the Bland and Altman method.[27] If there was significant disagreement in the interpretation or measurements, the image was again interpreted and measured under consensus of the two observers. The latter results were used to compare the values between ultrasound and histology. To decrease the possibility of erroneous boundary detection from a still frame image, the digitized still image of the arterial cross-section was positioned on a monitor adjacent to another monitor which played the video of the ultrasound images as the catheter moved back and forth through the plane of the reference needle.

The arterial images were divided into four quadrants arbitrarily using the needle reference echo as the starting point. Each observer was asked if he could identify in each quadrant, the internal elastic membrane, the echolucent media zone, and whether there was a predominant appearance of two or three layers on the ultrasound image. The internal elastic membrane was defined as a thin band of intense echoes, brighter than the reflections from the adventitia. The media zone was defined as an echolucent or low echogenic band between the adventitia and intima. The thickness of this zone had to be less than 300 μm.[10,28]

Definitions of Ultrasound Layers

Fig 1 shows the variations in appearance of ultrasound layers.[22] The first example (Fig 1A) is from a normal coronary artery that has a three-layer appearance constructed by an inner bright thin band with an adjacent echolucent zone and echogenic adventitia. This inner bright ring is caused by echo reflections from the internal elastic membrane. A three-layered appearance may also be observed when the internal elastic membrane is present in addition to intimal hyperplasia (Fig 1B). If the internal elastic membrane is absent, a three-layered image may still be seen if the media is relatively echolucent compared with the intima (Fig 1C). However, if the internal elastic membrane is absent and the media is not echolucent, then a two-layered appearance is observed (Fig 1D).

The area measurements of lumen, intima, media, and combined intima and media (total wall area) were compared among the four machines. The intima-media boundary was defined as the line of intense echoes at the internal elastic membrane. If no internal elastic membrane was observed, then the border between the highly echogenic intima and the echolucent media zone was chosen. If neither the internal elastic membrane or an echolucent zone were detected, the media area was considered as absent in that portion. In such cases, the boundary of the

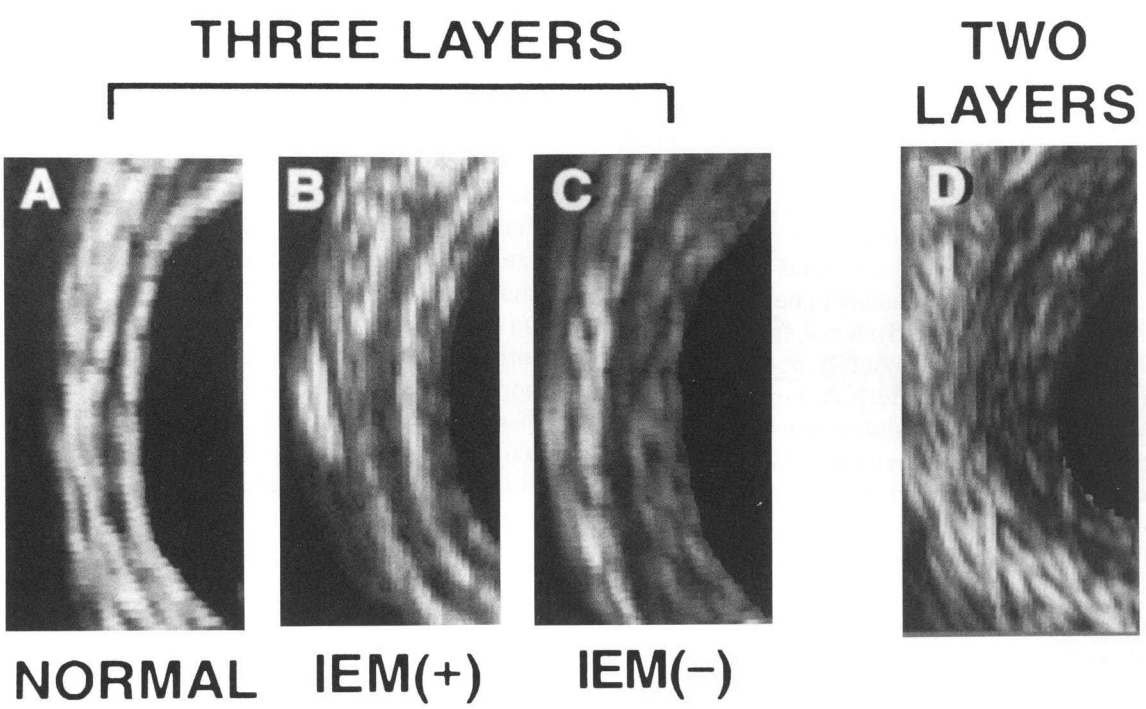

Fig 1. Examples of intravascular ultrasound images with a three-layered appearance (A-C) and a two-layered appearance (D) (IEM, internal elastic membrane, present (+) or absent (−)).

plaque was traced on the leading edge of the adventitia. If the internal elastic membrane was discontinuous, the boundary of the internal elastic membrane was extrapolated at the plaque-media interface to the next region where the internal elastic membrane was clearly visualized. Because the thickness of an intensely echogenic internal elastic membrane may be overestimated by video blooming, the middle of the peak intensity in the zone of the internal elastic membrane was traced to define the inner media boundary.[29]

Histological Preparation and Analysis

After intravascular ultrasound imaging was completed, the needle was removed and a suture was tied in its place. The specimens were processed for histology. They were dehydrated, decalcified, embedded in paraffin, cut, stained, and mounted on glass slides. Masson's trichrome and Verhoff's van Gieson stain were used.

The lumen, intima, media, and combined intima and media areas were measured. The histological slides were placed on a low-power microscope (Olympus stereo zoom Model-SZFILLD, Olymus 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.

Calibration of the histological images was accomplished by digitizing a 10 mm-long ruler focused through the microscope at the same image magnification as the histological slide.

The intima-media border in histology was defined as the boundary of the internal elastic membrane. If the internal elastic membrane was absent, the border of the media was defined as the inner edge of circularly arrayed smooth muscle layer. If a multilayered internal elastic membrane was present, the border was defined as the thickest internal elastic membrane with minimum disarray. If there was migration of smooth muscle cells into the intima, then the media border was defined as the inner edge of the circularly arrayed smooth muscle layer; however, these problems were rare in the present study using mildly diseased coronary arteries.

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. A chi-squared analysis was used to compare noncontinuous values between systems. The accuracy of ultrasound measurements compared with histological measurements was assessed with two different analyses: (1) linear regression, and (2) Bland and Altman analysis of agreement.[27] The latter analysis was used to compare the mean difference and standard deviation between the values from ultrasound and histology. The mean difference in measurements represents the bias of ultrasound relative to histology; the standard deviation (or confidence interval = ±2 SD) indicates the degree of agreement between the values from ultrasound and histology. The standard deviations were compared by the *F*-test. To compare the correlation coefficients, the *Z* transformation test was used. Interobserver variability was compared by linear regression analysis. In these analyses, a p value $< .05$ was considered significant.

RESULTS

The mean age of the 14 donors was 65 ± 18 years (range 44-87 years). Because the specimens were obtained from the coroner's office, no clinical information was available.

We excluded arteries that had insufficient image quality to measure the layer boundary. Of the 24 arteries imaged by Systems 1, 2, and 3, all studies had adequate quality to permit quantitative measurements. In System 4, there were only 10 (42%) arteries with sufficient image quality to permit adequate interpretation, $p < .0001$. Adequate histological slides were obtained from 23 of the 24 arteries; therefore, there was a total of 23 sets of ultrasound and histological images for Systems 1 through 3 and 9 sets for System 4. The histological measurements for lumen, intima, media, and intima plus media areas were not significantly different between the group of 23 arteries versus the group of 9 arteries available for analysis from all four systems, suggesting that the two sets of arteries represented comparable groups. All of the arteries had mild to moderate intimal hyperplasia.

Qualitative Differences Between Systems

Fig 2 shows a representative example of a coronary artery image from the four machines. On the trichrome stain, there was mild intimal hyperplasia which was recognized in all four ultrasound images. On the Verhoff's van Gieson elastin stain, the internal elastic membrane was preserved in the left side of the artery. In the image from System 3, the internal elastic membrane was detected on the left side of the image, and the echolucent zone of the media was identified. System 2 detected an echolucent zone but the internal elastic membrane was not clearly appreciated. System 1 also revealed the echolucent zone but the internal elastic membrane was not well distinguished. On the other hand, System 4 showed a very small fraction of a band of discontinuous echoes consistent with internal elastic membrane, but an echolucent media zone was difficult to appreciate. This resulted in a predominant appearance of two layers which would underestimate the media area.

Table 1 shows the incidence of identifying a three-layer appearance, the percent of quadrants with an identifiable internal elastic membrane, and the percent of quadrants showing an echolucent zone in 24 coronary arteries with mild intimal hyperplasia. System 3 provided a statistically higher likelihood of showing a three-layer appearance because of the increased incidence of detecting the internal elastic membrane ($p < .05$ *v* System 1 or System 4) and the echolucent zone ($p < .0005$ *v* System 1 or System 4). However, the same arterial images were more likely to be represented as a two-layer appearance by System 4 because of its diminished ability to identify the internal elastic membrane ($p < .05$ *v* System 3) or the echolucent zone ($p < .005$ *v* System 2 and $p < .0001$ *v* System 1 and System 3).

Accuracy of Morphometric Measurements

Table 2 shows the correlation coefficients between intravascular ultrasound and histological measurements of lumen area, intima area, media area, and intima plus media area. These values were from the group of 9 arteries in which adequate images could be obtained by all four systems. All the coronary artery specimens had mild intimal hyperplasia (mean area = 2.2 ± 1.3 mm^2), and by protocol design, none of the arteries had severe disease. In general, each machine provided close correlations for the area measurements, except for System 1 and System 4, which showed low correlation coefficients for media area ($r = .45$ and .40, respectively). The accuracy of lumen area measurements had relatively weaker correlations ($r = .75$ to .88) between ultrasound and histology compared with the accuracy of intima or intima plus media areas ($r = .92$ to .99) for all machines, although this difference did not reach statistical significance.

Table 3 shows the average values of area measurements by histology and the four ultrasound systems. By analysis of variance, the lumen area was overestimated by System 1 and System 3 compared with histology (both, $p < .05$). The lumen area calculated on System 1 was statistically larger than that by the System 2 ($p < .05$). The intima area was overestimated by all 3 mechanical rotation systems ($p < .01$). The media area was underestimated by System 1 and System 2 ($p < .05$ and $p < .0005$, respec-

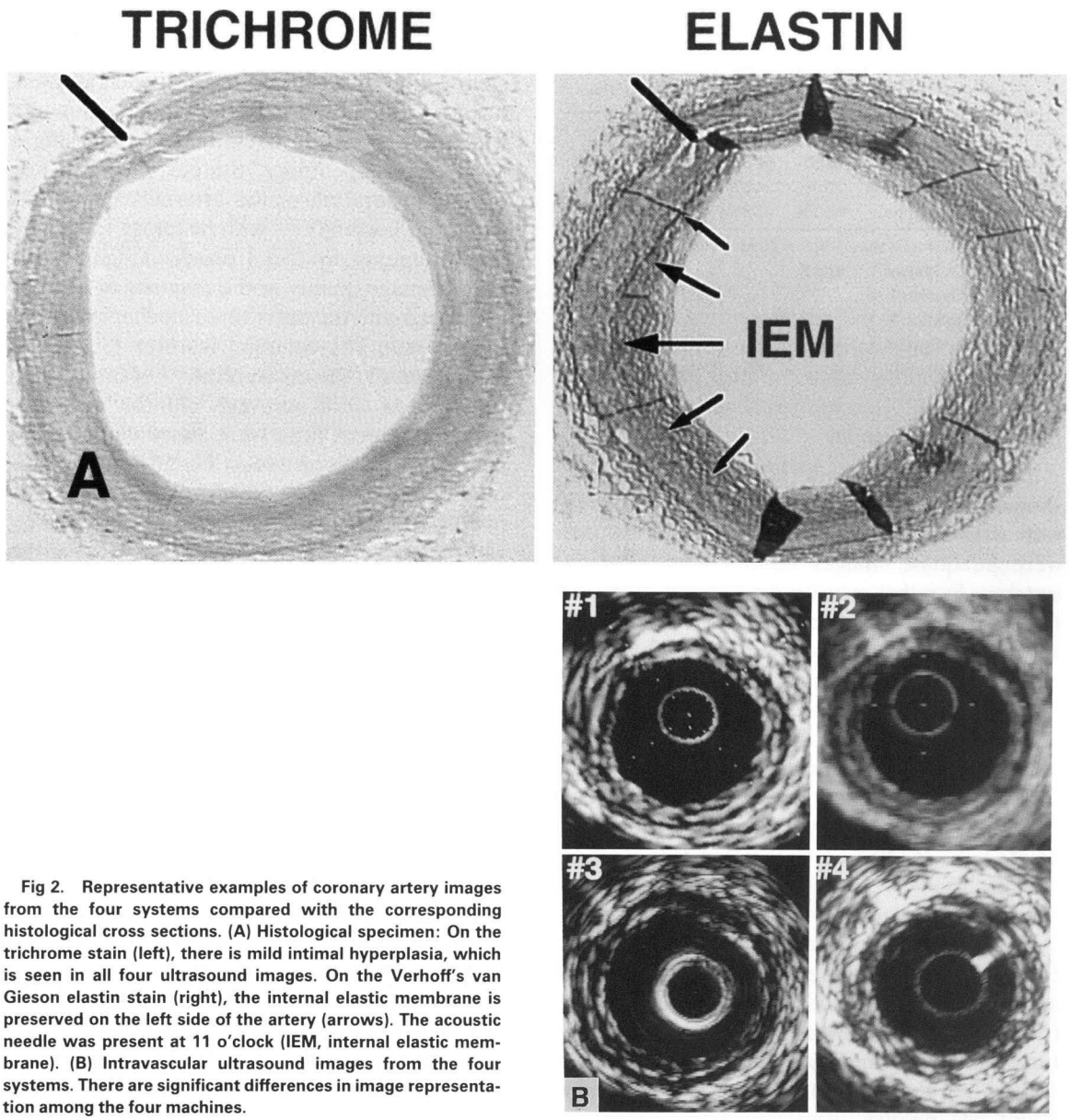

Fig 2. Representative examples of coronary artery images from the four systems compared with the corresponding histological cross sections. (A) Histological specimen: On the trichrome stain (left), there is mild intimal hyperplasia, which is seen in all four ultrasound images. On the Verhoff's van Gieson elastin stain (right), the internal elastic membrane is preserved on the left side of the artery (arrows). The acoustic needle was present at 11 o'clock (IEM, internal elastic membrane). (B) Intravascular ultrasound images from the four systems. There are significant differences in image representation among the four machines.

tively). The media area obtained by System 2 was also significantly lower than that of System 3 ($p < .05$). However, the combined intima plus media area was similar to the histological value for all four machines.

The accuracy of measurements was also compared using the Bland and Altman method (Table 4). All four systems had a positive bias for lumen, intima, and intima plus media area, and a negative bias for the media area. System 2 had a lower positive bias in lumen area measurements ($p < .0001$ *v* System 1, $p < .001$ *v* System 3) and higher negative bias for the media area ($p < .05$ *v* System 3) compared with the other systems. As a measure of the degree of agreement represented as the standard deviation of the difference between ultrasound values and histology, there was closer agreement with System 3 in media area measurements and System 4 had higher agreement in intima and media area measurements. There were no significant differences between the four systems for agreement in the measurements of lumen and intima area.

Table 1. The Incidence of Identifying a Three-Layer Appearance, the Percent of Quadrants With an Identifiable Internal Elastic Membrane, and the Percent of Quadrants Showing an Echolucent Zone

	System 1	System 2	System 3	System 4
Three-layered appearance	62.5%	56.3%	71.9%	22.5%*
Internal elastic membrane	20.8%	24.0%	39.6%†	17.5%‡
Echolucent media zone	53.1%	43.8%‖	58.3%‖	15.0%¶

NOTE: $N = 96$ for System 1-3, $n = 40$ for System 4.
*$p < .0001$ *v* System 1, 2, and 3.
†$p < .05$ *v* System 1, 4.
‡$p < .05$ *v* System 3.
‖$p < .0005$, *v* System 1.
¶$p < .0001$ *v* System 1, 3, and $p < .005$ *v* System 2.

Interobserver Variability

The assessment of interobserver variability is shown in Table 5. These correlation coefficients were derived from the 10 arteries in which there were adequate images obtained by all four systems. For the measurements of lumen, intima, and intima plus media area, the interobserver variability was excellent ($r = .96$ to .99), and there was no significant differences between systems. With respect to media area measurements, the variability was higher for all three mechanical rotation Systems 1, 2, and 3 ($r = .72$ to .75). System 4 showed considerable interobserver variability for measurements of media ($r = .26$, NS).

DISCUSSION

The major finding of the present study was that there was significant variability in the appearance of ultrasound images among the four systems studied which led to misinterpretation of plaque boundaries and limited the accuracy of morphometric measurements. System 1 had difficulty in depicting the media, System 2 underestimated the media area, System 3 more clearly identified tissue structures such as internal elastic membrane and the echolucent media which improved the likelihood of observing a three-layer appearance. System 4 showed less distinct separation of the arterial components with poor correlations with histology for media measurements. System 4 provided significantly poorer image quality in the majority of arteries compared with the other three mechanical rotating systems. The common features for all systems were: (1) the measurements of intima plus media area were accurate, (2) the measurements of lumen area were more variable but agreed well with histology, (3) all four systems overestimated the intima area, and (4) the interobserver variability of assessing morphometric measurements was negligible except for the media area measurements with System 4.

Table 2. Correlation Coefficients in the Relationship Between Histological and Ultrasound Area Measurements

	System 1	System 2	System 3	System 4
Lumen	.75*	.83‡	.80†	.88§
Intima	.92‖	.97¶	.98¶	.96¶
Media	.45 (NS)	.89§	.84‡	.40 (NS)
Intima + media	.99¶	.99¶	.98¶	.99¶

NOTE: $N = 9$ for all of the systems.
*$p < .05$.
†$p < .01$.
‡$p < .005$.
§$p < .001$.
‖$p < .0005$.
¶$p < .00001$.

The Reason of the Variability Between Systems

Systems 1, 2, and 3 use mechanically rotating drive shafts whereas System 4 uses a different technology consisting of 64-transducer elements circumferentially aligned and computer driven to provide a synthetic aperture.[20,26] In Systems 1 and 2, the mechanically rotating transducer is offset 8 to 10° from the long axis and there is no reflecting mirror. In System 3, the transducer and reflecting mirror relationships are fixed and the entire drive shaft assembly rotates mechanically around the long axis.[30] Each system design has potential benefits and problems.

Image quality is determined not only by ring down artifact, but also by multiple factors including frequency, resolution, distance from the catheter to the tissue, catheter size, dynamic range, gain setting, quality of image processing software, rotational speed, noise isolation, and ultrasound beam contour.[31-33] 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.

Compared with the three mechanical systems, System 4 was more likely to represent the artery as a two-layer structure. This results in an inability to measure the media and may lead to a mistaken estimation of the extent of plaque in

Table 3. The Comparison of Mean Area (mm^2) Values

	Histology	System 1	System 2	System 3	System 4
Lumen	3.7 ± 1.4	5.0 ± 1.4*,§	4.0 ± 1.3	4.7 ± 1.6*	4.1 ± 1.4
Intima	2.2 ± 1.3	3.7 ± 2.0†	3.6 ± 1.9†	3.6 ± 1.8†	2.7 ± 2.3
Media	1.9 ± 0.8	1.3 ± 0.7†	1.1 ± 0.9‡,‖	1.6 ± 0.8	1.2 ± 0.6
Intima + media	4.2 ± 1.9	5.0 ± 2.1	4.6 ± 2.1	5.1 ± 2.0	3.9 ± 2.3

NOTE: $N = 23$ for System 1, 2, 3, $n = 9$ for System 4.
*$p < .05$ *v* histology, †$p < .01$ *v* histology, ‡$p < .0005$ *v* histology.
§$p < .05$ *v* System 2, ‖$p < .05$ *v* System 3.

more diseased vessels. However, the overall accuracy in measuring the lumen, intima, and intima plus media area was comparable to the mechanical rotation systems. Duda et al compared a mechanically rotating drive shaft system at 20 MHz with a 64 element array transducer also at 20 MHz.[34] They showed similar accuracy in both systems for morphometric measurements of human femoral arteries for intimal and medial thickness.

This is the first study that compares these ultrasound systems directly with the same arteries and conditions. Extensive efforts were made to optimize all of the images from the four companies. Studies were performed with at least two catheters if the initial images did not appear satisfactory. Engineer representatives from all of the companies were invited to optimize their machines. With respect to System 4, the company representative reviewed many of these studies and felt that the images were optimized for the device that was commercially available at that time. Technology changes rapidly and newer devices now provide improved image quality. The equipment that was used in this study was the latest version available at the time and represented the equipment that was being used in clinical studies reported to that date in the literature.

Table 4. Mean Differences Between Histological and Ultrasound Area Values (mm^2) With the Bland and Altman Method

	System 1	System 2	System 3	System 4
Lumen	1.4 ± 0.7	0.3* ± 0.6	1.1 ± 0.8	0.8 ± 0.7
Intima	1.5 ± 1.3	1.4 ± 1.3	1.3 ± 1.2	0.9 ± 1.0
Media	−0.6 ± 0.9	−0.9† ± 0.7	−0.4 ± 0.6‡	−0.7 ± 1.0
Intima + media	0.8 ± 0.9	0.5 ± 1.0	1.0 ± 1.2	0.3 ± 0.3§

NOTE: $N = 23$ for System 1, 2, 3; $n = 9$ for System 4.
*Significant difference in mean value, $p < .0001$ *v* System 1, $p < .001$ *v* System 3.
†Significant difference in mean value, $p < .05$ *v* System 3.
‡Significant difference in standard deviation, $p < .05$ *v* System 4.
§Significant difference in standard deviation, $p < .005$ *v* System 1, $p < .001$ *v* System 2, $p < .0005$ *v* System 3.

Three-Layered Appearance

The ability to visualize a three-layered appearance of the artery wall is clinically significant because it permits the operator to distinguish the extent of the plaque from the surrounding adventitia. This is critical when assessing the amount of atherosclerosis and is necessary when used to guide atherectomy procedures.[35-37] There has been considerable controversy in the literature of the ability of IVUS to identify three layers and therefore accurately quantitate the amount of plaque. Some authors have reported that normal arteries show a three-layered appearance,[18-22] whereas others have suggested that a mild degree of intimal hyperplasia is necessary before one can separate the media from intima.[23-25] It has also been reported that a three-layer appearance is determined not only by the existence of an echolucent zone but also by the internal elastic membrane.[22] The results of this study help to explain the discrepancy within the literature on the reported incidence of a three-layered pattern. Among the four systems, there was significant variability in the ultrasound representation of these mildly dis-

Table 5. Interobserver Variability: Correlation Coefficients in the Relationship Between Two Area Values Obtained by Two Independent Observers

	Histology	System 1	System 2	System 3	System 4
Lumen	>0.99‡	0.98‡	0.98‡	>0.99‡	0.96‡
Intima	0.99‡	0.97‡	0.94‡	0.97‡	0.92‡
Media	0.97‡	0.72*	0.79†	0.75*	0.26 (NS)
Intima + media	>0.99‡	0.98‡	0.99‡	>0.99‡	0.96‡

NOTES: $N = 10$ for all of the systems.
*$p < .05$, †$p < .005$, ‡$p < .0001$.

eased coronary arteries. This difference in the ability to show a three-layered appearance was caused by each system's capacity to detect the internal elastic membrane and echolucent media zone. These variabilities also affect the accuracy of morphometric measurements.

Accuracy of Quantitative Measurements

The correlation coefficients for lumen area measurements between ultrasound and histology for all four systems were relatively lower than previously reported values (r = .75 to .88 for the present study v r = .85 to .98 for previous reports).[1-4,7-9,12,13] In addition, there was significant variability in the measurement of lumen area among ultrasound systems. Siegel et al reported that in mildly diseased coronary arteries, similar to those used in our study, histological processing resulted in a decrease in lumen area, but that absolute wall area did not change.[17] Although the difference in measurement of lumen size by intravascular ultrasound may be partly explained by shrinkage during histological preparation, the important point is that all four machines were compared with the same standard, ie, the same histological cross-section. Therefore, the variability shown in this study is caused by differences among these machines and not only to tissue preparation.

Synthetic Aperture Device

Nissen et al reported that in the synthetic aperture system, images frequently exhibit drop-out of endothelial reflections and that manipulation of the catheter and careful review of the dynamic imaging sequences were required to obtain optimal measurements of vessel wall structures.[38] One benefit of the synthetic aperture device is that it provides a central, nonrotating, over-the-wire system, which is more user-friendly than the mechanical rotation systems and is potentially more adaptable for combined imaging and interventional devices.

The major intent of the present study was not to rank the ultrasound systems, but to stimulate manufacturers to improve the quality of these intravascular devices. These results reflect the level of technology at the time of this study. These differences among the imaging systems may account for differences in interpretation between research groups. This awareness may be useful in understanding variances within the literature. It is important to understand the limitations of each system and to be cautious when interpreting studies performed with the different machines.

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