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The Reproducibility of Intravascular Ultrasound Imaging In Vitro

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To determine which factors may affect the image quality when an intravascular ultrasound catheter is used in vivo, the influence of blood, temperature change, and contrast media were evaluated. In addition, to confirm the reproducibility of intravascular ultrasound imaging to measure cross-sectional lumen area, intraobserver and interobserver variability were determined. The findings indicated that ultrasound images in blood are mildly attenuated, that changes from room temperature to body temperature do not have a significant impact on the image quality, that contrast media attenuates the image intensity in a dose-dependent manner, and that the intravascular ultrasound imaging catheter provides a reproducible method for measuring arterial lumen area with excellent intraobserver and interobserver correlation. (J AM SOC ECHO 1990;3:444-50.)

Intravascular ultrasound imaging is a new modality that provides visualization of the arterial lumen and wall structures in cross section. In vitro studies have shown that the three layers of arterial wall (intima, media, and adventitia) are clearly visualized on the ultrasound images. In addition, identification of abnormal tissue components such as atheromatous plaque and calcification have been documented.[1-5] With technologic advances in catheter design, these devices are being applied to study human peripheral and coronary arteries in vivo.[6-9]

Several factors may affect the image quality when this device is used in clinical studies. For example, although in vitro images have been obtained in a saline medium and at room temperature, in vivo images are obtained in blood and at body temperature. Iodinated contrast material also may be used in vivo to position the catheter, which might degrade the ultrasound image. In this study, these factors were evaluated to determine their influence on the quality of the ultrasound images. In addition, to confirm the reproducibility of this method of measuring the cross-sectional lumen area, intraobserver and interobserver variability were determined.

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METHODS

Intravascular Ultrasound Imaging Catheter

A prototype ultrasound imaging catheter with a single 20 MHz ultrasound transducer (InterTherapy Inc., Costa Mesa, California) was used in this study. The miniaturized transducer is located at the distal end of the catheter and the ultrasound waves are reflected from a metal mirror at 45 degrees so that the beam exits the catheter perpendicular to the long axis of the catheter. The distance between the transducer and the mirror is 2 mm to permit ringdown oscillations to occur within the canoe so that images are obtained up to the surface of the catheter. The diameter of the catheter is 1.2 mm. A cross-sectional image was obtained by manually rotating the transducer 360 degrees to generate an ultrasound B-mode image of the artery. The images were archived onto a computer disk.

Arteries

Human carotid, iliac, and femoral arteries containing variable degrees of atherosclerosis were obtained at autopsy. The arteries were stored in cold saline so-

lution and used within 1 week. Each artery was cut into 2 to 3 cm segments at the time of the experiment.

Procedures

The arterial segments were positioned vertically on a platform by use of a quick-drying glue. The catheter was advanced into the arterial lumen and control images were taken in a beaker filled with saline solution at room temperature (21° C). A total of 99 cross-sectional images were obtained from 15 artery segments at 1 to 2 mm intervals along the length of the artery. To accurately determine the location within the artery, a surgical needle was placed through the arterial wall, providing an acoustical reference point on the ultrasound image. After the control study, the arteries were imaged again at the same levels.

Blood. In three arteries, imaging was repeated in a blood medium. Fresh heparinized (100 U) blood was obtained and was used less than 3 hours after withdrawal from the patients. Sixty milliliters of discarded blood was obtained from each patient at the time of cardiac catheterization. The blood was stored at 0° C and was gradually warmed up to room temperature just before the experiment.

Body temperature. To evaluate the effect of temperature on image quality, ultrasound images were obtained in saline solution at body temperature in five arteries. The temperature of the saline solution was kept constant at 37° C by use of a heated water bath.

Contrast media. Two arteries were used for the contrast media study. Hypaque 50% contrast media (Winthrop Pharmaceuticals, New York, New York) was used in this study. Varying concentrations of contrast solutions (20% and 50%) were made by diluting the contrast with saline. Images in contrast media were taken at the three different concentrations. After the ultrasound images were obtained in the contrast media, the arteries were imaged again in saline solution to determine whether rinsing the ultrasound catheter with saline solution was effective to recover the image quality that might be distorted by contrast media.

Quantitative Analysis

For each of the variable conditions studied, the ultrasound images were recalled from computer memory and quantitative measurements were made of the lumen cross-sectional area by use of a digitized trackball. The measurements of lumen area when the artery was filled with saline solution were compared by a paired *t* test to the measurements of lumen area in a medium of blood. A paired *t* test was also used to compare the cross-sectional lumen area measurements in saline solution at room temperature versus 37° C. The *t* test was also used to compare the measurements of lumen area in saline solution versus the several concentrations of iodinated contrast media.

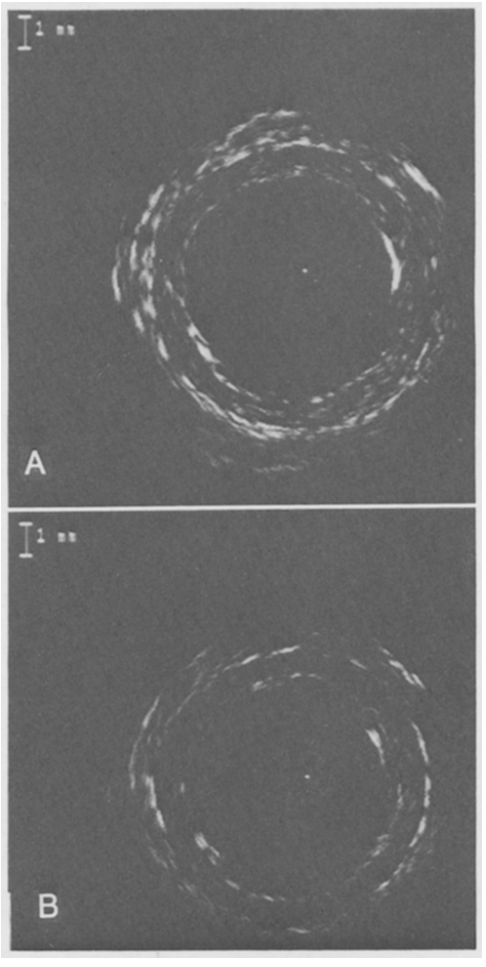

Figure 1 Cross-sectional ultrasound images of an artery segment obtained in saline solution **(A)** and in blood **(B)**. The intensity of the image obtained in blood is mildly attenuated. A bright halo reflection is noted around the central black area of the transducer. Imaging through blood reduced the displayed lumen area from 36.7 to 32.7 mm^2 in this artery.

Intraobserver and Interobserver Variances

To test the consistency and reproducibility of this method, five arteries were imaged in saline solution at room temperature with the same conditions as the

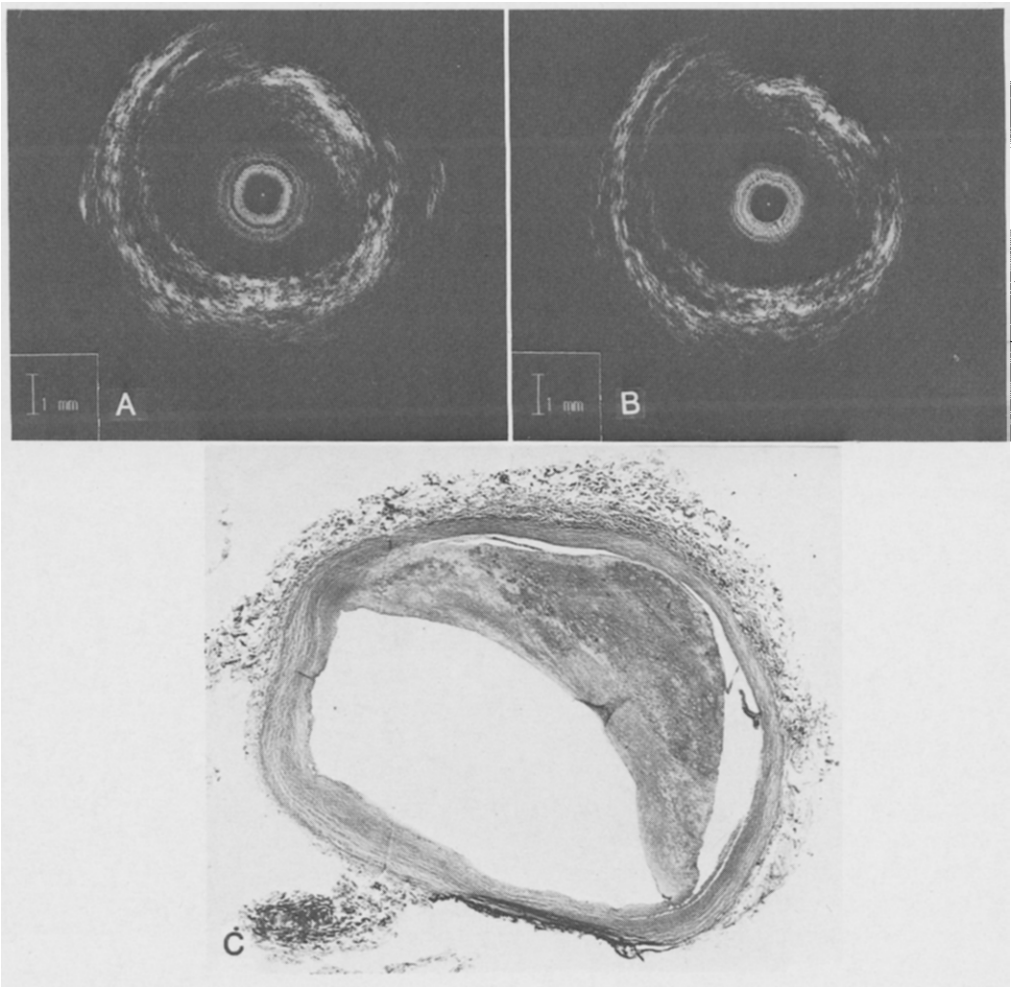

Figure 2 Cross-sectional ultrasound images of an artery obtained at room temperature (21° C; **A**) and body temperature (37° C; **B**), with the corresponding histologic cross-section (**C**). There was no image distortion or ultrasound attenuation of the image at 37° C compared with that at 21° C. The histologic section showed an eccentric atheromatous plaque with calcification at its base. The ultrasound image demonstrated the atheromatous plaque as an irregular mass projecting into the lumen and subtended 180 degrees of the lumen perimeter. The calcification was identified by intense ultrasound reflectance at the base of the atheroma from the 12 o'clock position to the 3 o'clock position with distal ultrasound dropout.

control study by the same observer and by an independent second observer on different days. After the study of each artery was completed, the computer images were restored from the disk and measurements were made of the cross-sectional lumen area. Intraobserver and interobserver variability of the measurements of lumen area were then compared by use of a linear regression analysis.

RESULTS

Ultrasound Imaging in Blood

A total of 27 images were obtained in blood from three arteries, but the images in one artery were inadequate because of poor image quality. A total of 21 images were appropriate for examination in this study. Compared with the images in saline solution, a mild attenuation of image intensity was observed. However, it was still possible to trace the arterial lumen, and the three layers of the arterial wall were also clearly recognized. A consistent finding observed in the images taken in blood was a bright halo of ultrasound reflectance that was noted around the central black area of the transducer (Figure 1). The mean cross-sectional area of the arteries in saline solution was 35.8 ± 2.7 mm^2. In the blood-filled arteries, the mean cross-sectional luman area was 33.8 ± 2.6 mm^2, which was mildly reduced (6%) from the measurements in saline solution ($p < 0.05$).

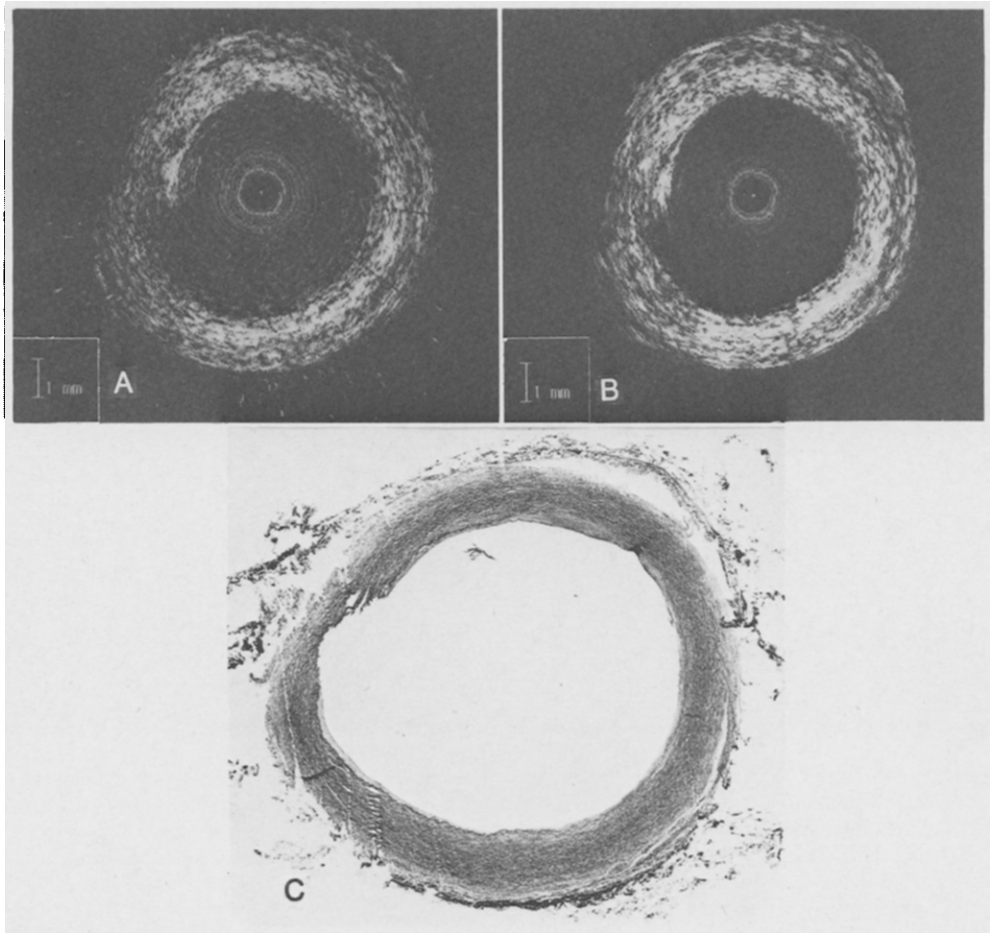

Figure 3 Cross-sectional ultrasound images of an artery obtained at 21° C **(A)** and at 37° C **(B)**, with the corresponding histologic cross-section **(C)**. In this artery, the scatter artifact initially observed at room temperature disappeared at 37° C **(B)**. The media, usually observed as a hypoechoic reflective band between the intima and adventitia, is not recognized in these ultrasound images. Histologic examination suggested that the ultrasound reflectivity of the media in this carotid artery was the result of abundant elastic fibers in the media **(C)**.

Ultrasound Imaging at Body Temperature

A total of 34 images were obtained from five arteries in warmed saline solution at 37° C. Compared with the control images, there was no image distortion or ultrasound attenuation of the images at 37° C (Figure 2). Rather, several of the images at 37° C were clearer than those of the control studies at room temperature. In these images, the scatter artifact, which was occasionally observed in the control study, disappeared (Figure 3). The mean cross-sectional lumen area at body temperature was not significantly different from that at room temperature (24.1 ± 14.9 versus 24.0 ± 14.4 mm^2).

Ultrasound Imaging in Contrast Media

Thirteen sites along the length of 2 arteries were imaged in three different concentrations of contrast media. Images obtained in iodinated contrast media showed attenuation in image intensity. The attenuation of the image was observed to be dose-dependent (Figure 4). Because there was a marked loss in resolution of the intimal boundary in 50% and nondiluted Hypaque solutions, measurement of cross-sectional area was not possible at seven sites (two in 50% solution and five in the nondiluted Hypaque solution). However, the image intensity returned quickly to the baseline level after the catheter and arteries were rinsed with saline solution (Figure 4, *E*). The mean cross-sectional lumen areas were 30.9 ± 21.9 mm^2 and 31.0 ± 21.9 mm^2 in the 20% and 50% Hypaque, respectively, which were not different from that of the control value (30.1 ± 21.1 mm^2). After the arteries and catheter were rinsed in saline solution, the mean lumen area was 31.6 ±

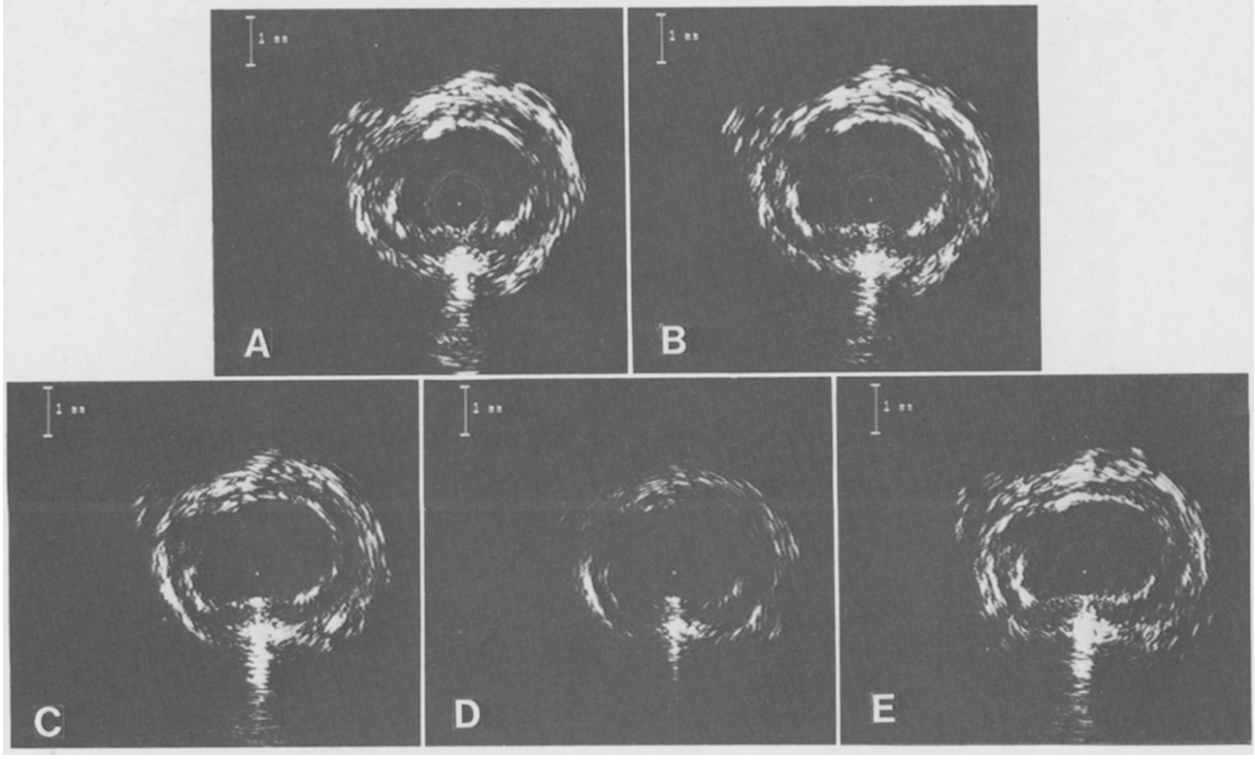

Figure 4 Cross-sectional ultrasound images of an artery obtained in several concentrations of contrast media (Hypaque solution). **A,** Baseline image without contrast. **B,** Twenty percent contrast solution. **C,** Fifty percent contrast solution. **D,** One hundred percent contrast solution. **E,** Immediately after rinsing with saline solution. Contrast media attenuates the image intensity in a dose-dependent manner; however, the image intensity quickly returned to the baseline level after rinsing with saline solution.

22.3 mm^2, which was unchanged from the baseline value.

Intraobserver and Interobserver Variances

A total of 25 cross sectional images were obtained at the same levels in five arteries by the same observer on different days. The mean cross-sectional lumen area determined by the same observer was quite similar (26.6 ± 18.0 versus 26.5 + 13.8 mm^2), with a correlation coefficient of $r = 0.99$ (Figure 5). Interobserver variance was determined at 23 levels in five arteries. There was no significant difference between the two observers (26.1 + 14.1 versus 24.6 + 12.5 mm^2). Linear regression analysis for the different observers yielded a very close correlation ($r = 0.98$; Figure 6).

DISCUSSION

The findings of this study demonstrate that intravascular ultrasound image quality is influenced by several factors that will be encountered during in vivo studies. There was an attenuation of image intensity when blood and contrast material were used as the fluid medium instead of saline solution. On the other hand, the temperature change from room temperature to body temperature did not have a significant impact on the image quality; if anything, the higher temperature improved visualization by reducing the artifact shadows.

The attenuation of image intensity observed in blood and contrast media appears to be caused by the absorption of ultrasound energy in these solutions.[10] The distance from the ultrasound transducer to the object of study is known to affect the image intensity by beam divergence and scatter.[10] This distance was the same in the control and subsequent studies. The frequency of ultrasound was also kept constant in this study. The half-power distance, that is, the distance at which the initial ultrasound intensity is reduced by one half, is reported to be 380 cm in water and 15 cm in blood, for a frequency of 2 MHz.[11] Although no data are available concerning

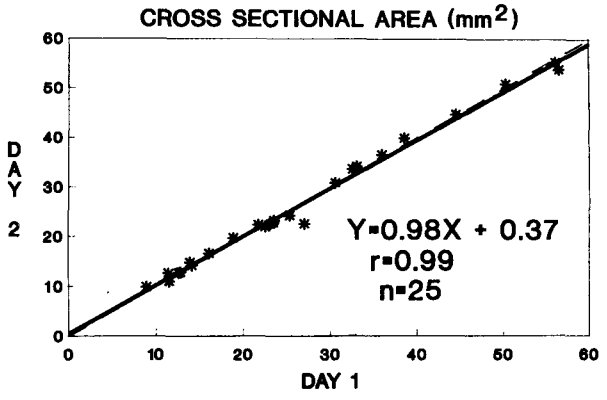

Figure 5 Intraobserver variability of measuring the cross-sectional lumen area. There was a close correlation (r = 0.99) between measurements made on 2 separate days.

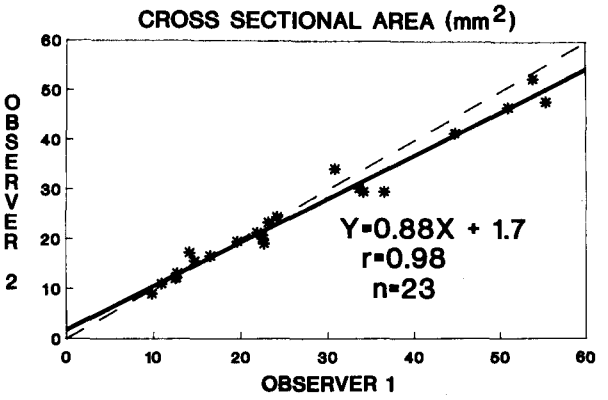

Figure 6 Interobserver variability of measuring the cross-sectional lumen area. There was a close correlation (r = 0.98) between separate observers of the measurements for cross-sectional lumen area.

the half-power distance in contrast media, it is reasonable to assume that the half-power distance in Hypaque solution is less than that of blood from our study because the image degradation is probably caused by absorbance of ultrasound by the contrast media. The mean lumen area in blood was reduced 6% compared with that in saline solution ($p < 0.05$). There are several possibilities for this observation. First, the velocity of ultrasound is faster in blood than in saline solution (1565 m/sec versus 1480 m/sec at 25° C). This implies that there should be some change in the size of the image displayed on the screen. The linear measurement error of this device caused by a change in the medium is expressed by the following equation:

$$\text{Error (mm)} = (D/2 + 2.0) \times (Vb/Vr - 1)$$

in which D is the diameter of an artery (in millimeters), 2.0 is the distance between the transducer and the mirror (in millimeters), Vb is the ultrasound velocity at 37° C in blood medium (1580 m/sec), and Vr is the ultrasound velocity in a medium at a given temperature. From this equation, it is anticipated that the diameter of the artery would be overestimated by 4% to 5% compared with the actual value when the artery is imaged in saline solution. This medium change from saline solution to blood may cause some reduction in the measured lumen area. Second, there is some effect in the ability to see the intima sharply and there could be some positional changes of the imaged site between the studies. However, these do not appear to be major factors because it was still possible to trace the intima without difficulty, because the shape of the imaged sites were quite similar between these studies, and because the acoustic reference marker was always imaged in the companion studies.

The bright halo-shaped reflectance (Figure 1) around the catheter was a highly specific phenomenon for images obtained in blood. The mechanism is not clear, but it seems to be related to the inhomogeneity of blood elements such as red cells or groups of red cells. This finding has been recognized in pig and human in vivo studies.[9] Hodgson et al.[8] also reported some decrease in signal intensity in images obtained in blood compared with that in saline solution using a phased-array transducer.

It is important to emphasize the effects of contrast media on the quality of the ultrasound images because contrast media will be used in association with this device in human clinical studies. Our findings demonstrate that the image intensity was significantly attenuated by contrast media; however, the image intensity was maintained at the baseline level when imaging was performed at the low concentration (20% Hypaque solution). In addition, the image intensity quickly returned to the baseline level after rinsing with saline solution. These findings indicate that the use of contrast material in vivo should not be a problem when a low concentration of contrast media is used or if frequent flushes with saline solution are provided.

The velocity of ultrasound is known to be dependent on temperature. When the temperature changes from 21° C to 37° C, the velocity increases from 1485 to 1540 m/sec (a difference of 4.8%).[12] According to the equation for estimating errors, there seems to be 4% to 5% measurement error in the diameter of the artery when the artery is imaged at 21° C. Thus, similar to the change in medium from saline solution

to blood, a change in temperature from 21° C to 37° C may cause some reduction in the measured lumen area. Contrary to our expectation, however, there was no significant change in lumen area at 37° C compared with that at 21° C. The reason for this result is still unclear, but the large size of the arteries may be partly responsible. The calculated error in diameter was less than 0.3 mm when the mean diameter of the arteries used in this study was 6.6 mm (range, 5 to 10 mm). This error may be more evident in a small artery such as a coronary vessel.

Another unexpected observation was the improved visualization of the images at the higher temperature (37° C). The precise mechanism of this phenomenon is unclear. The consistency and reproducibility of intravascular ultrasound imaging was confirmed in this in vitro study. There are still other factors that may influence image quality and the reproducibility of this technique. The images were obtained during stagnant flow conditions in the present study. It is known that the rheologic characteristics of blood change with different levels of blood flow; that is, formed elements such as red cells can develop rouleaux formation and become more echogenic as blood velocity decreases. Thus pulsatile flow may affect image quality in vivo. In addition, when this device is used in vivo, it may be difficult to maintain the catheter in a constant coaxial position between the arterial walls, especially in a tortuous artery or in arteries containing eccentric atherosclerotic lesions. Thus changes in positioning of the catheter is an important factor in obtaining reliable images and may affect observer variability. These factors were not addressed in the present study. However, the early in vivo clinical experience demonstrates that high quality intravascular ultrasound images can be obtained reliably with this device, which corroborates the in vitro findings of the present study.

This study demonstrated that ultrasound images in blood were mildly attenuated, that contrast media also attenuated the image intensity in a dose-dependent manner, that images of relatively large arteries are not significantly affected by temperature changes from 21° C to 37° C, and that the intravascular ultrasound imaging catheter provides a reproducible method for measuring arterial lumen area with excellent intraobserver and interobserver correlation.

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