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# High Frequency Epicardial Echocardiography for Coronary Artery Evaluation: in Vitro and in Vivo Validation of Arterial Lumen and Wall Thickness Measurements

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**The purpose of this study was to determine the accuracy of a new high frequency echocardiographic technique for the quantitative assessment of coronary artery luminal and wall dimensions. In 32 open chest animals, high frequency echocardiographic measurements (echo) of luminal diameter correlated well with in vitro histologic measurements (Histo) (r = 0.86; high frequency echo = 0.89 Histo + 0.79) (range 1.7 to 5.8 mm). Similar results were found in the evaluation of five human autopsy hearts studied in vitro. Coronary artery wall thickness measurements in human autopsy hearts showed a good correlation with high frequency echocardiographic measurements (r = 0.86; high frequency echo = 0.65 Histo + 0.24) (range 0.3 to 0.8 mm). In eight open chest calves, high frequency echocardiographic measurements of total vessel diameter correlated well with sonomicrometer measurements (Sono) (r = 0.94; high frequency echo = 1.03 Sono + 0.4) (range 2.1 to 5.3 mm).**

**Inter- and intraobserver variability measurements of high frequency echocardiographic measurements demonstrated excellent reproducibility (r = 0.95, interobserver variability for wall thickness; r = 0.97, interobserver variability for luminal diameter; n = 10 postmortem human coronary arteries). In conclusion, high frequency echocardiography is an accurate and reproducible method of measuring coronary luminal and wall geometry and may be a potentially useful tool for in vivo coronary artery evaluation in patients.**

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The clinical assessment of coronary artery anatomy depends, at present, solely on coronary angiography. This technique provides an arterial lumenogram in one or more longitudinal planes, but does not evaluate the lumen in cross section or the arterial wall unless there is calcification. The severity of lesions assessed by angiography has been shown to correlate poorly with pathologic and physiologic estimates of the magnitude and extent of coronary disease (1–4).

If a technique could be developed that directly evaluated the coronary artery lumen and wall in cross section, vessel morphology could be used to more precisely assess the extent of atherosclerosis. A new generation of high frequency ultrasound probes that have high resolution over a short depth of field holds potential for accurate evaluation of coronary artery anatomy. Sahn et al. (5,6) evaluated these ultrasound probes qualitatively for coronary imaging.

To establish the utility of this technique for the intraoperative detection and evaluation of coronary atherosclerosis, we undertook a quantitative validation study. Our purpose was to validate the accuracy of high frequency echocardiography for the evaluation of coronary artery wall and luminal measurements. We employed several approaches, including in vitro histology and in vivo sonomicrometry.

## Methods

### *Animal Preparations*

We studied 16 mongrel dogs weighing 18 to 25 kg and 3 sheep and 24 calves weighing 35 to 70 kg. These three

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species were chosen to provide a wide range of coronary artery sizes. Each animal was anesthetized with intravenous sodium pentobarbital, 750 to 1250 mg, and ketamine, 300 mg, intubated with a cuffed endotracheal tube and ventilated artificially with oxygen-enriched air with a mechanical respirator. Femoral artery and vein catheters were inserted for hemodynamic monitoring and vascular access. The thorax and pericardium were opened by means of a left thoracotomy, and a pericardial cradle was constructed that allowed access to the left anterior descending and left circumflex coronary arteries.

### *High Frequency Echocardiography*

A Biosound Surgiscan unit (Biosound Inc.) with a 12 MHz probe was used. This probe has a nominal axial resolution of 0.15 mm and a lateral resolution of 0.2 mm for two point structure resolution in a fixed system. Images were recorded on videotape for subsequent playback and analysis. Our analysis emphasized artery cross-sectional images. After high frequency echocardiographic imaging in animal and cadaver heart studies, the location along the coronary artery from which the echocardiographic image had been obtained was marked with a suture placed through the superficial connective tissue.

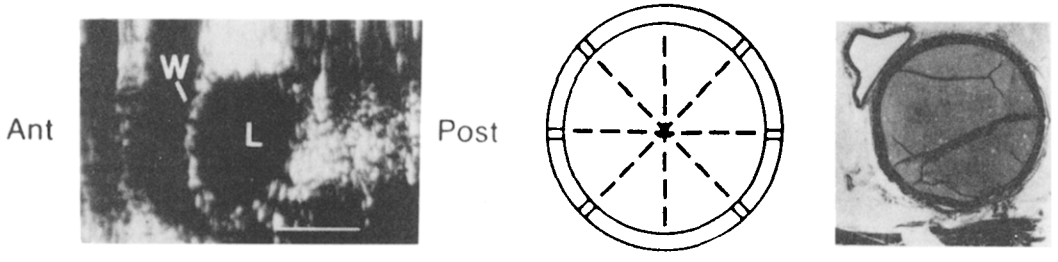
**Measurements.** The images were evaluated with an IREX (IREX Med Systems) digitizing system (Fig. 1). The echocardiographic image was displayed in cross section at that part of the cardiac cycle where the vessel diameter was largest. The inner and outer circumference of each vessel segment was outlined. Luminal area was directly measured. Luminal diameter (the mean of four equicircumferential measurements) and wall thickness (the mean of six circumferential measurements) were calculated. For atherosclerotic cadaver coronary arteries with eccentric lesions, the average of the circumferential wall thickness measurements was taken. For high frequency echocardiographic-sonomicrometer comparisons, total vessel diameter (that is, high frequency echocardiographic wall thickness plus high frequency echocardiographic luminal diameter) in a line approximating the line of the sonomicrometer crystals, was used.

To ensure that our high frequency echocardiographic evaluation was as accurate as possible, we minimized echocardiographic deficiences in several ways. Because of the characteristically poor lateral resolution of ultrasound imaging, some lateral wall images could not be evaluated. Therefore, we excluded all lateral wall measurements in our comparisons with histologic measurements. Echocardiographic images were analyzed if a high quality image was obtained in cross section and at least four of the possible wall interfaces could be adequately visualized (Fig. 1).

### *Histology*

To prepare vessels for histologic analysis the animals were killed with intravenous potassium chloride, the heart was removed, polyethylene cannulas were inserted into the proximal left anterior descending, left circumflex and right coronary arteries and 5 to 10 cc of a barium sulfate mixture (barium sulfate 1.2 g/ml, gelatin 0.2 g/ml and potassium iodide 0.3 g/ml, dissolved in a solution of distilled water with 1% octanol and 10% sodium biphosphate and sodium phosphate, dibasic) with 0.5 to 2.0 cc of 10% formalin as an activating agent, was infused (7). Vessels were perfused at a pressure equal to the mean arterial pressure that had been recorded during the in vivo high frequency echocardiographic evaluation. The heart was then fixed in a 2.5% formalin/distilled water solution for a minimum of 48 hours. After fixation, en bloc samples were removed and fixed in paraffin and 0.8$\mu$ thickness slices were cut, mounted and stained with a Verhoeff-Van Gieson stain. The slides were projected with a Leitz light microscope (Ernest Leitz & Co., Wetzler, Germany) onto a screen with 58× magnification. Using a light pen and a Zeiss digitizer (Carl Zeiss, Inc., Jena, Germany), the external and internal circumferance of the vessels were traced. Luminal area was directly measured. Mean luminal diameter (the mean of four equicircumferential measurements) (Fig. 1) and mean wall thickness (the mean of six circumferential measurements from endothelium to inner border of loose connective tissue) were

**Figure 1. Left**, Stop-frame videotape high frequency echocardiographic image of a calf circumflex coronary artery in cross section. The epicardial surface where the probe is placed is on the left side of the image. **Right**, Histologic section of a perfusion-fixed circumflex coronary artery in cross section. The artery was perfused with a barium-gelatin mixture at physiologic distending pressure. **Middle**, Convention used for making luminal diameter and wall thickness measurements. See text. The **horizontal calibration line** on the echocardiographic recording represents 3 mm. Ant = anterior; L = arterial lumen; Post = posterior; W = arterial wall.



calculated. From the mean luminal diameter and wall thickness data, luminal diameter to wall thickness ratios (luminal diameter/wall thickness) were calculated.

Specimens that were not completely distended by the barium gelatin mixture were excluded from analysis (10 of 75 animal coronary arteries) because artifacts resulting from incomplete distention would result in inaccurate measurements.

### *Sonomicrometry*

To measure coronary diameter, two miniature 7 MHz ultrasound transducers (2 × 2 mm) were implanted on opposing surfaces of the left circumflex and left anterior descending coronary arteries 2 to 5 cm from their origins. The ultrasound crystals (INSL-X, INSL-X Products Corp.) were attached to a Dacron backing (DuPont de Nemors & Co.,) and sutured to the outer adventitia of the coronary artery. Coronary diameter was measured continuously with an ultrasound dimension gauge (8) that measures the transit time of acoustic impulses traveling between the 7 MHz piezoelectric crystals. The distance between the crystals was displayed as a continous analog recording of the instantaneous external coronary artery diameter. We have found this technique to be extremely accurate for small measurements with the instrument having a resolution of 0.01 mm and drift not exceeding 0.01 mm (Drews TA, et al., personal communication, 1986). The measurements from the sonomicrometers utilized to compare with high frequency echocardiographic measurements were the largest intercrystal differences in a cardiac cycle corrected for the thickness of the ultrasound crystals, at the same site on the left anterior descending and left circumflex coronary arteries.

Sonomicrometer data were excluded when crystal alignment or signal interference resulted in the inability to obtain a stable sonomicrometer recording because of excessive noise (this occurrred in 17% of all sonomicrometer pairs).

### *Human Postmortem Hearts (n = 5)*

Within 12 hours of death and immediately after removal from the cadaver, the heart was washed in normal saline solution. Polyethylene cannulas were inserted into the proximal left anterior descending, left circumflex and right coronary arteries and connected to a perfusion pump. The heart was then suspended in a water tank and normal saline solution was infused through the cannulas at a mean pressure of 90 to 120 mm Hg. After high frequency echocardiographic scanning of the coronary arteries, the heart was removed and the vessels were perfused with the barium-gelatin mixture described earlier at the mean distending pressure that had been recorded in the water tank. The heart was then fixed in 2.5% formalin/normal saline solution for 48 hours. Small coronary artery samples were subsequently taken en bloc for histologic evaluation as described before. Four of 17 arterial segments could not be analyzed because of incomplete vessel distension or fixation with the barium gelatin mixture, or both.

### *Protocols*

**Delineation of vascular anatomy with high frequency echocardiography.** In all animal studies, the coronary artery identification was verified by injecting agitated saline solution through a left atrial cannula, with visualization by high frequency echocardiography of microbubbles in the arterial lumen. In all cases (43 animals), the microbubbles extended to the interface identified as the luminal-arterial wall border. The outer edge of the arterial wall was defined by high frequency echocardiography as the junction between the bright continuous echographic images that could be followed anteriorly around the coronary artery and the weaker random echoes posteriorly.

To demonstrate that high frequency echocardiography could accurately identify the interface between the arterial wall and the surrounding connective tissue, the following studies were done with an acoustical marker. In five dogs and two calves, a small segment of the left anterior descending coronary artery was dissected free from the underlying myocardium. An acoustical marker, consisting of a 1 mm plastic sheet, was placed between the coronary artery and myocardium. This acoustical marker was highly reflective of ultrasound, and thereby substantially attenuated the ultrasound energy penetrating farther into the myocardium. High frequency echocardiographic images were recorded with the acoustical marker in place and after the marker was removed. Comparisons were made between high frequency echocardiographic measurements of posterior wall thickness with and without the acoustical marker positioned behind the posterior wall.

**Histologic comparisons with high frequency echocardiography.** In 32 in vivo animals (11 dogs, 3 sheep, 18 calves), high frequency echocardiographic images of the coronary arteries were obtained with identification of the visualized region. After the animals were killed, histologic measurements of mean coronary artery luminal diameter, wall thickness and luminal diameter to wall thickness ratios were compared with high frequency echocardiographic measurements.

In five postmortem human hearts, high frequency echocardiographic images were obtained in the water tank with coronary artery perfusion, as described earlier, and were compared with subsequent histologic perfusion-fixed sections for mean coronary artery luminal diameter, wall thickness and luminal diameter to wall thickness ratios.

**Variability measurements.** To assess intraobserver variability, one observer made measurements of luminal diameter and wall thickness on one stop-frame videotape image using the digitizing tablet. Subsequently, the same

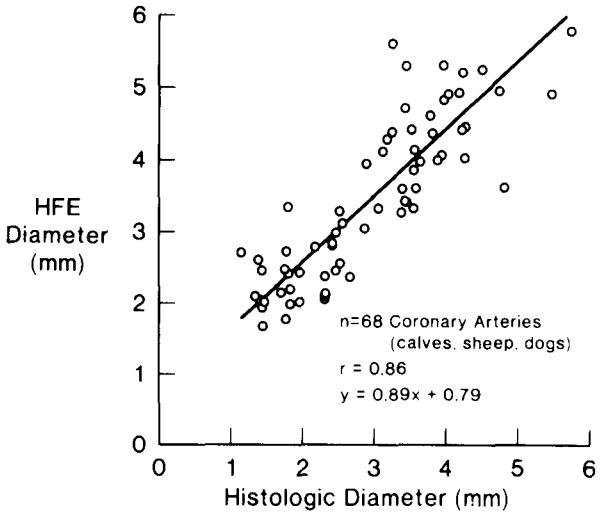



**Figure 2.** Comparisons between high frequency echocardiographic (HFE) and histologic measurements of arterial luminal diameter in animals (68 arteries).

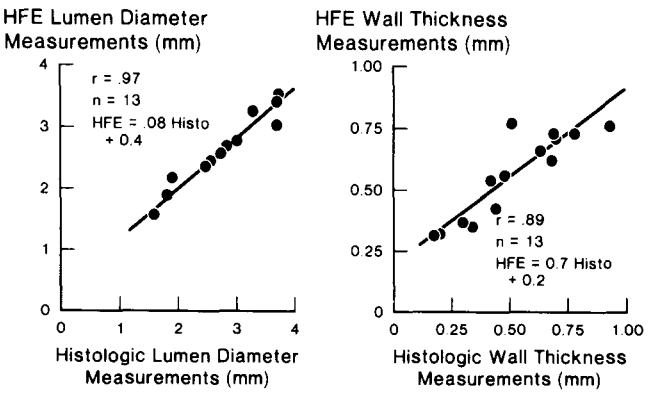



**Figure 4.** Comparisons between high frequency echocardiographic (HFE) and histologic luminal diameter and wall thickness measurements of 13 arteries in the five postmortem human hearts.

observer returned within 24 hours and used the same portion of the videotape (but not necessarily the same frame) to remeasure luminal diameter and wall thickness (25 normal animal arteries in vivo, 10 cadaver coronary arteries in vitro). To assess interobserver variability, two independent observers made separate measurements of wall thickness and lunminal diameter on one image (25 normal animal coronary arteries in vivo, 10 cadaver coronary arteries in vitro).

**Statistical analysis.** As appropriate, the following tests of statistical significance were made. Analysis of variance (ANOVA) was used if more than two groups of paired of unpaired data were compared. Paired *t* tests were used to evaluate two groups of paired data; unpaired *t* tests were used to evaluate two groups of unpaired data. Linear regression analysis was used to correlate paired data sets. Differences were considered significant when confidence limits exceeded 95% ($p < 0.05$). The results are expressed as mean ± SEM.

## Results

**Delineation of vascular anatomy with high frequency echocardiography and the acoustical marker.** With the acoustical marker studies, posterior wall thickness measurements were slightly larger when defined without the addition of the marker (0.3 ± 0.01, range 0.2 to 0.4 mm with the marker; 0.4 ± 0.02, range 0.3 to 0.5 mm without the marker; $p < 0.05$, $n = 14$). The measurements with and without the acoustical marker did not vary by more than 0.2 mm in individual arteries.

**Figure 3.** Comparisons between high frequency echocardiographic (HFE) and histologic luminal area measurements in 13 coronary arteries of five postmortem human hearts. An example of a high frequency echocardiographic image from a human heart is shown in the **bottom right corner**.

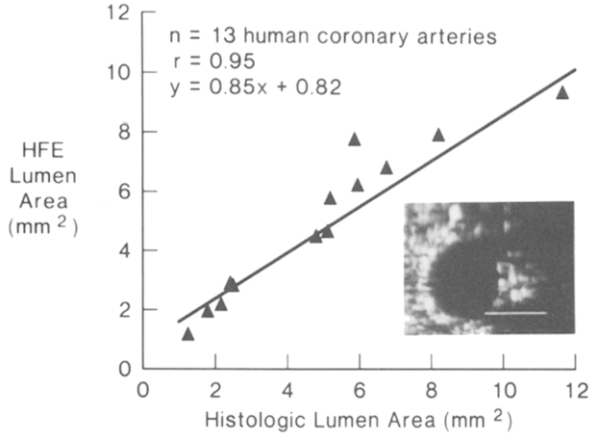
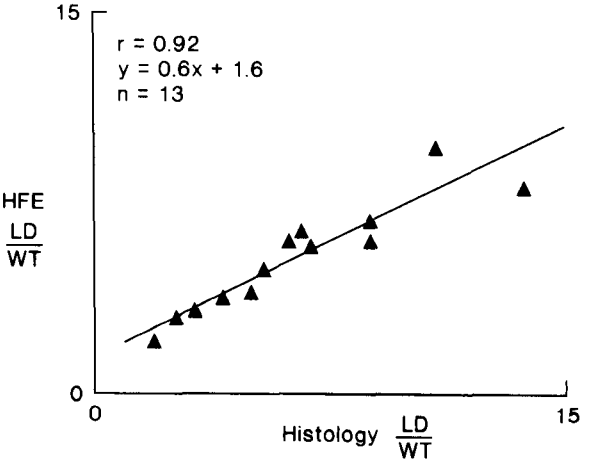



**Figure 5.** Comparisons of luminal diameter to wall thickness ratios (LD/WT) in 13 postmortem human coronary arteries by high frequency echocardiography (HFE) and histologic study.



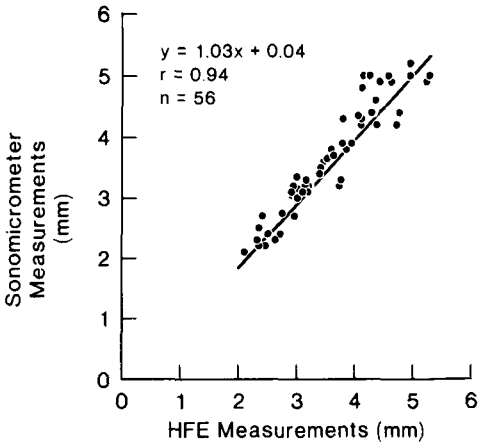



**Figure 6.** Comparisons of artery diameter measurements in 56 calf coronary arteries by high frequency echocardiography (HFE) and sonomicrometry.

**Histologic comparisons with high frequency echocardiography (Fig. 2).** In the animal studies there was a good correlation between high frequency echocardiography and histologic arterial luminal diameter measurements ($r = 0.86$, $n = 58$) (range 1.7 to 5.8 mm by histology). The wall thickness measurements in the cows and sheep by histology ranged from 0.2 to 0.6 mm (mean 0.3 ± 0.1) and by high frequency echocardiography from 0.2 to 0.5 mm (mean 0.4 ± 0.01 mm) ($r = 0.19$; $p$ = NS, $n = 36$). The high frequency echocardiographic measurements never overestimated histologic wall thickness values by more than 0.2 mm or underestimated them by more than 0.1 mm. In 35 calf coronary arteries, luminal diameter/wall thickness ratios were 11.9 ± 0.5 (range 6.9 to 16.1) by histology and 11.6 ± 0.4 (range 7.4 to 16.6) by high frequency echocardiography ($p$ = NS).

Figures 3 and 4 illustrate luminal area, luminal diameter and wall thickness comparisons between high frequency echocardiography and histologic studies for the 13 postmortem human coronary arteries, which were larger than the animal coronary arteries. In these cadaver hearts, luminal areas, luminal diameter and wall thickness comparisons between histologic study and high frequency echocardiography were quite accurate over the wide range of arterial lumen and wall sizes. Figure 5 illustrates the comparison of high frequency echocardiographic versus histologic luminal diameter/wall thickness ratios for the five postmortem human hearts. The mean luminal diameter/wall thickness ratios showed a good correlation between the two techniques.

**Sonomicrometry comparisons with high frequency echocardiography (Fig. 6).** There was an excellent correlation between high frequency echocardiographic measurements of total vessel diameter and the equivalent sonomicrometer measurements.

**Variability measurements.** In vivo animal intraobserver variability was excellent for arterial wall thickness and luminal diameter (Table 1). Interobserver variability was slight, although the variability was slightly greater, for the small wall thickness measurements. In vitro intraobserver and interobserver variability measurements for human coronary arteries were similar to those observed in normal animal studies (Table 1), except that intraobserver variability of wall thickness was greater for human than for animal coronary arteries.

## Discussion

The major finding of this study is that coronary artery luminal area, diameter and wall thickness can be accurately and reproducibly determined by high frequency echocardiography. The discussion will focus on a critical evaluation of our experimental approach.

**Quantitative comparison techniques.** Because there is no available reference standard to evaluate coronary artery

**Table 1.** Variability of Echocardiographic Measurements

| | Wall Thickness | Lumen Diameter |
|---|---|---|
| | (*r*) | (*r*) |
| Intraobserver variability | 0.95 | 0.99 |
| In vivo | n = 25 animal CA | n = 25 animal CA |
| | y = 0.96x + 0.02 | y = 0.98x + 0.09 |
| Intraobserver variability | 0.83 | 0.98 |
| In vitro | n = 10 human CA | n = 10 human CA |
| | y = 0.70x + 0.18 | y = 0.97x − 0.01 |
| Interobserver variability | 0.78 | 0.97 |
| In vivo | n = 25 animal CA | n = 25 animal CA |
| | y = 0.89x + 0.04 | y = 1.03x − 0.08 |
| Interobserver variability | 0.95 | 0.97 |
| In vitro | n = 10 human CA | n = 10 human CA |
| | y = 0.73x + 0.07 | y = 0.93x + 0.04 |

CA = coronary arteries.

measurements, we employed two complementary standards for quantitative comparison: histology and sonomicrometry. Histologic comparisons can accurately identify the arterial lumen and wall, but because they are in vitro evaluations, they are hampered by possible fixation artifacts (9). We attempted to minimize such artifacts by killing the animals with potassium chloride to ensure myocardial and arterial relaxation, which would allow maximal arterial perfusion. We then perfused the arteries with a barium-gelatin preparation at mean distending pressures identical to those observed in vivo. Specimens were excluded form analysis if perfusion was unable to completely fill or distend the lumen.

Although fixation artifacts in our histologic preparation were carefully controlled, they cannot be excluded entirely. Arterial shrinkage cannot be completely controlled and this technique has been shown to alter measurements by up to 10% (9). Therefore, to complement these histologic studies we also employed sonomicrometry, an in vivo technique that allows evaluation of dynamic changes in arterial dimensions (Drews TA, et al., personal communication, 1986) (8, 10, 11). Sonomicrometry, however, can only evaluate the artery in one dimension and cannot separate arterial wall from lumen. Thus, for comparative purposes, histology and sonomicrometry are complementary.

**Methodology and echocardiography.** Because it is impossible to perform in vivo validation studies in human coronary arteries, the animal model was chosen to evaluate in vivo measurement efficacy. A large range of animals with varying coronary artery sizes was chosen to evaluate a range of luminal diameters and areas that would approximate those in humans. Postmortem human hearts were evaluated to test the effects of epicardial fat and coronary atherosclerosis on image quality and quantitative measurements. Intra- and interobserver variability evaluations were performed to ensure that the high frequency echocardiographic measurements were reproducible.

Because the posterior artery wall lies immediately adjacent to myocardium, we undertook an acoustical marker study to assess our ability to identify the posterior wall-myocardial interface. We found a slight overestimation of wall thickness without the acoustical marker, but this did not overestimate thickness by more than 0.2 mm in any individual animal. This supports our ability to accurately identify the margins of the arterial wall.

There was a poor correlation for wall thickness measurements in the normal animal coronary arteries. This is probably because these thin animal coronary artery walls are at the limits of resolution of the probe. The correlation for wall thickness measurements by high frequency echocardiography versus histology in human postmortem coronary arteries was good; the walls of the human coronary arteries were thicker than those of the animals. This discrepancy in the correlation of coronary artery wall thickness measurements in the animal compared with the human heart may also be explained by the fact that the coronary arteries in humans had sonolucent epicardial fat that separated them from the surrounding myocardium and improved the ability of high frequency echocardiography to define the arterial wall thickness.

Because the 12 MHz high frequency echocardiographic probe has a mechanical transducer, near field noise due to secondary echo lobes should not be a problem. However, near field reverberations due primarily to the imaging lens cap could potentially result in image noise. This did not seem to be a problem during imaging and may have been due to the layer of sonolucent epicardial fat in the postmortem hearts and the sharp coronary artery wall/lumen interface in the animal arteries.

**Clinical applications.** This new high frequency echocardiographic technique yields accurate delineation of coronary artery wall and luminal geometry. This has unique potential for the in vivo intraoperative evaluation of the extent and degree of atherosclerosis. High frequency echocardiographic information can be correlated with techniques that assess the physiologic severity of coronary artery disease (3). It can provide independent in vivo validation of other techniques that indirectly measure luminal area and geometry, such as quantitative coronary angiography (12–14) and videodensitometry (15,16). High frequency echocardiography may be useful for evaluation of coronary bypass graft placement, insertion techniques and native vessel changes at surgery (17). Therefore, high frequency epicardial echocardiography should be valuable in the intraoperative detection, evaluation and quantitation of coronary artery disease.

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