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Anatomic and Functional Assessment of Stenosis Severity With Intravascular Ultrasound Imaging In Vitro

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An in vitro study was performed to evaluate the accuracy of intravascular ultrasound imaging compared with roentgenography for determining the cross-sectional area of a lumen; and to determine if the functional significance of an irregular stenosis is predicted more accurately by intravascular ultrasound than roentgenography. Varying degrees of stenosis were made in 17 rubber tubings by adjusting a plastic constrictor. The cross-sectional areas at the normal and the stenotic segments were determined by intravascular ultrasound, roentgenography, and then measured directly from an acrylamide gel cast of the lumen. To evaluate the functional significance of a stenosis, the pressure drop across the stenosis was measured using a fluid pumping circuit. The actual pressure drop was then compared with the predicted pressure drop derived from hydrodynamic equations using cross-sectional areas obtained by intravascular ultrasound or roentgenography. There was an excellent correlation between the cross-sectional areas at the tightest stenosis measured by intravascular ultrasound compared with the area from the acrylamide cast (7.2 ± 2.6 *v* 6.6 ± 2.4 mm^2, mean ± SD, $r = .93$). Measurements of cross-sectional area from the roentgenograms (10.9 ± 3.9 mm^2) also provided a relatively good correlation with those from the acrylamide casts ($r = .84$); however, the roentgenograms consistently overestimated the cross-sectional area of the stenosis. The mean values of the actual pressure drop and the predicted pressure drop by intravascular ultrasound and roentgenograms were 15.7 ± 13.5, 11.3 ± 11.9, and 4.3 ± 4.5 mmHg, respectively. The correlation with the actual pressure drop was close with intravascular ultrasound ($r = .83$) and with roentgenography ($r = .76$). However, roentgenograms consistently underestimated the pressure drop. These in vitro results suggest that intravascular ultrasound may be a more accurate method not only for the determination of anatomic morphology, but also for an assessment of the functional significance of a stenosis.

PRECISE ASSESSMENT of stenosis severity is fundamental for the diagnosis and management of patients with coronary artery disease. Angiography is the standard to determine not only the anatomic but also the functional assessment of stenosis severity in the coronary and peripheral vasculature.[1] However, there are several limitations to projection imaging techniques such as angiography. Visual interpretation of angiograms is known to have substantial intra- and interobserver variability, and postmortem measurements do not always correlate with angiographic findings.[2-5] Quantitative angiography or videodensitometric analysis of angiograms is reported to provide a more accurate assessment of stenosis severity.[6-9] Even with these techniques, it may be difficult to correctly measure the cross-sectional area of stenoses if the atherosclerotic lesion is irregular and asymmetric.[10]

Distinct from angiographic projection imaging, intravascular ultrasound imaging is a new modality that provides tomographic cross-sectional images of the artery lumen and wall structure that correlate closely with measurements from histology.[11-15] Clinical studies with this device show that it is feasible to obtain high quality images from peripheral and coronary arteries in patients with atherosclerotic disease.[16,17]

The hypothesis of this study is that cross-sectional imaging by intravascular ultrasound provides a more accurate assessment of stenosis severity than angiographic longitudinal projection imaging. To test this hypothesis, angiographic and ultrasound measurements were made in a plastic tube model of an irregular stenosis and were compared with direct measurements of the lumen using an acrylamide cast. These morphometric measurements were then used to predict the functional significance of the stenosis as determined by the Pouiselle resistance in a pulsatile flow system.

METHODS

Arterial stenosis in rubber tubing. A total of 17 plastic tube segments from three different types of tubing were used in this study. The length of the plastic tube segment was approximately 12 cm. The inner diameter and the thickness of the three types of tubing were 1.5, 1.6, and 3.0

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cm, and 3.7, 5.7, and 5.7 mm, respectively. An external stenosis was created on the middle portion of each tube with a 5 mm wide plastic constrictor. Varying degrees of stenosis could be made by changing the circumference of the constrictor by moving the band through a ratchet mechanism. The application of the constrictor changed the circular lumen cross-section to an irregular, tear-drop shape. The degree of the stenosis was not changed during the experiment in each tube.

Ultrasound imaging. The intravascular ultrasound imaging catheter used in this study consists of a single 20 MHz transducer located at the distal end of a flexible cable shaft (Intertherapy Inc, Costa Mesa, CA). The ultrasound beam was reflected by a metal mirror so that the beam exited perpendicular to the long axis of the catheter. The transducer sub-assembly (1.2 mm O.D.) is enclosed within a catheter sheath (4.9 F = 1.67 mm). High-resolution, real time cross-sectional images of a vessel are obtained by rotating the transducer assembly at 1800 rpm by a motor drive system.

The plastic tube was attached to three-way connectors at both ends and was filled with saline. The ultrasound catheter was then introduced from one end through an 8Fr introducer sheath. A pressure manometer was connected to the opposite end and the other two end connectors were occluded with plastic tubings and forceps. A constant pressure of 80 mmHg was applied by the pressure manometer during ultrasound imaging. Cross-sectional ultrasound images of the tubing were obtained at 2 mm intervals along the length of the stenosis including the tightest stenotic portion. These images were then stored in the ultrasound machine computer. Cross-sectional area measurements of the lumen were made of each sequential 2 mm segment.

Roentgenography. The plastic tube was placed parallel to the X-ray film and held 10 cm above the film with two metal arms at each end. The tube was filled with contrast material (Hypaque 60%) and inflated to a constant pressure of 80 mmHg. After the initial roentgenogram was taken (40 KV, 1 ms), the plastic tube was rotated 90° along its axis and a second orthogonal roentgenogram was obtained. Two metal clips were placed on the tube at a known distance to define a magnification scale. On the roentgenogram, the plastic could be seen and was used to match corresponding sites in the two views. Orthogonal diameters of the plastic tube were measured at every 2 mm intervals in each film along the length of the stenosis including the tightest stenotic portion. The cross-sectional areas were then measured by the following equation (Da, diameter in one view; Db, diameter in the other view).

$$\pi \times \frac{\mathrm{Da} \times \mathrm{Db}}{4}$$

Acrylamide gel cast. To accurately determine the inner size of the plastic tube, an acrylamide gel cast was made of each tube. Polyacrylamide gels were formed by copolymerization of acrylamide and bis-acrylamide (N-N′-methylene-bis-acrylamide). Polymerization was initiated by ammonium persulfate and TEMED (tetramethylethylenediamine). The polymer chains are a complex "web" polymer with a characteristic porosity depending on the polymerization conditions and monomer concentrations.[18]

Monomer stock solution (30% T) was made before each experiment and stored at 4°C in the refrigerator. Three hundred milliliters of stock solution contained 87.6 g of acrylamide (29.2 g/100 mL), 2.4 g of bis-acrylamide (0.8 g/100 mL) and distilled water. Ten milliliters of monomer stock solution, 5 mL of buffer solution (1.5 mol/L tris-HCL, Ph 8.8) and 5 mL of distilled water were combined in an Erlenmeyer flask. When the gel solution reached room temperature, it was degassed under a vacuum of 125 torr for 10 minutes with constant agitation. Then 200 mL of 10% ammonium persulfate was added along with 2 mL of 0.1% bromophenol solution. Immediately after 5 mL of acrylamide was poured into a 10 mL plastic syringe, 0.05 mL of TEMED was added and the whole solution was injected into the tubing. The cast was made within 3 to 5 minutes under a constant pressure of 80 mmHg, and then taken out from the tubing. The cast was cut with a razor at both the tightest stenotic portion and the normal portion, which was approximately 3 cm away. Cross-sections of the cast were photographed and measurements of the cross-section areas were made using a Kurta digitizing pad. The measurements were then compared with those from the ultrasound images and roentgenograms.

Pressure-flow measurements. Each plastic tube with its artificial stenosis was placed in an experimental preparation consisting of a reservoir and a circulating roller pump (Travenol Labs Inc, Deerfield, IL, Code 6M6002) which maintained pulsatile flow. The circulating fluid used in this study was 33% sucrose solution to simulate the viscosity of blood. The density was 1.142 g/cm^3 and the viscosity was 4.0 centipoise.[19] Absolute flow was measured at the distal end by counting the volume per minute into a graduated cylinder. Prestenotic and poststenotic pressures were measured by transducers that were connected to the proximal and distal ports in the tubing setup. By changing the power of the roller pump, the hydrodynamic variables of pressure and flow were measured in each stenotic tube. The relationship between the mean pressure drop across the stenosis at varying flow was determined.

Prediction of the pressure drop across the stenosis. Using the Pouiselle hydrodynamic equation, the pressure drop across each stenosis was calculated[6] (ΔP, pressure drop across the stenosis; μ, absolute fluid viscosity; L, stenosis length; An, the cross-sectional area at the normal portion; As, the cross-sectional area of the stenotic portion; As_j, cross-sectional area at each level (j) throughout the length of the stenotic segment; Q, flow; ρ, fluid density).

$$1.\quad \Delta P = FQ + SQ^2$$

$$2.\quad \Delta P = \sum_{j=1}^{i} \frac{8\pi\mu L}{As_j^2} Q + \frac{\rho}{2}\left(\frac{1}{As^2} - \frac{1}{An^2}\right) Q^2$$

The component of friction loss is summated at multiple cross-sectional areas along the length of the stenosis, but the energy loss of separation only depends on the normal and most stenotic areas.

The first part of this equation represents the viscous friction loss (F) and the second part represents the energy loss caused by separation (S) of laminar flow. From the cross-sectional areas and stenosis length obtained, either from the ultrasound images or roentgenograms, two different predictions could be made at a given flow rate using the above equation. To determine which method more accurately predicts the pressure drop across the stenosis, the predicted pressure losses from the two methods were compared with the actual measurements at the same flow levels.

STATISTICAL ANALYSIS

All data were expressed as mean ± SD. The cross-sectional area of the normal and stenotic segments and the percent area stenosis of each plastic tube obtained by roentgenograms and ultrasound imaging were compared with the measurements from the acrylamide cast by a linear regression analysis. The correlation coefficient (r), the intercept and the slope as well as standard error of the estimate (SEE) were determined. The calculated pressure drop across the stenosis derived from the roentgenograms or ultrasound images, was also compared with the actual measured pressure drop by a linear regression analysis.

RESULTS

Ultrasound images. A total of 164 cross-sectional images (8 to 11 images/tubing) were obtained from 17 plastic tubes. The quality of all the images was satisfactory for quantitative analysis. Figure 1 shows a series of ultrasound images from a plastic tube that were obtained along the course of the stenosis at 4 mm intervals. As shown in this figure, the plastic tube used in this study was a strong reflecting material. Ultrasound images clearly delineated the change in morphology and degree of the artificial stenosis of the plastic tube.

Measurements of cross-sectional area. Figure 2 shows the comparison between the contrast radiographs and the acrylamide cast in two orthogonal views. At the level of the normal portion of the plastic tube, the mean cross-sectional area measured from the acrylamide cast, ultrasound catheter, and roentgenogram were 21.6 ± 4.9 mm^2, 21.7 ± 5.8 mm^2, and 25.9 ± 6.0 mm^2 respectively ($P < .01$). Measurements from the roentgenograms correlated well with those from the acrylamide casts in the normal portion ($Y = 1.20X - 1.3$, $r = .98$, SEE = 1.14). There was also an excellent correlation between the measurements from the ultrasound catheter and acrylamide cast ($Y = 1.12X - 2.55$, $r = .96$, SEE = 1.76).

The mean cross-sectional area at the point of tightest stenosis measured by the ultrasound catheter was 7.2 ± 2.6 mm^2. At this same level,

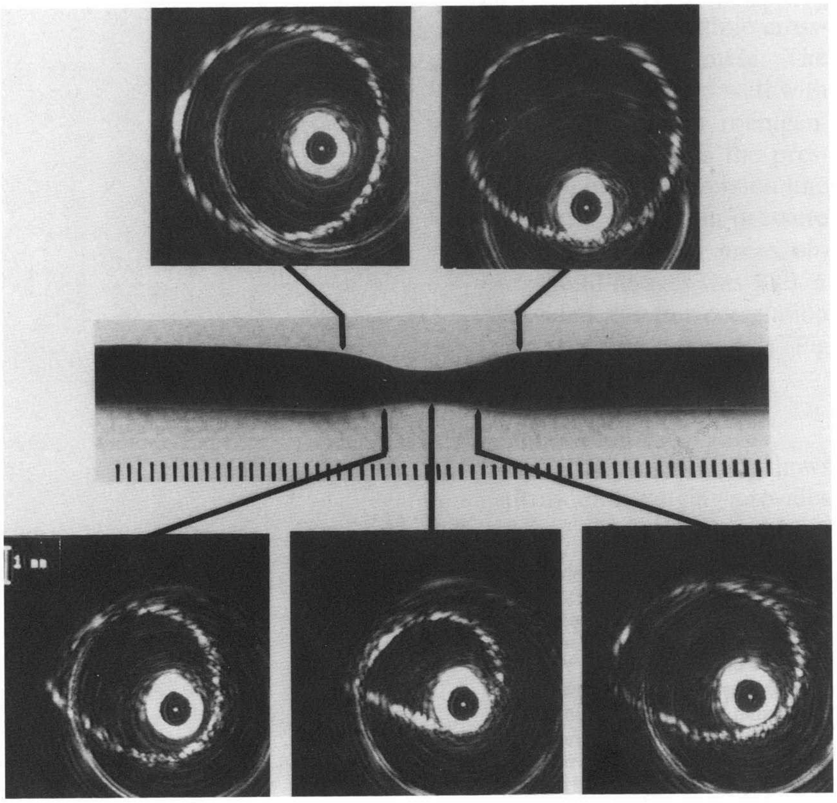

Fig 1. Ultrasound images from a plastic tube stenosis obtained at 4 mm intervals. Ultrasound images delineated the changes in morphology and the degree of the artificial stenosis created in the plastic tube model. The first central echo reflection is caused by the introducing sheath of the ultrasound catheter. There is also a secondary circular echo reflection from the sheath that has smoother echoes than those from the plastic tube.

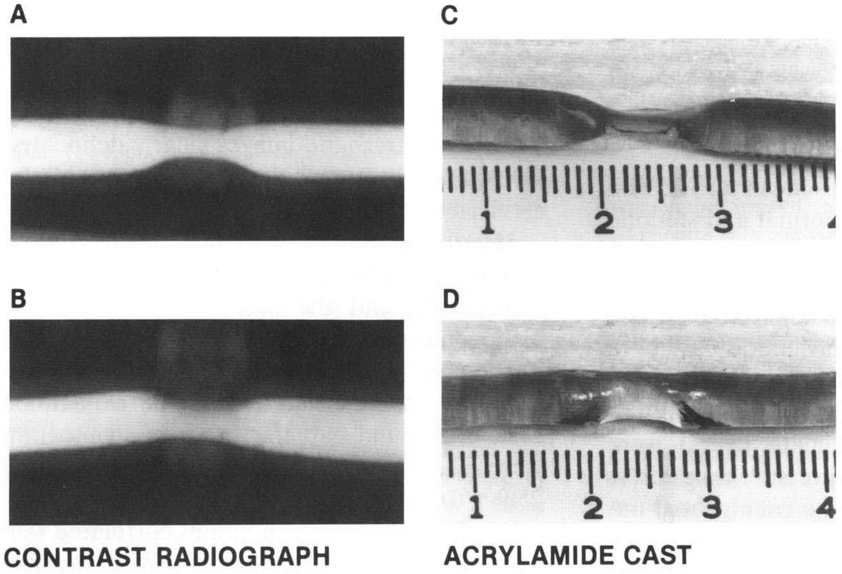

Fig 2. Contrast radiographs of a stenotic plastic tube in orthogonal projections compared with the acrylamide cast made from the same stenotic tube.

the mean cross-sectional area from the acrylamide cast was 6.6 ± 2.4 mm^2. The cross-sectional views of an ultrasound image and an acrylamide cast slice obtained at the stenotic and normal segments of the same plastic tube are shown in Fig 3. The ultrasound images accurately represented the morphology of the casts. An excellent correlation was found

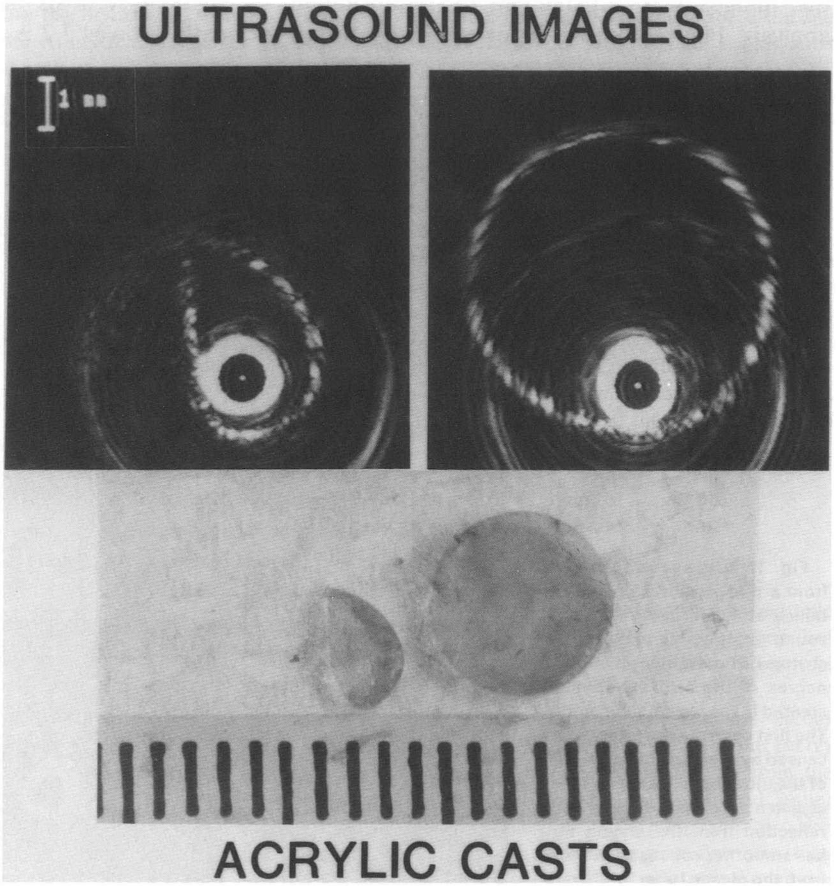

Fig 3. Cross-sectional views of ultrasound images and acrylamide casts obtained at the most severe stenosis and a normal segment of a plastic tube model. The morphology of the casts and the ultrasound images were similar. The 1 mm marker and ruler are at different magnification in this photograph.

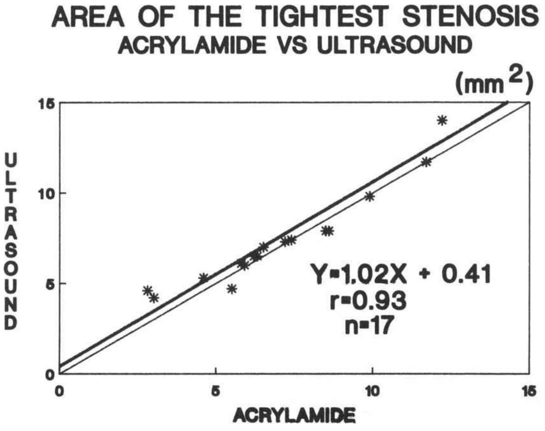

Fig 4. Correlation of the cross-sectional area at the most severe stenotic segment between the ultrasound images and the acrylamide casts. There was a close correlation between the measurements (Y = 1.02X + 0.41, $r = .93$).

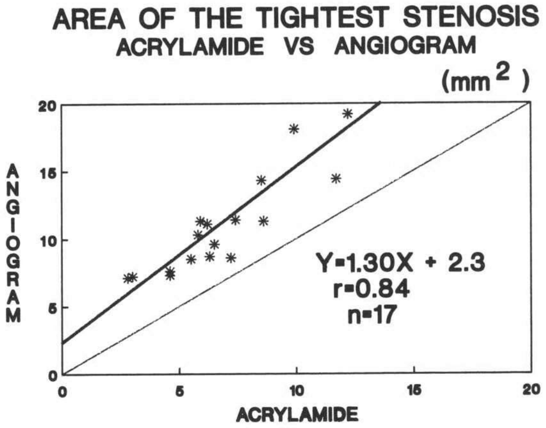

Fig 5. Correlation of cross-sectional area at the most severe stenotic portion between the roentgenograms and acrylamide casts. There was a good correlation between the measurements from the roentgenograms and acrylamide casts; however, the roentgenograms consistently overestimated the cross-sectional area of the stenosis (Y = 1.30X + 2.3, $r = .84$).

Table 1. Cross-Sectional Area and Percent Stenosis

	Cast	Ultrasound	Angiography
Area (mm^2)	6.6 ± 2.4	7.2 ± 2.6	10.9 ± 3.9
% Stenosis	63 ± 12	65 ± 13	56 ± 15

between the ultrasound images and the acrylamide casts at the level of stenosis (Y = 1.02X + 0.41, $r = .93$, SEE = 0.98; Fig 4). The mean cross-sectional area calculated from the roentgenograms at the stenosis was 10.9 ± 3.9 mm^2 which also correlated closely with the acrylamide casts (Y = 1.30X + 2.3, $r = .84$, SEE = 2.07, Fig 5); however, the roentgenograms consistently overestimated the cross-sectional area of the acrylamide cast stenosis by a mean of 65% ($P < .01$) (Table 1).

Percent stenosis was calculated as (1 − area of the tightest stenosis/area of the normal portion) × 100(%). The mean percent stenosis determined from the acrylamide cast, ultrasound imaging, and roentgenogram were 63.8% ± 12.1%, 65.0% ± 12.9% and 56.1% ± 14.9%, respectively ($P < .01$). Measurement of percent stenosis from the ultrasound images showed a good correlation with the acrylamide casts (Y = 0.98X − 1.74, $r = .92$, SEE = 5.19). The correlation between the measurements of percent stenosis from the roentgenograms and the casts consistently underestimated the percent stenosis, with a Y intercept of −17.0% (Y = 1.07X − 17.0, $r = .87$, SEE = 7.61).

Pressure flow relationship. The pressure drop across the stenosis was measured at 10 different flow levels in each plastic tube, providing 170 data points to assess the pressure-flow relationship. The mean prestenotic pressure, poststenotic pressure, and pressure drop across the stenosis were 45.4 ± 21.8 mmHg, 29.8 ± 9.9 mmHg, and 15.7 ± 13.5 mmHg, respectively at a mean flow level of 12.5 ± 4.7 mL/sec (range 4.3 to 24.5 mL/sec).

The mean predicted pressure drop derived from the roentgenograms using multiple cross-sectional areas was 4.3 ± 4.5 mmHg. The predicted loss of pressure correlated well with the measured drop ($r = .76$); however, roentgenography consistently underestimated the pressure drop, with the slope of the regression line at 0.25 (Fig 6). In contrast, the mean pressure drop using multiple cross-sectional areas obtained from the ultrasound images was 11.3 ± 11.9 mm Hg and provided a better correlation with the measured pressure drop ($r = .83$) (Fig 7).

DISCUSSION

Cross-sectional area. The present study shows that intraluminal ultrasound imaging provides accurate measurements of cross-sectional areas, both at circular ($r = .93$) and irregular stenotic ($r = .96$) segments, when compared with direct measurements of a gel cast. Biplanar contrast radiographs obtained in a manner similar to clinical angiography accurately predicted the cross-sectional area of normal circular segments of the model tubes ($r = .98$) but consistently underestimated the degree of stenosis

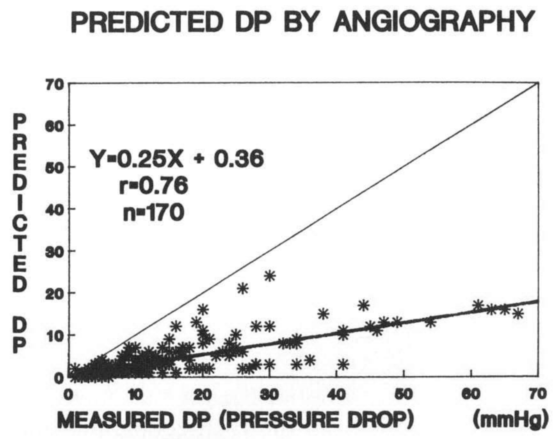

Fig 6. Correlation between the actual pressure drop (DP) across the stenosis and the predicted pressure drop by roentgenograms. The roentgenograms consistently underestimated the pressure drop, although the correlation with the actual measurements was relatively good (Y = 0.25X + 0.36, *r* = .76).

and had a weaker correlation coefficient (*r* = .84).

Factors that contribute to errors in the angiographic measurement of stenosis include observer variability[2-4] and edge detection inaccuracy.[5-9] These variables are unlikely to have been a factor in this study because of the excellent correlation of cross-sectional area measurements of the normal segment of the tubes obtained with gel casts and contrast radiography. Edge definition was not a problem because the edges were well demarcated even at the stenotic segments of the radiograms, and there was no overlap. Magnification errors also are unlikely to be a significant explanation for the discrepancy between the contrast radiograph data and the gel casts because the percent area stenosis, which is independent of magnification, was also consistently underestimated.

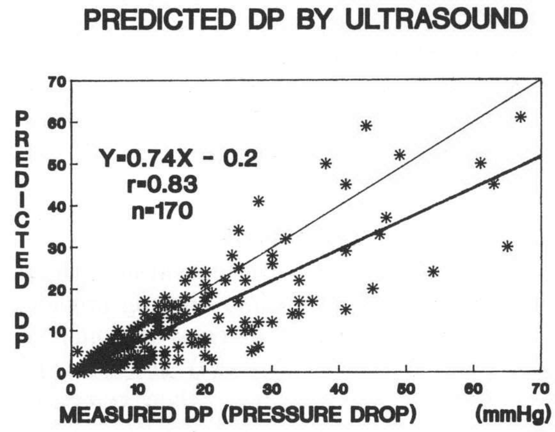

Fig 7. Correlation between the actual pressure drop (DP) across the stenosis and the predicted pressure drop by ultrasound imaging. The predicted pressure drop by ultrasound imaging correlated closely to the actual measurements (Y = 0.74X − 0.2, *r* = .83).

An important factor in the calculation of the lumen area from contrast radiographs is that the formula assumes an elliptical cross section. In our model, the induced stenosis had a teardrop configuration as shown in Fig 3. The effect of this irregular geometry was that the actual cross-sectional area at the stenosis was smaller than the area calculated from contrast radiographs. Stenoses in human arteries generally are eccentric and may be irregular, which could produce an underestimation of stenosis severity as shown in this study.[10] In addition, angiograms underestimate the degree of stenosis caused by the superposition of contrast over irregular plaque features obscuring the precise contour of the plaque and the degree to which it impinges on the lumen.

The ability to visualize an artery in cross-section is one of the most important features of intravascular ultrasound imaging. In vitro studies with normal human arteries show that the luminal boundary of the intima, the muscular media, and the adventitia are clearly identified with intravascular ultrasound. Moreover, in atherosclerotic arteries, the location and the amount of plaque can also be accurately identified.[11,12,15] Thus, both quantitative and qualitative measurements of arterial stenosis are feasible with this device in peripheral and coronary arteries.[20] Preliminary studies also show that high quality images can be obtained in vivo following coronary angioplasty or peripheral atherectomy,[16,17] which are procedures that may leave an irregular lumen cross-section.

Several limitations of intravascular ultrasound for the measurement of vessel cross-sectional area have been reported.[21,22] Coaxial and central placement of the ultrasound catheter is necessary to obtain an accurate cross-sectional image of the vessel, otherwise the shape of the vessel may be distorted and the cross-sectional area may be inaccurate. We obtained a close correlation between the measurements from ultrasound images and the acrylamide casts (r = .93). In addition, the ultrasound images accurately represent the morphology of the casts (Fig 3) in this study. There was no special care taken to keep the catheter in the center of the lumen; however, when the diameter of the catheter is similar to the artery diameter, the catheter is prevented from deviating laterally or inclining to one side.

Functional significance of a stenosis. Brown et al[6] and Gould et al[1] have shown that quantitative analysis of coronary artery stenoses predicts resistance to blood flow. Brown et al used highly magnified cine angiograms to trace the luminal edges of coronary stenoses in orthogonal projections. The cross sectional area was calculated from the orthogonal diameters and estimated the atheroma area.[6] Assuming an elliptical lumen, the Pouiselle equation was used for hydraulic resistance to flow through a stenosis to predict the drop in pressure across the stenosis for varying levels of coronary blood flow. Gould et al validated this hemodynamic model in a series of animal experiments, where pressure-flow curves were generated for stenoses of varying severity.[1] The accuracy of the equation to predict the pressure drop across a stenosis depends largely on the ability to measure the cross-sectional areas of the normal and stenotic segments.

Until recently, angiographic assessment of arterial stenosis was the only means of determining the dimensions of the lumen and, by inference, the atherosclerotic plaque. However, angiography is a form of projection imaging that does not directly measure the cross-sectional area. The diameter of the lumen is used to derive the area assuming that the lumen is elliptical. Although this assumption is correct in some cases, pathological studies indicate that many stenoses are irregular or crescentic in cross-section, especially after balloon dilation. The hypothesis of this study was that directly measuring the cross-sectional area of a stenosis by intravascular ultrasound would be a more accurate method of quantitation than angiography. This hypothesis was tested by two methods. The first study compared the cross-sectional area measured by ultrasound imaging and angiography with direct measurements of acrylic casts. The second method was to determine which technique was better for providing the physiological significance of a stenosis by comparing the observed pressure-flow dynamics with the predicted values using the Pouiselle equation from the angiographic and ultrasound data.

In the present study, a better correlation with the actual pressure drop (r = .83) was obtained with the measurements from the ultrasound catheter. The roentgenographic prediction of ΔP also correlated well with the actual data (r = .76); however, similar to the underestimation of stenosis severity, the roentgenograms consistently underestimated the pressure drop by approximately 70%. These results are consistent with the hypothesis that intravascular ultrasound imaging provides a more accurate measurement of cross-sectional area at the stenotic segments. The magnitude of the underestimation of the functional stenosis severity by angiography may be more profound in the clinical setting because the stenosis morphology of human atherosclerotic arteries is more variable than the mildly irregular morphology created in our model.[10] Angiography has been used as the gold standard for identification of the presence and severity of coronary artery disease compared with noninvasive tests, such as treadmill exercise and thallium stress tests. However, the ability of angiography to identify the physiological significance of a stenosis has been questioned and does not correlate with coronary flow reserve as measured by Doppler velocity during surgery or at catheterization.[7,8] The results of this study suggest that this poor correlation may be because of the inability of angiography to delineate the cross-sectional area of irregular stenoses.

Limitations. There are several limitations to our study. First, to avoid changes in vessel size caused by pulsatile flow, a rigid plastic tube was used to simplify the calculation of the predicted pressure drop. An elastic human artery may have a more complicated pressure-flow relationship, although diseased human arteries are frequently noncompliant and do not dilate during pulsatile flow.[16] Second, we did not take into account the vasodilation of peripheral vasculature distal to the stenosis, which may have an important role in determining the functional significance of a stenosis in vivo. Despite these limitations, it appears that intravascular ultrasound imaging is more suitable than angiography for assessing stenosis severity because it can directly visualize the cross-sectional area of the vessel.

CONCLUSIONS

This in vitro study shows that (1) roentgenography usually overestimates the cross-sectional area of a stenosis. Thus, the prediction of the functional significance of the stenosis from the roentgenograms may be inaccurate. (2) Intravascular ultrasound imaging permits direct measurement of the cross-sectional area of the lumen and therefore, provides a more accurate measurement of cross-sectional area. With the more accurate measurements of cross-sectional area from the ultrasound images, it is possible to more accurately predict the functional significance of a stenosis. These results indicate that intravascular ultrasound imaging may be a more appropriate method not only for the determination of the anatomic morphology of a stenosis, but also for the assessment of the functional significance of the stenosis.

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