Intravascular Ultrasound Study of Angiographically Mildly Diseased Coronary Arteries

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Objectives. We hypothesized that intravascular ultrasound may identify significant coronary artery narrowing in the mildly diseased coronary artery of patients with insignificant or one- or two-vessel coronary artery disease.

Background. Necropsy studies have revealed that coronary angiography may underestimate stenosis severity in vessels that appear mildly diseased. Intravascular ultrasound has been shown to detect atherosclerotic changes in angiographically normal coronary arteries and to correlate better with histologic findings.

Methods. In 22 patients, we performed intravascular ultrasound imaging (3.5F catheter, 30-MHz transducer) in 37 coronary arteries that were considered mildly diseased (<50% diameter narrowing) by qualitative angiography. The angiographic diagnosis was no significant coronary artery disease in eight patients, one-vessel disease in seven and two-vessel disease in five. Each vessel, except for the left main coronary artery, was divided into proximal, mid and distal segments. Percent area narrowing and minimal lumen diameter were subsequently quantified by both ultrasound and quantitative angiography.

Necropsy studies of coronary arteries performed soon after coronary angiography have demonstrated that the severity of coronary artery narrowing in angiographically mildly diseased coronary arteries may be underestimated (1-3). This underestimation appears to be most marked in vessels that demonstrate 50% to 75% arterial area narrowing at necropsy (3).

Intravascular ultrasound imaging of the coronary arteries has been shown to detect atherosclerotic plaque in patients with no evidence of disease by angiography (4-6). These findings illustrate the accuracy of this ultrasound technique in detecting early atherosclerotic disease in angiographically normal vessels. However, systematic intravascular ultrasound examination has not been performed of coronary vessels with mild angiographic disease (<50% diameter narrowing). We hypothesized that this imaging modality would identify patients who may have significant coronary artery narrowing despite minimal abnormalities on angiography. This study was designed to test this hypothesis by performing intravascular ultrasound of coronary arteries with qualitatively determined mild disease in patients with either angiographically insignificant or one- or two-vessel coronary artery disease.

Results. Mean maximal arterial area narrowing by ultrasound in the 67 segments studied was 36 ± 20% (range 0% to 80.2%) and 19 ± 23% (range 0% to 82%) by quantitative angiography of these same segments (p < 0.001, paired t test). Mean minimal lumen diameter of the segments was 3.3 ± 0.9 mm by ultrasound and 2.7 ± 0.8 mm by quantitative angiography. In 10 patients there were 19 angiographically mildly diseased segments where the percent arterial area narrowing by ultrasound was >50%.

Intravascular ultrasound revealed that the more proximal (reference) segment had >25% intimal thickening in 12 of the 19 underestimated segments. In six stenosed segments (32%), total vessel area increased compared with that of the adjacent proximal vessel segment due to compensatory dilation.

Conclusions. Intravascular ultrasound identifies potentially significant coronary artery disease in vessels that appear to be only mildly diseased by angiography.

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and the proximal, mid and distal segments of the left anterior descending, left circumflex and right coronary arteries. Patients were excluded if they demonstrated any angiographic evidence of spasm during or immediately after intravascular study. The study was approved by the University of Nebraska Institutional Review Board for the Protection of Human Research Subjects. All patients gave written, informed consent.

**Quantitative angiography.** Quantitative angiography was performed after qualitative interpretation of angiograms. Angiographic diameter narrowing was measured from angiographic projections using a hand-held caliper method. Measurements were made where the artery was perpendicular to the axis of sight. Care was taken to minimize parallax distortion. The catheter served as calibration and was measured in the best visualized area proximal to the distal 3 cm of the catheter. Vessels (other than the left main coronary artery) were divided into proximal, mid and distal segments.

Measurements of minimal lumen diameter in each segment were of the narrowest portion of the segment and were compared with measurements of the closest adjacent segment (always within 1 cm of the lesion). Interobserver measurements were made in two orthogonal views, except in three cases where foreshortening in one view prohibited this. Angiographic area narrowing was derived from the measured lumen diameter, assuming a circular or oval vessel. Percent stenosis was defined as the difference between the maximal and minimal areas in the segment divided by the maximal area.

All clinical data with regard to indications for catheterization and mean fasting low and high density lipoprotein levels were obtained, if possible. Hemodynamic and left ventricular function data were recorded at cardiac catheterization.

**Intravascular ultrasound.** After completion of the diagnostic catheterization or before coronary angioplasty, an 8F sheath was inserted into the right or left femoral artery. An 8F guide catheter was then introduced into either the left main or right coronary artery. A 3.5F monorail catheter with a 30-MHz mechanical transducer proximal to its tip (Boston Scientific Corporation) was then advanced into the distal coronary artery under fluoroscopy. According to the manufacturer, the optimal axial resolution (within the focal point of 1 mm) is 150 μm, and the lateral resolution is 150 μm. Beyond the focal point of the transducer, lateral resolution decreases to a greater degree than axial resolution.

The mechanical transducer was connected to an imaging console (Hewlett-Packard Sonos 100). The image could then be optimized using compression, time-gain compensation and postprocessing controls to give the blood in the coronary lumen a slight degree of reflectivity. Images were then recorded on videotape (sVHS, 0.5 in. [1.27 cm]) during pullback from the distal to the more proximal segments of the vessel.

**Imaging protocol.** The vessel that appeared mildly diseased by qualitative angiography (<50% diameter narrowing) was chosen for intravascular ultrasound imaging and quantitative angiography of the proximal, mid and distal segments. If the patient had two-vessel coronary artery disease, the vessel without significant angiographic narrowing was studied. When more than one vessel was mildly diseased by angiography, the uninvolved vessel that appeared the most favorable for placing the intravascular catheter was chosen.

Pulsed fluoroscopy or cineangiography of the ultrasound catheter was performed at each segment to ensure that this same region was analyzed by quantitative angiography. When prominent narrowing was observed, the catheter was advanced forward and backward to define the extent of intimal thickening in the immediately adjacent segment and to determine changes in lumen diameter and total vessel area in relation to the more proximal segment.

Off-line measurements of area stenosis and minimal lumen diameter with intravascular ultrasound were made of the most severely stenosed region in all three (proximal, mid and distal) segments. Plaque area was determined by planimetry as the area bounded by the middle echolucent layer (media) and intimal-lumen border. Lumen area was determined by planimetry as the area inside the intima-lumen border (Fig. 1). Percent area stenosis was calculated as plaque area divided by plaque plus lumen area (total area) multiplied by 100%. Minimal lumen diameter of each vessel segment was determined by measuring the smallest distance between intima-lumen borders 180° from each other, going through the geometric center of the lumen.

Plaque morphology was characterized as calcific if sharp, bright echoes were seen, with clear areas of shadowing within the plaque (see 12 o'clock region of the intravascular ultrasound image in Fig. 3), and hypoechogenic if the plaque was relatively echolucent throughout. If there was a brightly echogenic inner border overlying a hypoechogenic region, this was considered to be fibrous plaque (7). Regions were still considered fibrous plaque if a brightly echogenic segment resulted in significant ultrasound attenuation leading to eventual shadowing. Concentric plaque was considered present when nearly 100% of the vessel circumference was covered by plaque and eccentric when a variable arc of the vessel circumference was free of disease (8).

**Interobserver variability/statistical comparisons.** Quantitative angiographic and intravascular ultrasound measurements of the same 30 coronary artery segments were made by two independent experienced cardiologists. The cardiologists were unaware of the results of the other quantitative angiographic and ultrasound measurements.

Statistical comparisons of the two techniques were made using the paired t test. Correlations between the two techniques were made by a Pearson correlation coefficient. Interobserver variability of both intravascular ultrasound area narrowing and quantitative angiographic findings was calculated as the absolute difference in measurement between observers, divided by the maximal measurement of the two observers multiplied by 100%.
Results

Baseline characteristics of the study patients. The mean age of the patients studied was 62 ± 10 years. A total of 22 patients were studied, but 2 were excluded because of angiographic evidence of spasm in the vessel studied during intravascular ultrasound imaging. In both instances, the spasm resolved clinically and angiographically with intracoronary administration of nitroglycerin. Twelve patients were male, and eight were female. The indications for cardiac catheterization were prolonged rest chest pain or shortness of breath, considered clinically to be due to myocardial ischemia in 15; a positive stress echocardiogram or thallium study in 3; suspected aortic stenosis in 1; and status post-heart-lung transplantation in 1. Twelve patients had a history of hypertension, 12 had a significant smoking history and 6 had a positive family history for premature coronary artery disease. None of the patients had diabetes. Mean fasting low density lipoprotein levels (determined when available within 1 week of catheterization) were 133 ± 39 mg/dl, whereas fasting high density lipoprotein levels were 43 ± 14 mg/dl. At cardiac catheterization, the mean rest left ventricular end-diastolic pressure was 18 ± 7 mm Hg. Left ventricular ejection fraction (by single-plane left ventriculography or by echocardiography performed within 1 week of catheterization) averaged 54 ± 13%. The angiographic diagnosis (visual estimation before quantitative angiography) after catheterization was two-vessel coronary artery disease in five patients, one-vessel disease in seven patients and angiographically insignificant disease (<50% diameter narrowing in all vessels) in eight patients.

Intravascular ultrasound findings. A total of 67 segments in 37 vessels were studied. One vessel was analyzed in 7 patients, two vessels were analyzed in 12 patients and three vessels in 1 patient. A total of 11 left main, 13 left anterior descending, 7 left circumflex and 6 right coronary arteries were studied. In nine vessels, the distal segment of the right or left coronary artery could not be reached by the 3.5F ultrasound catheter.

Ultrasound determination of mean maximal arterial area narrowing in the vessels with angiographically mild disease was 36 ± 20% by ultrasound (range 0% to 80%) compared with a mean percent area stenosis by quantitative angiography of 19 ± 23% (range 0% to 82%, p < 0.001). Mean minimal lumen diameter was 3.3 ± 0.9 mm by ultrasound and 2.7 ± 0.8 mm by quantitative angiography.

Ten patients (Table 1) were found to have at least one ≥50% arterial area narrowing in the angiographically mildly diseased vessel by intravascular ultrasound imaging. Of these 10 patients, the visual angiographic diagnosis before ultrasound imaging was one- or two-vessel coronary artery disease in 8. The remaining two patients with area stenoses >50% detected by intravascular ultrasound had the angiographic diagnosis of no significant coronary artery disease.

In these 10 patients, 19 vessel segments had an area stenosis of ≥50% by ultrasound. Quantitative angiography detected >50% arterial area narrowing in only 9 segments of these patients. The morphology of the plaque by ultrasound was echogenic with focal calcifications in 10 segments and either hypoechoic or brightly echogenic without shadowing in 9. The lesion was concentric (involving nearly 100% of the vessel circumference) in 11 segments and eccentric in 8.

Correlation between quantitative angiography and intravascular ultrasound. Mean arterial area narrowing by ultrasound in the 19 arterial segments with >50% narrowing was 60 ± 9%. Figures 2 and 3 are examples of regions considered to have <50% area narrowing by quantitative and qualitative angiography but >70% arterial area narrowing by ultrasound.

There was no correlation between percent arterial area narrowing by ultrasound and the arterial area narrowing by quantitative angiography (r = 0.28). As shown in Figure 4, the major reason for the poor correlation was underestim-
tion of area narrowing by quantitative angiography. However, there was a significant correlation ($r = 0.59$, $p = 0.0001$) between minimal lumen diameter by ultrasound and quantitative angiography (Fig. 5).

In the segment with $>50\%$ area stenosis by ultrasound that were underestimated by quantitative angiography, ultrasound measurements were performed in the more proximal reference segment to elucidate the mechanism for underestimation by angiography. Table I demonstrates both the area stenosis and total vessel area (plaque plus lumen) in the stenosed region and more proximal vessel segment in the 10 patients with angiographic underestimation. Twelve segments were associated with $>25\%$ area stenosis in the adjacent proximal segment. In seven segments, the total vessel area decreased by $<2 \text{ mm}^2$ from the more proximal segment to the stenosed segment. In 6 of these 19 segments (32%), there was an actual increase in total vessel area in the $50\%$ stenosed segment compared with that of the more proximal segment. Despite the significant underestimation of area stenosis, quantitative angiography underestimated the severity of the minimal lumen diameter in only two patients (Patients 5 and 10, Table I). In one patient with a $>60\%$ area stenosis in the left main coronary artery, the more proximal region of this artery was too calcified to determine area stenosis or total vessel area.

**Interobserver variability.** Two experienced cardiologists analyzed 30 segments of the same coronary arteries by intravascular ultrasound and quantitative angiography to determine interobserver variability for both techniques. The cardiologists were unaware of both the results of the other imaging modality and the initial observer's results with either imaging modality.

There was a very strong correlation between results obtained by these two independent observers with regard to percent arterial area narrowing by ultrasound ($r = 0.98$, SE = 4%). The mean arterial area narrowing of the 30 segments did not differ between the two independent observers ($33 \pm 20\%$ by Observer 1, $33 \pm 20\%$ by Observer 2). In contrast, the two angiographic observers differed significantly on assessment of the same 30 coronary artery segments by quantitative angiography ($28 \pm 24\%$ for Observer 1, $15 \pm 22\%$ for Observer 2). The interobserver variability by ultrasound was significantly less than that by quantitative angiography (mean interobserver variability $10 \pm 9\%$ by ultrasound and $46 \pm 43\%$ by quantitative angiography).

The correlation between percent area narrowing using the quantitative angiographic measurements of observer 2 and intravascular ultrasound data was very similar to the correlation obtained with observer 1 ($r = 0.26$ for Observer 2, $r = 0.28$ for Observer 1). Therefore, the two observers' measurements of percent area narrowing by quantitative angiography both correlated poorly with intravascular ultrasound measurements.

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Angiographic Diagnosis</th>
<th>Vessel Studied by IVUS</th>
<th>CAD Segment $&gt;50%$ by IVUS</th>
<th>Plaque + Lumen Area</th>
<th>IVUS % Stenosis of Proximal Reference Segment</th>
<th>Minimal Lumen Diameter</th>
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<tbody>
<tr>
<td>1</td>
<td>1-vessel CAD (LAD)</td>
<td>RCA</td>
<td>Distal RCA</td>
<td>17.0</td>
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<td>2</td>
<td>2-vessel CAD (LCx, RCA)</td>
<td>LAD, LMCA</td>
<td>Distal LAD</td>
<td>13.4</td>
<td>73</td>
<td>2.4</td>
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<tr>
<td>3</td>
<td>No sign of CAD</td>
<td>RCA</td>
<td>Mid-LAD</td>
<td>8.6</td>
<td>69</td>
<td>1.9</td>
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<tr>
<td>4</td>
<td>1-vessel CAD (LAD)</td>
<td>LCx Marg, LCx</td>
<td>Distal RCA</td>
<td>19.1</td>
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<td>3.7</td>
</tr>
<tr>
<td>5</td>
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<td>LAD, LMCA</td>
<td>Mid-LAD</td>
<td>18.8</td>
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<tr>
<td>6</td>
<td>1-vessel CAD (RCA)</td>
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<td>17.3</td>
<td>57</td>
<td>3.0</td>
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<td>7</td>
<td>1-vessel CAD (RCA)</td>
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<td>Distal LAD</td>
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<td>Mid-LCx</td>
<td>9.9</td>
<td>56</td>
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<tr>
<td>9</td>
<td>1-vessel CAD (RCA)</td>
<td>LAD, LMCA</td>
<td>Proximal LAD</td>
<td>13.6</td>
<td>10</td>
<td>2.4</td>
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<tr>
<td>10</td>
<td>1-vessel CAD (RCA)</td>
<td>LCx, LAD</td>
<td>LMCA</td>
<td>14.3</td>
<td>50</td>
<td>2.0</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LCx Marg = left circumflex marginal branch; LMCA = left main coronary artery; NO = not obtainable because of acoustic shadowing (calcification); Pt = patient; QA = quantitative angiography; RCA = right coronary artery.
Figure 2. Angiographic, fluoroscopic and intravascular ultrasound demonstration of an angiographically mildly diseased distal left anterior descending coronary segment (arrow). Intravascular ultrasound-derived percent arterial area narrowing in this region was >70%. Guide wire artifact is evident at the 1 o'clock position.

Discussion

There are two principal findings of this study. First, the data provide in vivo confirmation of necropsy observations that coronary angiography underestimates coronary artery narrowing in epicardial vessels that appear to have mild disease. Second, two reasons for the angiographic underestimation appear to be diffuse atherosclerotic involvement extending into the more proximal reference segment and compensatory enlargement of the vessel when plaque burden increased to preserve lumen size.

Diffuse coronary plaque in the angiographically mildly diseased coronary artery. Diffuse coronary artery plaque in a vessel with mild disease in patients with angiographically significant disease in other vessels has been observed at detailed necropsy examinations (3,9). In one study of 467 3-mm coronary segments from 10 patients, only 10% of segments were found to have <25% narrowing (3). Our findings confirm these observations in an in vivo setting and extend earlier observations with coronary intravascular ultrasound that revealed diffuse plaque narrowing in vessels that appeared to be normal or have minimal disease by angiography (4,6). In 12 of the 19 vessel segments that demonstrated at least 50% area narrowing by ultrasound, the segment proximal to the stenosis had >25% area narrowing. The reference segment for determining percent area narrowing by quantitative angiography in our study was the region immediately proximal to any perceived angiographic narrowing. Ultrasound demonstrated in these 12 cases that a significant amount of plaque extended into this more proximal segment. Therefore, the correlation between percent area narrowing by intravascular ultrasound and quantitative angiography would be closer if the ultrasound study also used this reference segment (instead of the actual site of stenosis) for the calculation of percent area narrowing.

Compensatory dilation in the stenosed region of the angiographically mildly diseased coronary artery. Despite the ultrasound finding of development of a 50% area stenosis in the vessel segment, the total vessel area (plaque plus lumen area) in this segment did not change or became larger than the more proximal segment in seven lesions. Because angiography only outlines the vessel lumen, compensatory dilation of the vessel in the region of the stenosis would lead to underestimation of plaque burden. In an autopsy series, compensatory vessel enlargement has been observed to occur in the coronary arteries in response to atherosclerosis (10). High frequency epicardial ultrasound has also demonstrated that both lumen area and outer circumference of the vessel increase in the regions of atherosclerotic plaque, resulting in total arterial areas that are larger than the more proximal normal vessel (11,12). We found that in four diseased segments (from Patients 1, 2, 7 and 8 in Table 1), total vessel area increased by >15% compared with that of the more proximal segment.

Other components, such as plaque morphology, may have played a role in the underestimation of disease severity of the vessel with mild disease by angiography. We found
that in 8 of the 19 segments in which the mildly diseased vessel at angiography demonstrated a >50% area stenosis by ultrasound, the plaque morphology by ultrasound was noncircular (eccentric). Even when quantitative angiography is able to carefully measure the diameter stenosis in two orthogonal views, it would still be unable to accurately characterize an eccentrically stenosed lumen. Other investigators (13) have found with epicardial echocardiography that up to 50% of atherosclerotic lesions are noncircular.

Finally, in two cases there was a significant underestimation of minimal lumen diameter severity by quantitative angiography. Other investigators (14) have also demonstrated (in a vessel that angiographically appeared mildly diseased) significant coronary artery narrowing by intravascular ultrasound despite taking multiple angiographic views of the same vessel to prevent underestimation of minimal lumen diameter severity. It is therefore possible in these two instances that the angiogram was not truly perpendicular to the stenosis or that there was blooming of the iodine, resulting in obfuscation of the stenosis.

Limitations of the study. We demonstrated that intravascular ultrasound imaging may be clinically useful in determining whether significant stenoses exist in coronary arter-

Figure 4. Graph demonstrating the lack of correlation between quantitative angiographically (QA) and intravascular ultrasound (IVUS)-derived percent arterial area narrowing in the 67 segments studied.

Figure 5. Graph demonstrating the significant correlation for minimal lumen diameter by intravascular ultrasound (IVUS) and quantitative angiography (QA) in the 67 mildly diseased coronary artery segments.
ies with angiographically mild disease. However, the methodology of this study has technical limitations that need to be overcome. 1) We used pulsed fluoroscopy of the ultrasound catheter combined with angiography to determine whether the same region in the particular coronary segment was being studied by intravascular ultrasound (Fig. 2 and 3). We do not now have a more precise method of confirming this. Three-dimensional ultrasound techniques that allow reconstruction of the entire vessel (including branch points) may improve the ability to compare area stenosis and minimal lumen diameter by these two techniques. 2) A hand-held caliper method was used to determine quantitative angiographic measurements. This is not as accurate as automated digital methods or caliper methods where there is no parallax distortion and may account for the significant interobserver variability in these measurements (15). 3) Catheter angulation in the epicardial vessels that did not have a straight course may have caused overestimation of vessel area (16). However, the relative size of the coronary artery in relation to the catheter was small (the maximal coronary artery diameter in vessels other than the left main coronary artery in our study patients was 4.5 mm). Other investigators (17) have shown that when the size of the catheter in relation to the coronary artery lumen is relatively small, the impact of catheter angulation on vessel lumen measurements should be small.

Although both angiography and intravascular ultrasound measurements were obtained at the same catheterization, we cannot exclude spontaneous changes in vessel tone due to the intravascular ultrasound catheter that may have caused changes in lumen size. Six of the 10 patients who had a >50% arterial area narrowing by ultrasound were receiving either calcium channel antagonists or nitrates at the time of their study. The finding of disease underestimation in these patients decreases the possibility that our observations were due to changes in vessel tone.

Finally, there are technical and safety limitations with intravascular ultrasound. This technique cannot quantify arterial area narrowing when significant calcification (resulting in acoustic shadowing) exists. This was true in only one of the vessel segments in our study. In the remainder we could determine by planimetry the intimal-medial or medial-adventitial (or both) boundary by extrapolating between the two regions of calcification with minimal interobserver variability. Intravascular ultrasound is also a more invasive approach, requiring instrumentation of the artery with a guide wire and catheter. This requires additional anticoagulant therapy and has occasionally resulted in coronary spasm, which occurred in two patients in our study.

**Clinical implications.** Eight of the 10 patients in our study who had >50% arterial area narrowing by intravascular ultrasound in an artery with angiographically mild disease had one- or two- vessel coronary artery disease, whereas only two of these 10 patients had no angiographically significant coronary artery disease. Therefore, it is mainly in the patients with one- or two- vessel coronary artery disease that qualitative and occasionally quantitative angiography may be underestimating the extent of disease. It will be important to determine whether this narrowing in the vessel with angiographically mild disease vessel is functionally significant or leads to either incomplete revascularization or medical treatment of the patient.

Because we only studied vessels that were considered insignificantly narrowed at catheterization, we did not determine whether potentially significant narrowing exists in angiographically noncritically narrowed segments of a vessel with an angiographically significant lesion. This information could also be obtained with intravascular ultrasound and could lead to a more complete estimation of atherosclerotic involvement in angiographically diseased coronary arteries.

These two clinical implications of this study therefore suggest that intravascular ultrasound may be necessary to better characterize the angiographically uninvolved vessels in patients with one- or two-vessel coronary artery disease and thus provide better quantification of severity of coronary artery disease.

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**References**


