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Atherosclerosis in Angiographically "Normal" Coronary Artery Reference Segments: An Intravascular Ultrasound Study With Clinical Correlations

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Objectives. **This study evaluated the magnitude, patterns and clinical correlates of atherosclerosis in angiographically "normal" reference segments in patients undergoing transcatheter therapy for symptomatic coronary artery disease.**

Background. **Pathologic studies indicate that the extent of coronary atherosclerosis is underestimated by visual analysis of angiographically normal coronary artery segments. Intravascular ultrasound allows detailed, high quality cross-sectional imaging of the coronary arteries in vivo.**

Methods. **Intravascular ultrasound was used to study angiographically normal coronary artery reference segments in 884 patients evaluated for transcatheter therapy for symptomatic native coronary artery disease. The reference segment was the most visually normal intravascular ultrasound cross section within 10 mm proximal to the target lesion but distal to any major side branch. Results are presented as mean value ± 1 SD.**

Results. **Only 60 (6.8%) of 884 angiographically normal reference segments were normal by intravascular ultrasound. Reference segment percent cross-sectional narrowing measured 51 ± 13% and correlated poorly with the target lesion percent cross-sectional narrowing ($r = 0.166$, $p < 0.0001$). Reference segments contained less calcific and dense fibrotic plaque and proportionately more soft plaque elements. Independent predictors of reference segment percent cross-sectional narrowing were male gender, patient age, diabetes mellitus, hypercholesterolemia and presence of multivessel disease. Independent predictors of reference segment calcification were patient age and serum creatinine levels. Reference segment percent cross-sectional narrowing in 723 patients undergoing transcatheter therapy was similar to that in patients studied for diagnostic purposes; however, reference segment arc of calcium was greater in treated patients (43 ± 81 vs. 25 ± 57, $p = 0.015$). Reference segment disease was not an independent predictor of subsequent angiographic restenosis or clinical events within 12 months of follow-up.**

Conclusions. **Atherosclerosis is ubiquitous in angiographically normal coronary artery reference segments. Reference segment disease parallels the severity of target lesion disease and is associated with many of the conventional risk factors for coronary artery disease. Because of its sensitivity in detecting atherosclerosis in angiographically normal reference segments, intravascular ultrasound should enhance the study of risk factors for atherosclerosis and the results of therapies to control disease progression.**

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Contrast angiography has been the standard for evaluating extent of coronary artery disease. However, pathologic studies indicate that the extent of coronary atherosclerosis is underestimated by visual analysis of angiographically "normal" coronary artery segments (1–10).

Intravascular ultrasound allows detailed, high quality cross-sectional imaging of the coronary arteries in vivo. The normal coronary artery wall (intima, media and adventitia), the major components of the atherosclerotic plaque (lipid, fibrous connective tissue and calcium) and the changes that occur in coronary artery dimensions and anatomy with the atherosclerotic disease process can be studied in vivo using intravascular ultrasound in a manner not achievable using other imaging modalities. Specifically, the presence and composition of atherosclerosis in angiographically normal reference sites can be quantified (11–13).

The purpose of this study was 1) to evaluate the magnitude of atherosclerosis in angiographic reference segments; 2) to compare the patterns (e.g., composition and distribution) of atherosclerosis in angiographic reference segments with those of atherosclerosis at the lesion site; and 3) to study the clinical correlates of atherosclerosis located within the angiographic reference segments.

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Methods

Patients. Intravascular ultrasound was used to study angiographically normal coronary artery reference segments in 884 patients evaluated for transcatheter therapy for symptomatic native vessel coronary artery disease (680 men, 204 women; mean [±SD] age 60 ± 12 years, range 32 to 88). Target lesion location was the left main coronary artery in 39 patients, left anterior descending coronary artery in 364, left circumflex coronary artery in 135 and right coronary artery in 346. Catheter-based revascularizations were performed in 723 (82%) of 884 patients. Revascularizations included balloon angioplasty (n = 133), directional coronary atherectomy (n = 254), rotational atherectomy (n = 168), excimer laser angioplasty (n = 137) and stent placement (n = 31). The clinical, angiographic and intravascular ultrasound records from these 884 patients form the basis of this report.

Clinical demographics. The hospital charts of all patients were reviewed independently by a registered nurse to obtain clinical demographics and laboratory results.

Angina was categorized as stable, accelerated, postinfarction or rest. A recent myocardial infarction occurred within 6 weeks before the study; a remote myocardial infarction occurred >6 weeks before the study. In addition, a history of coronary artery bypass surgery and the presence of multivessel coronary artery disease (>50% diameter stenosis in two or more epicardial coronary arteries) was noted.

Risk factors for coronary artery disease that were tabulated included diabetes mellitus (medication dependent, including oral hypoglycemic drugs and insulin), hypertension (medication dependent only), hypercholesterolemia (medication dependent or serum cholesterol ≥240 mg/dl) and smoking (still smoking or having stopped smoking <6 months before the study). Laboratory data recorded included baseline admission hematocrit, platelet count and serum creatinine levels.

Angiographic analysis. All cineangiograms were analyzed using a computer-assisted, automated edge detection algorithm (ARTREK, Quantitative Cardiac Systems) by a core angiographic laboratory that had no knowledge of the ultrasound results. With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter in diastole before and after intervention was measured from orthogonal projections, and the results from the "worst" view were recorded. The reference segment diameter was averaged from 5-mm long angiographically normal segments proximal to the lesion but distal to a major side branch; when a normal proximal segment could not be identified (e.g., ostial lesion location or diffuse disease), a distal angiographically normal segment was analyzed. The percent diameter stenosis before and after intervention was then calculated. Qualitative variables (e.g., eccentricity and calcification) were also tabulated.

Intravascular ultrasound analysis. Intravascular ultrasound studies were performed using one of two commercially available systems. The first (CVIS/InterTherapy Inc.) incorporated a single-element 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft, which was rotated at 1,800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time; with this system the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. Because the transducer moves within a stationary imaging sheath, proximal catheter velocity is accurately translated to the transducer immediately without first straightening coronary artery curves or taking up slack within the coronary circulation. The second (Hewlett Packard and Boston Scientific Corporation) incorporated a single-element 30-MHz beveled transducer rotated at 1,800 rpm within a 3.5F short monorail imaging catheter. With this system the catheter was advanced or withdrawn manually with fluoroscopic guidance to perform the imaging sequence. Intravascular ultrasound studies were recorded on 0.5-in. high resolution sVHS tape for off-line analysis.

The reference segment was selected as the most visually normal cross section within 10 mm proximal to the target lesion but distal to a major side branch. In circumstances where a proximal reference segment could not be identified (e.g., ostial lesion location or diffuse disease, as previously described), then a distal reference (also within 10 mm of the target lesion but proximal to a major side branch) was analyzed.

Validation of normal coronary artery anatomy, plaque composition and morphology and quantitative measurements have been reported previously (14–21). Because media thickness cannot be measured accurately (20), plaque+media cross-sectional area was used as a measurement of the amount of atherosclerotic plaque. Total wall thickness was used to calculate the eccentricity index.

With computer planimetry, the target lesion and reference sites were assessed quantitatively using the following measurements: 1) lesion site external elastic membrane cross-sectional area (mm^2); 2) lesion site lumen cross-sectional area (mm^2); 3) Plaque+media cross-sectional area (mm^2) = External elastic membrane cross-sectional area − Lumen cross-sectional area; 4) % Cross-sectional narrowing = (Plaque+media cross-sectional area) × 100/(External elastic membrane cross-sectional area); 5) Eccentricity index = (Maximal total wall thickness)/(Minimal total wall thickness). An eccentricity index of 1.0 indicated purely concentric target lesion plaque distribution.

Target lesion and reference site plaque composition were assessed visually. The presence of significant amounts of calcium, dense fibrous tissue or soft plaque was tabulated independently for each lesion. These were not mutually exclusive, and mixed lesions containing more than one type of atherosclerotic plaque were tabulated as containing each plaque type. Calcium produced bright echoes (brighter than the reference adventitia) with acoustic shadowing of deeper arterial structures and was quantified by measuring its circumferential arc (in degrees) with a protractor centered on the lumen (22).

Dense fibrous tissue produced echoes that were as bright as or brighter than the reference adventitia but without acoustic

shadowing. The absence of acoustic shadowing differentiated dense fibrous tissue from calcium.

Soft plaque was less dense than the reference adventitia. Soft plaque is heterogeneous and contains various amounts of loose connective tissue, lipid, intimal hyperplasia or thrombus.

Patients were studied after giving written, informed consent. Intravascular ultrasound imaging is performed as part of ongoing protocols approved by the Institutional Review Board of the Washington Hospital Center.

Follow-up. All patients were followed prospectively for 1 year by a registered nurse (at 3, 6, 9 and 12 months after study) to identify major clinical events (death, Q wave myocardial infarction, coronary artery bypass surgery or repeat transcatheter therapy). Copies of pertinent documents were obtained and reviewed for verification.

In 247 of these patients, follow-up angiograms were available for analysis by the core angiographic laboratory. A binary definition of restenosis (≥50% diameter stenosis at angiographic follow-up) was used.

Statistics. Statistical analysis was performed using BMDP (23). Data are presented as mean value ± 1 SD. Categoric data were compared using chi-square analysis. Continuous variables were compared using the Student *t* test. Univariate and multivariable linear regression analyses were used to select the best predictors for reference segment percent cross-sectional narrowing and arc of calcium. Univariate variables with a p value <0.2 were entered into the multivariate model. Backward stepping was used to determine the best predictors of reference segment disease. The correlation coefficient, R and ΔR (change in R caused by adding one or more predicted variables into the model) was presented for the final (multivariable) model.

Univariate and multivariate logistic regression analysis was used to select the best predictors of angiographic restenosis and of late clinical events within 1 year of successful transcatheter therapy. Univariate variables tested included 1) preintervention and postintervention qualitative and quantitative angiographic lesion assessment; 2) preintervention and postintervention quantitative (e.g., lumen cross-sectional area, percent cross-sectional narrowing, arc of calcium) and qualitative (e.g., plaque composition) intravascular ultrasound lesion assessment; and 3) quantitative and qualitative intravascular ultrasound reference segment assessment. Univariate predictors with a p value <0.2 were entered into the multivariate model. A backward elimination and maximum likelihood estimation were used to select the independent predictors of angiographic restenosis and event-free survival.

Results

Clinical variables. Patient demographic data and laboratory results are presented in Table 1.

Angiographic results. Reference segment lumen diameter measured by quantitative coronary angiography was 3.1 ± 0.6 mm.

Table 1. Patient Demographic Data for 884 Native Coronary Artery Reference Segments Studied by Intravascular Ultrasound and Quantitative Coronary Arteriography

Angina	
Stable	230 (26%)
Accelerated pattern	486 (55%)
Postinfarction	115 (13%)
Rest pain	53 (6%)
Smoking history	203 (23%)
Diabetes mellitus	221 (25%)
Hypertension	460 (52%)
Hypercholesterolemia	539 (61%)
Recent myocardial infarction	88 (10%)
Remote myocardial infarction	256 (29%)
Multivessel disease	654 (74%)
Previous coronary bypass graft surgery	141 (16%)
Left ventricular ejection fraction	50 ± 10%
Creatinine	1.2 ± 1.1 mg/dl

Data presented are number (%) of patients or mean value ± SD.

Intravascular ultrasound analysis. Only 60 (6.8%) of 884 reference segments evaluated by intravascular ultrasound were normal or had a three-layered appearance suggesting intimal thickening. Percent cross-sectional narrowing measured 50.7 ± 12.7% (Fig. 1), and the arc of calcium measured 40 ± 78°. When compared with the target lesion, the reference segment external elastic membrane cross-sectional area was similar; the lumen area was larger; and the plaque+media cross-sectional area, percent cross-sectional narrowing, arc of calcium and

Figure 1. Intravascular ultrasound images of right coronary artery showing proximal, mid and distal angiographic reference segments containing significant atherosclerosis with percent cross-sectional narrowings (CNS) of 71%, 57% and 63%, respectively (**single arrows**). **Left**, Left anterior oblique projection; **right**, right anterior oblique projection. Target lesion is indicated by **double arrows**.

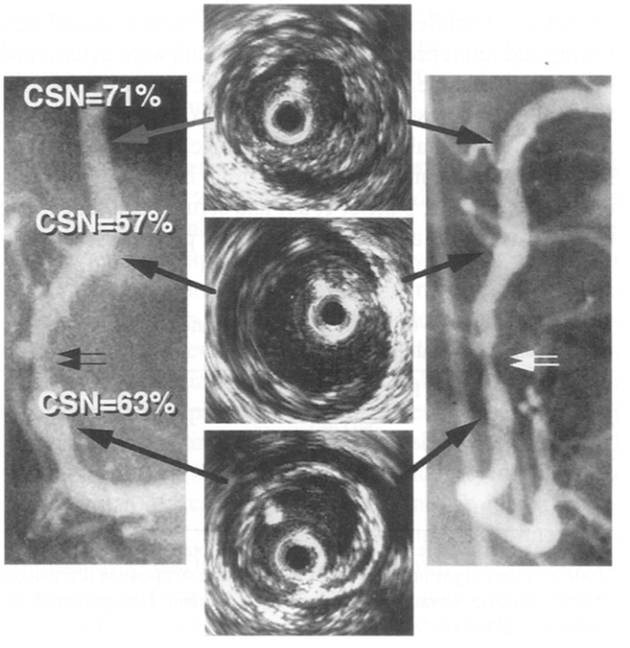

Table 2. Comparison of Reference Segment and Target Lesion Intravascular Ultrasound Measurements

	Reference Segment (mean ± SD)	Target Lesion (mean ± SD)	p Value
EEM CSA (mm^2)	19.5 ± 6.4	19.8 ± 6.9	0.54
Lumen CSA (mm^2)	9.5 ± 5.9	2.8 ± 2.9	< 0.0001
P+M CSA (mm^2)	10.0 ± 4.4	17.0 ± 6.5	< 0.0001
CSN (%)	50.7 ± 12.7	85.4 ± 11.9	< 0.0001
Arc of calcium	40 ± 78°	113 ± 109°	< 0.0001
Eccentricity index	2.7 ± 1.4	3.2 ± 2.1	< 0.0001

CSA = cross-sectional area; CSN = cross-sectional narrowing; EEM = external elastic membrane; P+M = plaque+media.

eccentricity index were smaller (Table 2). Reference segment percent cross-sectional narrowing correlated poorly with target lesion percent cross-sectional narrowing ($r = 0.166$, $p < 0.0001$); however, reference segment arc of calcium correlated somewhat better with target lesion arc of calcium ($r = 0.367$, $p < 0.0001$). Reference segments contained less calcific and dense fibrotic plaque and proportionately more soft plaque elements than did the target lesions ($p < 0.0001$) (Table 3). Reference segment disease did not vary with target lesion location (p = NS) (Table 4).

Reference segment percent cross-sectional narrowing in patients who underwent transcatheter therapy was similar to that in patients studied for diagnostic purposes (50.8 ± 12.8% vs. 49.9 ± 13.6%, respectively, p = NS). However, reference segment arc of calcium was greater in treated patients (43 ± 81° vs. 25 ± 57°, p = 0.015).

Last, reference segment external elastic membrane cross-sectional area correlated with plaque+media cross-sectional area ($r = 0.81$, $p < 0.0001$), further evidence of compensatory (or adaptive) arterial remodeling.

Clinical correlates of reference segment disease. Clinical predictors of reference segment percent cross-sectional narrowing and reference segment arc of calcium were determined by multivariate linear regression analysis. Univariate predictors of percent cross-sectional narrowing (at a significance of $p < 0.05$) were male gender, patient age, diabetes mellitus, hypercholesterolemia, remote myocardial infarction, smoking, multivessel disease, platelet count and serum creatinine levels (but not unstable angina). Multivariate predictors are presented in Table 5. Univariate predictors of reference segment arc of calcium (at a significance of $p < 0.05$) were male gender, patient age, smoking, previous coronary artery bypass graft surgery, hematocrit and serum creatinine levels. Multivariate predictors are shown in Table 6. There was no relation between reference segment plaque composition and clinical presentation.

Table 3. Comparison of Reference Segment and Target Lesion Intravascular Ultrasound Plaque Composition

	Reference Segment*	Target Lesion*†
Normal	60 (7%)	10 (1%)
Calcific	148 (17%)	334 (38%)
Fibrotic	164 (19%)	382 (43%)
Soft	649 (73%)	394 (46%)

*Because these were not mutually exclusive, totals exceed 100%. †$p < 0.0001$, reference segment versus target lesion plaque composition distribution, reference segment versus target lesion calcium location. Data presented are number (%) of lesions.

Table 4. Reference Segment Disease According to Target Lesion Location

	Cross-Sectional Narrowing (%)	Arc of Calcium (degree)
LMCA	52.7 ± 16.3	50 ± 80
LAD	51.2 ± 12.6	38 ± 73
LCx	49.4 ± 13.1	41 ± 81
RCA	49.9 ± 12.7	34 ± 70

Data presented are mean value ± SD. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

Angiographic follow-up. Angiographic follow-up was available in 247 of the 723 patients who underwent transcatheter therapy (mean duration of follow-up 6.4 ± 3.8 months). Reference segment arterial (external elastic membrane) and lumen areas and dimensions and percent cross-sectional narrowing were univariate predictors for subsequent restenosis. However, by multivariate logistic regression analysis, no one reference segment measurement was a consistent independent predictor of subsequent angiographic restenosis, follow-up angiographic percent diameter stenosis or follow-up angiographic minimal lumen diameter. The only consistent independent predictors of follow-up angiography were all lesion related and included the final ultrasound lumen cross-sectional area and final percent cross-sectional narrowing.

Clinical follow-up. Mean duration of clincial follow-up in this study was 7.2 ± 4.2 months. Event-free survival in the 723 patients who underwent transcatheter therapy was 77%. Reference segment lumen area and dimensions and percent cross-sectional narrowing (but not arc of calcium or reference segment plaque composition) were univariate predictors of the need for subsequent target lesion revascularization. However, by multivariate logistic regression analysis, reference segment percent cross-sectional narrowing was not a significant independent predictor of subsequent major ischemic events during the follow-up period. Only lesion-related variables were independent predictors of subsequent clinical events. Similarly, only lesion-related variables were independent predictors of

Table 5. Multivariate Predictors of Reference Segment Percent Cross-Sectional Narrowing

	Coefficient	R	ΔR	p Value
Diabetes mellitus	3.9343	0.1289	0.1289	< 0.001
Male gender	4.6656	0.1796	0.0507	< 0.001
Patient age	0.1422	0.2159	0.0306	< 0.001
Hypercholesterolemia	2.4072	0.2357	0.0198	< 0.01
Multivessel disease	2.4622	0.2513	0.0156	< 0.05

Table 6. Multivariate Predictors of Reference Segment Arc of Calcium

	Coefficient	R	ΔR	p Value
Patient age	0.9707	0.1884	0.1884	< 0.001
Serum creatinine	9.6046	0.2250	0.0366	< 0.005
Hematocrit	−1.7415	0.2452	0.0202	< 0.01

subsequent clinical events in the patients who were studied only for diagnostic purposes and who did not undergo acute revascularization.

Discussion

This systematic analysis of a large consecutive series of patients studied by independent chart review, intravascular ultrasound and quantitative coronary arteriography indicates that atherosclerosis is invariably present in angiographic coronary artery reference segments. In this study of 884 target lesions, only 6.8% of the angiographically normal coronary artery reference segments studied were found to be normal by intravascular ultrasound; the percent cross-sectional narrowing averaged 51 ± 13%. Because we measured the most visually normal cross section within 10 mm of the target lesion, this measurement minimizes the amount of atherosclerosis present in these angiographic reference segments.

Coronary arteriography uses contrast medium to visualize the coronary artery lumen in one or more longitudinal planes, measuring a reduction in lumen caliber rather than the extent of atherosclerosis. Relative measurements of arterial narrowing (percent diameter stenosis) are the most commonly used angiographic measurements of disease significance and are based on absolute diameters of both the apparently "normal" reference segment and the target lesion. Fundamental in this calculation is the assumption that the normal segment is free of significant atherosclerotic disease.

Pathologic studies indicate that the extent of coronary atherosclerosis is underestimated in the analysis of angiographically normal coronary artery segments. An important explanation for the discrepancy between pathologic and angiographic findings is compensatory dilation of the arterial wall as a response to the accumulation of atherosclerotic plaque (24–26). Arterial dilation occurs in direct relation to the cross-sectional area of accumulated plaque. In the present study, the reference site external elastic membrane cross-sectional area correlated strongly with the plaque+media cross-sectional area ($r = 0.81$, $p < 0.0001$). An absolute reduction in lumen diameter does not occur until the lesion occupies >40% to 50% of the area within the internal elastic lamina (40% to 50% cross-sectional narrowing) (25,26). In the present study, the percent cross-sectional narrowing *averaged* 51%. These findings indicate that reference segment disease frequently affects the reference segment lumen dimensions in patients undergoing transcatheter therapy.

Intravascular ultrasound analysis. Although early pathologic studies were criticized because geometric artifacts were potentially introduced by the study of nondistended vessels in vitro, these findings were later confirmed in vivo using high-frequency epicardial echocardiography (27) and, more recently, using intravascular ultrasound (13,14,28). In the present study, reference segment disease tended to parallel target lesion disease. However, reference segment plaque distribution was less eccentric than target lesion plaque distribution. Qualitative analysis of plaque composition showed that reference segments contained relatively less calcium and fibrosis and relatively more soft plaque elements. There was no correlation between clinical presentation (e.g., unstable vs. stable angina, presence or absence of a recent myocardial infarction) and the reference segment percent cross-sectional narrowing or qualitative assessment of plaque composition.

Risk factors for atherosclerosis. Previous studies (29,30) have shown that risk factors for development of coronary atherosclerosis include 1) nonmodifiable genetic factors such as heredity, age and male gender; 2) behavioral factors, such as dietary intake of saturated fatty acids, lack of exercise and cigarette smoking; and 3) atherogenic traits, such as dyslipidemia, hypertension, glucose intolerance and obesity. With the exception of age, dyslipidemia is the most powerful predictor of coronary artery disease.

In the present study, independent clinical predictors of intravascular ultrasound reference segment disease severity (percent cross-sectional narrowing) were diabetes mellitus, male gender, patient age, hypercholesterolemia and presence of multivessel disease.

Risk factors for calcification. Calcification is part of the natural history of atherogenesis (31–33). In the present study, the amount of reference segment calcification tended to parallel target lesion calcium. Previously reported risk factors for coronary artery calcification have included patient age (34,35), primary or secondary hypercalcemia (36), hypercholesterolemia (37,38), renal disease (39), multivessel coronary artery disease (31–33), previous coronary artery bypass graft surgery (22) and history of smoking (22). In the present study, using multivariate analysis, patient age and serum creatinine levels were the most important predictors of reference segment calcification.

Impact on restenosis. Angiographic models of restenosis have indicated that vessel size, as measured by reference lumen diameter, is an independent predictor of restenosis after transcatheter therapy (40–45). Recently, it has also been suggested that atherosclerosis within coronary angiographic reference segments may be an independent predictor of restenosis (46). However, reference lumen diameter is not just a measure of vessel size; it is also influenced by the accumulation of atherosclerotic plaque even though compensatory arterial dilation tends to occur to preserve lumen size. Our study failed to identify a single intravascular ultrasound reference segment measurement (external elastic membrane or lumen cross-sectional area or percent cross-sectional narrowing) that consistently predicted restenosis. However, the number of follow-up angiographic studies was small, and a larger sample size may be necessary to answer this question with certainty.

Impact on clinical events. Findings of the International Atherosclerosis Project and others indicate that cardiovascular morbidity and mortality vary with the extent of coronary artery disease (47,48). Unlike hemodynamic models that suggest an additive effect of multiple lesions (i.e., the presence of one lesion makes another more risky), there instead appears to be a complex relation in which major cardiovascular event rate, morbidity and mortality vary with the overall plaque burden (49,50). Thus, reference segment disease should be an important determinant of long-term patient outcome.

However, >80% of the patients in the present study underwent catheter-based interventions at the time of the intravascular ultrasound study. The presence of reference segment disease was *not* an independent predictor of clinical events in these patients during the follow-up period of 7.2 months. Because the need for target lesion revascularization dominated this follow-up period, lesion-related variables were the only independent predictors of subsequent clinical events.

In ~20% of the patients studied, intravascular ultrasound imaging was performed only for diagnostic purposes. Although these patients did not undergo early revascularization, they were still followed up clinically. In these patients, reference segment disease still did not predict subsequent clinical events.

The propensity of plaques to become unstable and undergo fissuring and thrombosis and cause acute coronary events is directly related to the amount of extracellular lipid (51–55). Thus, the lipid-rich reference segment plaque may be the precursor of the clinically unstable lesion (13,28). However, from the present study it appears that the relation of reference segment disease and long-term patient outcome will require prolonged periods of observation, especially periods of observation remote from the peak occurrence of restenosis. Alternatively, the approach to quantitative and qualitative ultrasound analysis used in this study may be have been limiting. For example, gray-scale image analysis (which is dependent on system and software characteristics) may be inadequate for accurate tissue characterization. Raw radiofrequency signal analysis (although not widely available) is a far more reliable method of separating atherosclerotic plaque into its component elements. Similarly, better measures of the atherosclerotic plaque burden (e.g., plaque volume) may help to identify more sensitive ultrasound markers of subsequent clinical events.

Conclusions. Atherosclerosis is ubiquitous in angiographically normal coronary artery reference segments. Although it contains less fibrocalcific plaque, reference segment disease tends to parallel the severity of target lesion disease and is associated with many of the conventional risk factors for coronary artery disease. However, reference segment disease did *not* predict angiographic restenosis or clinical events in the first 12 months of follow-up. Because of its sensitivity in detecting atherosclerosis in angiographically normal reference segments, intravascular ultrasound should enhance the study of risk factors for atherosclerosis and the results of therapies to control disease progression.

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