Quantitative Arteriography of Apparently Normal Coronary Segments With Nearby or Distant Disease Suggests Presence of Occult, Nonvisualized Atherosclerosis

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Objectives. The aim of this study was to evaluate, using quantitative arteriography, whether the diameter of visually normal coronary segments might be influenced by the relative proximity of visually apparent disease.

Background. Severity of coronary artery lesions is commonly referenced against a presumed normal nearby coronary segment with the presumption that visually smooth segments are relatively free of atherosclerotic disease.

Methods. Angiograms from 136 male patients with focal coronary disease were examined, and visually normal segments in the proximal portions of the major vessels were identified for measurement of mean segment diameters. Normal segments with immediately adjacent disease were compared with normal segments with distal disease in the same vessel and compared with normal segments in vessels for which the only other visible disease was in distant vessels. Angiograms with entirely normal findings from 26 age-matched men with atypical chest pain were used as controls. Segments were measured after nitroglycerin administration by means of computer-assisted quantitation.

Results. Mean diameters of visually normal segments with distant disease were smaller than those of control segments (p < 0.05). Normal left main and proximal left anterior descending coronary artery segments in patients with disease within the same vessel were significantly smaller than normal segments in patients with distant disease (p < 0.05). Normal segments with immediately adjacent disease had smaller mean diameters than normal segments with distal disease in the same vessel (p < 0.05).

Conclusions. Visually normal coronary segments have progressively smaller lumen diameters, depending on the relative proximity of visible disease. Measurement of percent stenosis on the basis of the diameter of apparently normal adjacent reference segments can result in underestimation of coronary lesion severity.

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Coronary angiography is widely accepted as a definitive method for evaluating the extent and severity of coronary artery disease. Clinical decisions and studies of coronary artery disease commonly use percent stenosis to report lesion severity. An assumption in calculating percent stenosis is that a visibly normal reference segment of the coronary artery adjacent to the lesion is free from atherosclerosis. However, there is considerable evidence from anatomic and physiologic studies that coronary atherosclerosis is far more extensive than visually estimated by conventional angiography (1-6). Inapparent or mild angiographic lumen narrowing may, in reality, correspond to a substantial concentric atheroma mass (5).

Quantitative coronary angiography has been shown to measure coronary dimensions with a high degree of accuracy and reproducibility (7). With quantitative angiographic techniques, it may be possible to detect differences in coronary artery lumen diameters that reflect the presence of diffuse and otherwise inapparent atherosclerosis. This study compares lumen diameters from angiographically apparently normal coronary artery segments in patients with focal disease elsewhere with segment diameters in control subjects with completely normal coronary arteries.

Methods

Coronary disease and control subjects. One hundred thirty-six coronary angiograms from male patients with definite coronary artery disease but containing one or more visually normal segments in the proximal portions of the major coronary arteries were selected for study. These visually normal segments were free of lumen irregularities and were located in the left main coronary artery or proximal portions of the left anterior descending, left circumflex or right coronary arteries.

Coronary angiograms with entirely normal findings from 26 male subjects of similar age provided control segments. These

Table 1. Number of Visually Normal Coronary Artery Segments Studied in Each Group

	No. of Normal Segments in 26 Normal Control Subjects	No. of "Normal" Segments in 136 Patients With Coronary Artery Disease			
		Disease Limited to Distant Location	Disease Anywhere Within the Same Vessel	Disease Within the Same Vessel and Immediately Adjacent	Disease Within the Same Vessel but Distal Location
LM	21	5	66	52	14
pLAD	22	16	21	9	12
pLCx	23	21	37	16	21
pRCA	23	20	26	10	16
Total	89	62	150	87	63

Data presented are number of visually normal segments. LM = left main coronary artery; pLAD = proximal left anterior descending coronary artery; pLCx = proximal left circumflex coronary artery; pRCA = proximal right coronary artery.

subjects had angiography for atypical chest pain and were free of left ventricular hypertrophy, valvular heart disease, cardiomyopathy or other cardiac disease. All angiograms were obtained using 5- to 7-in. (12.7- to 17.8-mm) intensifier modes and were considered suitable for analysis by computer-assisted quantitative coronary arteriography.

Cardiac catheterization. Selective coronary arteriography was performed using the percutaneous femoral approach. Sublingual nitroglycerin (0.4 mg) was given 3 min before all contrast injections to patients with coronary artery disease and to control subjects to minimize the effect of varying vascular tone and to enhance visualization of vascular detail. Catheters with cylindric metallic (tantalum) markers of precisely known diameters were used to provide calibration for 89% of subjects because of their precision and reproducibility (8). Nonmetallic catheter margins were used for the remainder. Films were recorded at 30 to 45 frames/s. Multiple projections including cranial and caudal angulated views were obtained for all patients.

Quantitative coronary angiography. All coronary cineangiographic films were analyzed by computer-assisted edge detection using a 35-mm cine film transport mechanism mounted on a movable stage (9). End-diastolic cine frames, identified by an electrocardiogram-triggered mark on the frames, were selected and magnified (×3.5). Coronary segments were centered in the image field. The image was then digitized with a video processor controlled by a desktop computer and displayed on a graphic computer terminal linked to a light pen. The margins of either the catheter or coronary segments were traced manually using the light pen. Using these lines as initial search locations, the automatic edge-finding algorithm drew and smoothed the edges, defining the edge as the peak of the first derivative of the gray-scale density gradient perpendicular to the long axis of the catheter or vessel as estimated from the initial manual tracings. When the computer algorithm was unable to resolve vessel boundaries in areas of noise or vessel crossings, manual editing of short segments of boundary with the light pen was used to correct the computer-generated boundary. At no time did the length

of a manually entered margin exceed 20% of the total length of the quantitated segment. After the light pen indicated the segment's starting and end points, the mean diameter of the segment was computed from perpendiculars constructed through the length of a computer-generated center line. The mean diameter of the segment was used for the analysis. The quantitation system has been shown to measure coronary dimensions from different end-diastolic cine frames with an average standard deviation of the measurement differences of ± 0.033 mm (10). Three standard deviations, corresponding to 0.1 mm, is considered the threshold for a "significant" difference.

Cineangiographic analysis. Only coronary segments that were clearly visualized were quantitated and used for analysis. Projections were selected that best displayed the segment in profile. Segments were excluded if they were too short or overlapped other vessels. Segment lengths varied from 0.5 to 3.5 cm and did not extend across major side branches that would affect mean diameter.

In patients with coronary disease, one or more proximal segments were identified as visually normal by two experienced observers before quantitative measurements. A total of 212 visually normal left main coronary artery, proximal left anterior descending artery, proximal left circumflex artery and proximal right coronary artery segments were identified in the 136 patients (Table 1). The average of 1.6 visually normal proximal segments per patient reflects the fact that most patients in this study had one- or two-vessel disease, although patients with three-vessel disease and normal left main coronary artery segments were also included. The visually normal segments were then divided into two main groups according to the location of coronary disease evident elsewhere in the coronary arteriogram (Fig. 1). Normal segments in patients without visible disease elsewhere within the same coronary vessel but with visible disease present in other vessels were considered to have *distant* coronary artery disease. For the left main coronary artery, this meant that there was no visible disease in the entire left anterior descending artery and left circumflex artery vessels (i.e., disease present in the right

Figure 1. Criteria for relating normal segments with distant coronary disease to disease within the same vessel and immediately adjacent and to disease within the same vessel but distal are displayed for each normal segment location. Diagrams are drawn in the left anterior oblique projection. LM = left main coronary artery; pLAD = proximal left anterior descending coronary artery; pLCX = proximal left circumflex coronary artery; pRCA = proximal right coronary artery.
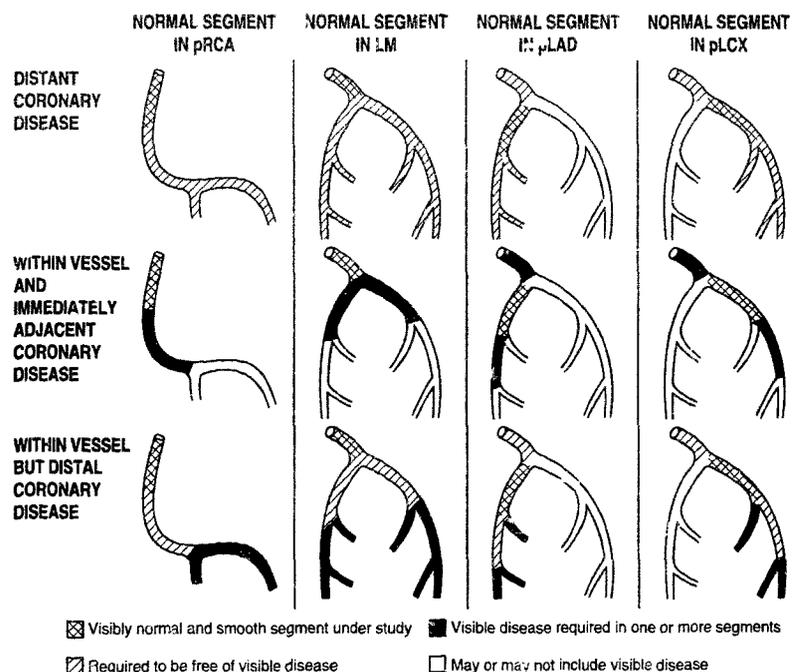
coronary artery only). For proximal left anterior descending artery and proximal left circumflex artery normal segments, there was no further disease in the same vessel, including branches and the left main coronary artery. For normal segments in the proximal right coronary artery, there was no disease distally in the same vessel, including branches (i.e., disease present in the left coronary distribution).

Visually normal proximal left anterior descending artery, proximal left circumflex artery and proximal right coronary artery segments in patients who had visible disease elsewhere within the same vessel were considered to have within-vessel coronary disease. For normal left main coronary artery segments, adjacent disease included abnormal segments in the left anterior descending artery, left circumflex artery or both. These visibly normal segments, exhibiting coronary disease within the same vessel, were further subdivided into those with immediately adjacent abnormal segments and a second group with visibly normal intervening segments between the normal segment and more distal diseased segments (Fig. 1). All assignments of normal segments as associated with distant disease, with distal disease within the same vessel or with immediately adjacent disease were made without prior knowledge of the coronary dimensions. Because of size differences among different proximal segments, each was analyzed separately.

Statistical methods. Analysis of variance was used to make multigroup comparisons. The Fisher protected least significant difference (PLSD) multiple comparison test was used when the overall F test was significant. A Student unpaired t test was used for comparing two groups of unpaired data. Differences were considered significant when the confidence limits exceeded 95% ($p < 0.05$). The results are expressed as mean value ± SD.

Results

The mean age of patients with coronary artery disease (mean age 49 ± 5 years, range 35 to 55) was not significantly different from that of control subjects (mean age 47 ± 7 years, range 36 to 54) Similarly, the body surface area of patients with coronary disease (2.05 m^2) was not different from that of control subjects (2.03 m^2). Both measurements were distributed in a similar manner between the coronary disease and control groups. The number of normal segments studied in each group for each vessel is shown in Table 1. Measurements of 89 left main coronary artery, proximal left anterior descending artery, proximal left circumflex artery and proximal right coronary artery segments were obtained from the 26 control patients who had completely normal findings on the coronary arteriogram. In some subjects (five for left main coronary artery, four for proximal left anterior descending artery, three for proximal left circumflex artery, three for proximal right coronary artery), one or more segments were too short or obscured to be measured.

Mean diameters of normal segments in the control subjects with entirely normal coronary arteries and in patients with coronary disease are listed in Table 2. Mean diameters of left main coronary artery normal segments in patients having distant coronary disease and in patients having disease within the same vessel were both smaller than mean diameters of left main coronary artery segments from control subjects (Fig. 2) (p = NS for the group with distant coronary disease, p < 0.05

Table 2. Mean Diameters of Normal Segments by Location and by Clinical and Angiographic Group

	Normal Segment Diameter (mm)			
	LM	pLAD	ʌ	pi
Subjects with entirely normal coronary arteries (mm)	4.48 ± 0.50	3.55 ± 0.43	ʳ ʳ ʾ.	ɔ.ʾ ʾ 0.43
Patients with				
Distant disease	4.35 ± 0.31	3.12 ± 0.42ˢ	2.95 ± 0.36	3.22 ± 0.05
Disease within same vessel	3.82 ± 0.45*	2.80 ± 0.49	2.73 ± 0.67*	2.98 ± 0.55ᵀ
Distal location	4.02 ± 0.30	3.00 ± 0.53	2.95 ± 0.65	3.17 ± 0.50
Adjacent location	3.76 ± 0.29†	2.54 ± 0.31†	2.44 ± 0.61†	2.68 ± 0.53†

*p < 0.05 versus control subjects without coronary disease. †p < 0.01 versus with disease within same vessel but distal location. Abbreviations as in Table 1.

for the group with within-vessel disease). Mean diameters of the left main coronary artery normal segments in patients with distant disease were significantly larger than normal segments with within-vessel disease (p < 0.05).

Mean diameters of proximal left anterior descending artery normal segments in patients having distant coronary disease and in patients having disease within the same vessel were both smaller than corresponding mean diameters of proximal left anterior descending artery segments from control subjects (Fig. 2) (p < 0.05 for both groups). Mean diameters of proximal left anterior descending artery normal segments in patients with distant disease were larger than those of normal segments with adjacent disease (p < 0.05).

Mean diameters of proximal left circumflex artery normal segments in patients having distant coronary disease and in patients having disease within the same vessel were smaller than corresponding mean segment diameters from control subjects (Fig. 2) (p = NS for the group with distant coronary disease, p < 0.05 for the group with adjacent disease). Mean

diameters of the proximal left circumflex artery normal segments in patients with distant disease were larger, but not significantly, than normal segments with adjacent disease.

Mean diameters of proximal right coronary artery normal segments in patients having distant coronary disease and in patients having disease within the same vessel were smaller than corresponding segment diameters from control subjects (Table 2, Fig. 2) (p = NS for the group with distant coronary disease, p < 0.05 for the group with adjacent disease). Mean diameters of the proximal right coronary artery normal segments in patients with distant disease were larger, but not significantly, than normal segments with adjacent disease.

Mean diameters of normal segments in all four proximal locations in patients with immediately adjacent diseased segments were significantly smaller than diameters of normal segments in control subjects (p < 0.05 for all locations) and significantly smaller than diameters in patients with distal disease within the same vessel (Table 2, Fig. 3) (p < 0.05 for all locations).
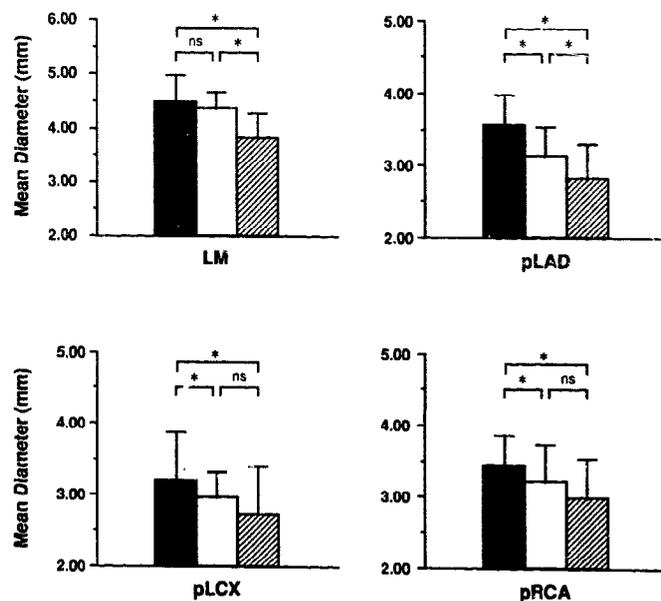

Figure 2. Mean diameters of visually normal segments from the left main (LM) and proximal portions of left anterior descending (pLAD), left circumflex (pLCX) and right (pRCA) coronary arteries are shown for each of three groups of subjects: normal subjects (solid bars), those patients with distant coronary disease (open bars) and those with disease within the same vessel (hatched bars). Values are expressed as mean ± SD. *p < 0.05.
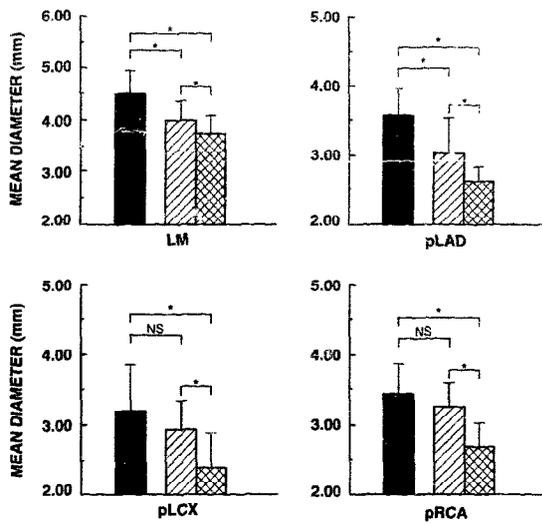
Figure 3. Mean diameters of the visually normal left main (LM), proximal left anterior descending (pLAD), left circumflex (pLCX) and right (pRCA) coronary artery normal segments are shown for three groups of subjects: normal subjects (solid bars), those patients with disease distally within the same vessel (hatched bars) and those with disease immediately adjacent to the normal segment (crosshatched bars). Mean diameters of all visibly normal segments with immediately adjacent disease were significantly smaller than segments with distal disease. *p < 0.05.

Discussion

Angiographically inapparent coronary disease. Post-mortem studies of coronary arteries of patients with coronary artery disease have demonstrated that atherosclerosis is more widespread than is predicted from coronary angiograms (1,5). Arnett et al. (1), in a semiquantitative pathologic study, found that 90% of 467 segments of coronary artery examined in patients with coronary artery disease had diffuse atherosclerosis. The concentric homogeneous thickening of the subintimal layer of the atherosclerotic process appeared to be the major reason for angiographic underestimation of coronary narrowing. It is also true that postmortem studies tend to skew toward the most severe cases (11). When a vessel is undistended, lumen collapse may exaggerate the apparent severity of atherosclerosis. It is also true that postmortem studies tend to skew toward the most severe cases. Therefore, the direct applicability of these pathologic data to vessels studied in vivo under normal distending pressure is uncertain.

McPherson et al. (3), by studying the epicardial coronary arteries at the time of cardiac surgery using intraoperative high-frequency echocardiography, demonstrated the presence of substantial diffuse intimal atherosclerosis even when angiograms revealed only discrete lesions. Many segments that had absent or apparently trivial angiographic narrowing were found to have severe atherosclerosis. Recent studies using intravascular ultrasound have demonstrated an often extensive and severe, diffuse atherosclerosis in angiographically apparently normal segments (12).

The present study, using quantitative coronary angiography, shows that angiographically "normal" coronary segments in patients with coronary artery disease elsewhere are significantly smaller than age- and gender-matched control subjects. In addition, the degree of diameter reduction in visually normal segments is related to the proximity of the coronary disease. Furthermore, even in coronary vessels without visible disease throughout their length, normal segment dimensions are smaller than those of control segments, suggesting the presence of intramural atherosclerosis without lumen encroachment. Our findings conform to previous observations made in pathologic examinations, intraoperative epicardial echocardiographic and in vivo intravascular ultrasound studies. Our findings are also consistent with a recent study by Seiler et al. (13). In that study, which used a three-dimensional reconstruction technique for analyzing coronary angiograms, coronary artery lumen area in patients with coronary disease was found to be 30% to 50% smaller than the normal size predicted from the summed distal dependent branch lengths and regional left ventricular mass. Seiler et al. also suggested that this resulted from the presence of diffuse atherosclerosis in these segments.

Limitations of angiographic coronary dimensions. In addition to the presence of diffuse atherosclerosis, other factors, including proximal or distal segment location, age, gender, cardiac size, valvular lesions, ventricular hypertrophy and coronary vasomotor tone, can affect vessel dimension (14-19). We tried to minimize the impact of these factors in this study by using only the left main and the proximal portions of three main coronary arteries, by using age- and gender-matched control subjects, by excluding patients with valvular lesions and other cardiac disease and by using nitroglycerin to eliminate variations in basal vasomotor tone. Hypertensive heart disease with myocardial hypertrophy can affect coronary size; however, the number of subjects in each group is sufficient to mitigate individual variation. It seems reasonable to conclude that the differences in lumen diameters of apparently normal segments between control subjects and patients with coronary disease and between segments associated with distant, distal or adjacent visible disease result from the presence of diffuse atherosclerosis. This conclusion is consistent with the more definitive findings from direct visualization of coronary arteries by intravascular ultrasound (20,21) and from postmortem examination.

Theoretically, lumen diameters below thresholds defined from normal subjects by quantitative coronary angiography might be used to identify regions of diffuse atherosclerosis in visually normal coronary segments. However, it should be emphasized that the patient-to-patient variability of coronary dimensions is large (14). Use of quantitative measurements in an individual patient to detect concentric atherosclerosis in visibly normal segments is likely to have low sensitivity unless the changes exceed previously published thresholds.

The coronary diameter measurements in this study were obtained on the basis of a single angiographic projection of the segments. It is often not possible to obtain truly orthogonal

projections of the coronary artery segments analyzed in this study. In previous studies, 14% to 50% of coronary segments could not be adequately imaged in orthogonal projections (22,23). Furthermore, intravascular ultrasound studies of normal or nearly normal coronary arteries have demonstrated a circular cross-sectional profile such that a single diameter measurement accurately reflects the diameter of the lumen from all perspectives (unpublished observation). Thus, diameter measurements from multiple projections should not alter the conclusions of this study.

Limitations of reference diameter as an index of normality. Percent stenosis, which is a function of both lesion and adjacent "normal" reference diameter, has been questioned as a guide to the functional significance of a lesion (6). Measurement of the physiologic significance of coronary artery lesions by Harrison et al. (2), using Doppler-derived coronary reactive hyperemic responses after transient coronary occlusion at the time of cardiac surgery, documented that the hemodynamic significance of a coronary stenosis was more accurately predicted by the vessel minimal cross-sectional area than by percent cross-sectional area or percent diameter stenosis. They also demonstrated a striking degree of heterogeneity of cross-sectional area of the proximal left anterior descending segment adjacent to an obstructive lesion. This heterogeneity is best explained by the presence of a variable degree of diffuse coronary atherosclerosis undetectable by conventional coronary angiography and accounts for the failure of percent stenosis to correlate with physiologic flow impairment. Our findings confirm that the assumption that the adjacent segment is free from disease, on which measurements of percent stenosis are critically dependent, is incorrect.

The results of this study suggest that coronary atherosclerosis is more extensive than estimated by conventional visual analysis of angiography. Our quantitative measurements were matched against control subjects who had no visibly evident coronary disease. It is possible that subintimal thickening is present in the control subjects; however, this would mean that the observed differences were underestimated.

Angiographically visible coronary disease typically depends on recognition of variations, eccentricities and irregularities in lumen diameter. The atheromas that produce these visibly evident lesions are typically more advanced and microscopically complex than the smooth subintimal thickening that produces concentric but angiographically undetectable disease. Moreover, Glagov et al. (24) have shown that early atheroma development may be accompanied by vessel wall compensation to minimize lumen encroachment. Detection of this angiographically "invisible" coronary disease has been accomplished in this study using quantitative measurements and matched comparison subjects.

Summary. Quantitative angiographic results as well as the findings of intravascular ultrasound suggest that angiographically evident disease in coronary artery disease patients represents only a small fraction of the total vascular involvement by atherosclerosis. In a very broad sense, these findings serve to remind physicians dealing with cardiovascular diseases that

atherosclerosis is a diffuse process—this fact is often forgotten, with most emphasis being placed on the focal manifestations of this disease. Moreover, measurement of percent stenosis on the basis of the diameter of an ostensibly normal reference segment is subject to considerable variability and underestimation of actual severity compared with estimates when a truly normal reference segment is available.

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