Arterial Calcification and Not Lumen Stenosis Is Highly Correlated With Atherosclerotic Plaque Burden in Humans: A Histologic Study of 723 Coronary Artery Segments Using Nondecalcifying Methodology

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Objectives. This study was designed to evaluate whether calcium deposition in the coronary arteries is related to atherosclerotic plaque burden and narrowing of the arterial lumen.

Background. Many studies have recently documented the feasibility of electron beam computed tomography to detect and quantify coronary artery calcification in patients. Although these studies suggest a general relation between calcification and severity of coronary artery disease, the value of coronary calcium in defining atherosclerotic plaque and coronary lumen narrowing is unclear. Previous pathologic comparisons have failed to detail such a relation in identical histologic sections. This finding may be due to atherosclerotic remodeling.

Methods. A total of 37 nondecalcified coronary arteries were processed, sectioned at 3-mm intervals (723 sections) and evaluated by computer planimetry and densitometry.

Results. A significant relation between calcium area and plaque area was found on a per-heart basis (n = 13, r = 0.87, p < 0.0001), per-artery basis (left anterior descending coronary artery [LAD]: n = 13, r = 0.89, p < 0.0001; left circumflex coronary artery [LCx]: n = 11, r = 0.7, p < 0.001; right coronary artery [RCA]: n = 13, r = 0.89, p < 0.0001) and per-segment basis (n = 723, r = 0.52, p < 0.0001). In contrast, a poor relation existed between residual histologic lumen area and calcium area for individual hearts (r = 0.48, p = NS), individual coronary arteries (LAD: r = 0.59, p = NS; LCx: r = 0.10, p = NS; RCA: r = 0.59, p = NS) and coronary segments (r = 0.07, p = NS). Longitudinal changes in external elastic lamina areas were highly correlated with changes in plaque area values (r = 0.60, p < 0.0001), whereas lumen area did not correlate with plaque size change (r = 0.01, p = NS).

Conclusions. Coronary calcium quantification is an excellent method of assessing atherosclerotic plaque presence at individual artery sites. Moreover, the amount of calcium correlates with the overall magnitude of atherosclerotic plaque burden. This study suggests that the remodeling phenomenon is the likely explanation for the lack of a good predictive value between lumen narrowing and quantification of mural calcification.

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Occlusive coronary artery disease (CAD) is a major cause of death in the United States (1). It is well known that atherosclerosis begins early in life and typically progresses silently until clinical symptoms occur late in the disease (2). Early detection of asymptomatic coronary atherosclerosis has been hindered by the lack of sensitive and specific diagnostic tests (3,4). Coronary arterial calcification occurs almost exclusively in atherosclerotic plaques (5), and a high degree of correlation exists between severity of CAD and calcification of the vessel wall (6–10). Although the process of calcification is incompletely understood (11), calcified lesions found in coronary arteries have been considered for many years to be markers of advanced atherosclerotic disease (5). However, several studies (12–14) have recently shown that intramural calcium deposition may occur early in atherosclerosis, and its extent follows atherosclerotic plaque development.

A growing number of investigations (15–17) have shown the feasibility of using electron beam computed tomographic (EBCT) scanning to detect and quantify coronary artery calcification in living subjects. Although these studies suggest a general relation between calcification and the severity of angiographic disease, the interpretation of these scans in predicting lumen narrowing remains unclear (18–20). Calcification instead may have a closer association with segmental histopathologic disease severity (21). The lack of a good predictive value between calcification and angiography may be due to the phenomenon of remodeling, where arteries increase in size, compensating for atherosclerotic plaque growth to preserve lumen size (22).

Abbreviations and Acronyms

CAD	=	coronary artery disease
EBCT	=	electron beam computed tomography (tomographic)
EEL	=	external elastic lamina
GMA	=	glycolmethylmethacrylate
IEL	=	internal elastic lamina
IROI	=	intensity range of interest
LAD	=	left anterior descending coronary artery
LCx	=	left circumflex coronary artery
RCA	=	right coronary artery

The purpose of the present study was to quantitate the relation between calcium area, lumen stenosis, atherosclerotic plaque area and remodeling in autopsy-derived coronary artery specimens. Previous pathologic (21,23), angiographic (20,24) and intravascular ultrasound studies (25) have not specifically examined calcium in terms of a quantitative definition of disease in the identical arterial segments.

Methods

Study group. Thirteen intact human hearts were obtained from consecutive autopsies of 12 men (31 to 84 years old, mean [±SD] 54 ± 18) and one woman (41 years old). No attempt was made to select hearts of patients with atherosclerotic disease, and only two patients had an antemortem diagnosis of CAD and died of complications of myocardial infarction. Of the remaining patients, four died of metastatic carcinoma, one of peritonitis, one of trauma, one of carbon monoxide poisoning, one of alcoholic hepatitis and one of idiopathic cardiac failure. No known diabetes (defined as blood serum glucose >100 mg/dl), hypercholesterolemia (defined as total cholesterol blood level >200 mg/dl) or hypertension (defined as blood pressure values >150/90 mm Hg) was documented in this series of patients. Five patients were smokers at the time of death and three had a positive family history for CAD.

Autopsied specimens. Each heart was perfused and fixed at physiologic pressure to maintain coronary artery morphologic integrity. The three major coronary arteries of each heart were dissected free, placed in 70% ethanol and dehydrated through ascending concentrations of alcohol. Sequential blocks were obtained from 3-mm cut intervals along the entire length of all arteries (~9 cm for each artery or until the artery diameter was too small to sample).

Other histopathologic studies of calcified coronary arteries typically use decalcification to facilitate sectioning the vessel. Because the primary purpose of this study was to quantify calcification and atherosclerosis in identical sections, a *nondecalcifying* technique was used in the samples preparation. Coronary artery blocks were embedded in glycolmethylmethacrylate (GMA) using a temperature-controlled method previously reported (14). Briefly, arteries were infiltrated for 3 days in a mixture of 81% (vol/vol) uninhibited methylmethacrylate, 8% (wt/vol) polyethylene glycol distearate, 6.5% (vol/vol) 2-hydroxyethyl methacrylate, 4% dibutylphthalate and 0.65% benzoyl peroxide. The specimens were then placed in a fresh monomer containing an accelerator and allowed to polymerize onto aluminum chucks in a vacuum chamber at room temperature under nitrogen atmosphere. The hardness and clarity of this plastic monomer allowed excellent preservation of calcium content and cell morphology during preparation of sections.

Cross sections 200-μm thick were cut from the GMA-embedded specimens using an Isomet low speed saw (Buhler Ltd.) and then ground on a glass stone to 100-μm thickness. Sections were stained with hematoxylin-eosin, Lawson's elastic van Gieson and Goldner's-Masson trichrome. Two arteries were damaged during sectioning. Of the remaining 37 coronary arteries, a total of 723 coronary artery sections, representing sequential sections of the entire arteries, were prepared for analysis.

Contact microradiography. The 100-μm thick cross sections were placed on a spectroscopic plate (Eastman Kodak) for contact microradiography and exposed to radiation in the low kV(p) range (20 kV) for 5 min. The microradiographs were then placed in developer liquid (Eastman Kodak), fixed, washed in distilled water for 10 min and dried. Computerized planimetry was performed on a total of 723 microradiograms as described below.

Histologic measurements. Each arterial segment was captured using a microscope objective ($\times$1), and the following morphometric measurements were made by computerized planimetry: 1) lumen area; 2) area circumscribed by the internal elastic lamina (IEL); and 3) the innermost border of the external elastic lamina (EEL). In areas where the integrity of the IEL was destroyed or disrupted, an arc representing the IEL-damaged segment was visually interpolated from contiguous areas in which the integrity of the IEL was present. If more than 25% of the arterial circumference did not allow adequate IEL visualization, the sample was excluded from analysis. Histologic examples are shown in Figure 1, A and B.

Calcium area measurements were performed as follows. The contact microradiography image was captured and digitized in the computer, and an intensity histogram was selected that displayed the distribution of gray levels (from black to white) within the image. Calcific areas were differentiated against the black background by setting the upper and the lower threshold values for an intensity range of interest (IROI) that yielded the best identification of calcific regions as judged by the operator. This method does not require the eye to trace intricate calcified regions, so that accuracy is maintained for measuring regions of diffuse or complex, interstitial deposition of calcium within atheromatous plaques. The number of calcific pixels within the IROI was then automatically counted by the computer. This value was divided by a pixel size calibration factor (k, pixels/mm^2) to obtain the area of calcium in square millimeters. The calibration constant k was calculated on a standardized microscope slide bearing a scored 1-mm square as the number of pixel counts within 1 mm^2 (pixel count/mm^2). The imaging system resolution was 0.009 mm/
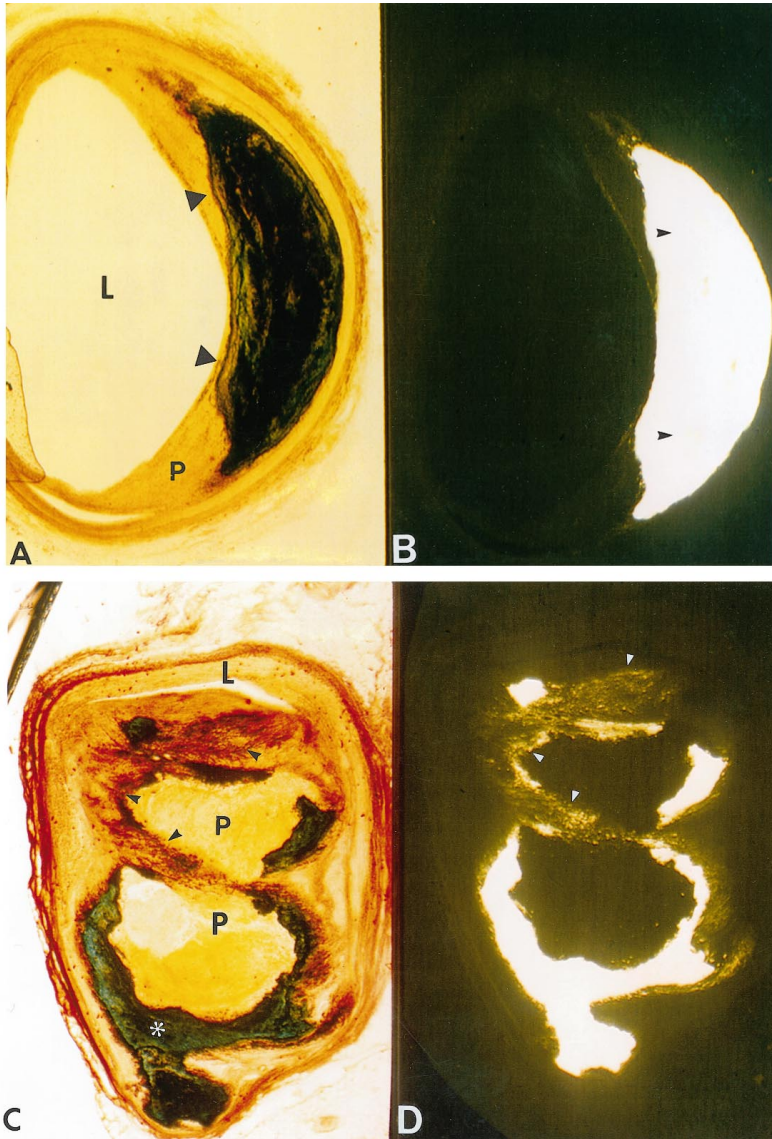
Figure 1. Photomicrographs of nondecalcified human coronary arteries. **A and B,** Extensive calcium (**arrowheads**) is deposited relatively uniformly within a noncritical plaque (P), as shown by light microscopy (**A,** elastic van Gieson ×4, reduced by 35%) and by microradiography (**B**). **C and D,** In contrast, a large plaque with near total lumen (L) occlusion shows a large peripheral focus of dense calcium (**asterisk**) and a rim of microfocal mineralization (**arrowheads**) scatter distributed around the vessel circumference by light microscopy (**C,** elastic van Gieson ×2, reduced by 35%) and by microradiography (**D**).

pixel. Consistency was determined throughout the computer analysis by repeated analysis of 10 fields from a microradiograph demonstrating a variation of <3%. A significant correlation of pixel counts (i.e., sectional counts) was observed between two independent observers (r = 0.91, p < 0.005).

Definition of terms. Plaque area was calculated as the difference between IEL area and lumen area for each segment (IEL area minus lumen area). The difference in consecutive lumen area values (Δlumen), IEL area values (ΔIEL), EEL area values (ΔEEL) and plaque area values (Δplaque) were also calculated. These values reflect the longitudinal change in the lumen, IEL, EEL and plaque areas along each artery.

Histopathologic area stenosis was calculated for each section by the formula

Percent area stenosis = (1 − [Lumen area/IEL area]) × 100.

Data were related for each of the histologic variables for whole hearts (n = 13), individual coronary arteries (n = 37) and coronary artery segments (n = 723).

Statistics. Data are expressed as the mean value ± SD. Correlations between histologic measurements were using a linear regression model. The square-root transform was used to minimize the effect of data skewness (nonnormal distribution of values) on the correlation (26). Statistical significance of correlation was determined using the Pearson product moment method. Statistical significance was assumed at p < 0.05.

Results

Histologic distribution of CAD. At histologic examination atherosclerotic disease severity was variably represented. Two hearts had maximal stenosis between 25% and 50%. In eight patients maximal coronary stenosis was between 50% and 75% and in three patients maximal stenosis was ≥75%. The percent area stenosis distribution for the 723 histologic segments was as follows: <25% stenosis in 39.6% of the total (n = 286); between 26% and 50% stenosis in 35.1% of the total (n = 254);

between 51% and 75% stenosis in 20.6% of the total (n = 149) and >75% stenosis in 4.7% of the total (n = 34). The mean percent area stenosis was 35.9 ± 21.2%.

The mean (±SD) lumen area for the 723 segments was 4.24 ± 2.68 mm^2 (range 0.1 to 18.4). The mean IEL area was 7.09 ± 4.63 mm^2 (range 0.6 to 34.1), and the mean EEL area was 8.41 ± 5.23 mm^2 (range 0.9 to 35.7). The mean total plaque area was 2.84 ± 3.14 mm^2 (range 0.1 to 32.5). Of the 723 coronary segments evaluated, 69 (9.5%) had no detectable coronary artery calcification (zero mm^2 of calcium). In the remaining segments, coronary calcific area was 0.27 ± 0.91 mm^2 (range 0.13 to 6.8). Most frequently, calcific areas appeared as homogeneous, large calcific blocks within the atherosclerotic plaque (Fig. 1A). In some cases, calcium deposition was scattered around the vessel wall (Fig. 1B).

Correlation of age with whole-heart coronary plaque and calcium area. There were high correlations between patient age and the square root of the summed whole-heart plaque area values (n = 13, r = 0.76, p < 0.002, data not shown), and between patient age and the square root of the summed whole-heart calcium area values (n = 13, r = 0.82, p < 0.0005, data not shown). Both plaque and calcium areas increased directly with advancing patient age.

Correlation between coronary artery plaque area and calcium area. Average whole-heart, summed histologic coronary plaque area was 157.7 ± 131.3 mm^2 (range 15.2 to 481.4), and average whole-heart, summed histologic calcium area was 29 ± 46.7 mm^2 (range 0.58 to 156.2). The average of plaque area values for the left anterior descending coronary arteries (LAD) was 7.30 ± 55 mm^2, and the average of calcium areas was 1.54 ± 13 mm^2. For left circumflex coronary arteries (LCx), the average plaque area was 3.35 ± 19.9 mm^2, and the average calcium area was 0.34 ± 2.27 mm^2. The right coronary artery (RCA) values were 5.64 ± 52.2 mm^2 and 0.72 ± 6.99 mm^2 for the average plaque area and average calcium area, respectively.

Results of linear regression analysis between the square root of coronary calcium area values and the square root of plaque area values for each of the 723 coronary artery segments are shown in Figure 2A. Correlation was significant (r = 0.52, p < 0.0001). Data were also correlated on a per-heart basis (n = 13, r = 0.87, p < 0.0001; data not shown) and on a per-artery basis (LAD: n = 13, r = 0.89, p < 0.0001; LCx: n = 11, r = 0.7, p < 0.001; RCA: n = 13, r = 0.89, p < 0.0001; data not shown).

However, in segments demonstrating little or no detectable calcium by microradiography (left part of x-axis in Fig. 2A), there were several in which atherosclerotic plaque was variably present at histologic examination. Figure 3A shows one artery in which there was diffuse segmental coronary plaque and no associated coronary calcium area. In this artery the total coronary plaque area was 114.87 mm^2, with a total associated calcium area of 2.58 mm^2. In contrast, Figure 3B shows data from another coronary artery in which there was a good correlation between the segmental presence of plaque (total plaque area 126.6 mm^2) and calcification (total calcific area
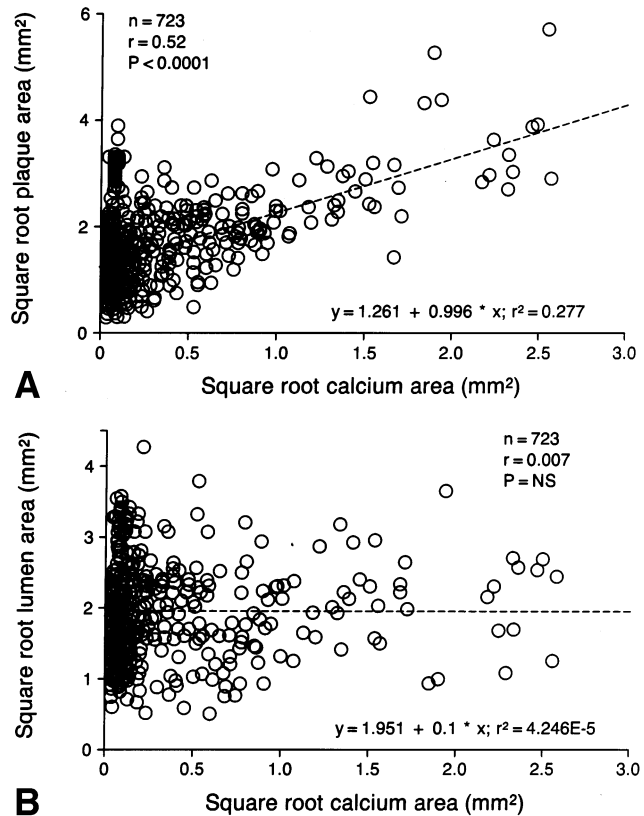

Figure 2. A, Graph showing square root of coronary calcium area values (mm^2) detected by histopathologic and microradiographic analysis versus square root of plaque area values (mm^2) for each of the 723 coronary artery segments. **B,** Graph showing square root of coronary calcium area (mm^2) detected by histopathologic and microradiographic analysis versus square root of lumen area (mm^2) for each of the 723 coronary artery segments. No relation existed.

32.04 mm^2) longitudinally from the coronary ostium along the artery. These two extremes demonstrate the potential for individual variability of calcification in atherosclerosis.

Correlation between coronary lumen area and calcium area. The total (summed, whole-heart) histologic lumen areas and the total (summed, whole-heart) histologic calcium areas were correlated for individual hearts (n = 13, r = 0.48, p = NS; data not shown) and for individual coronary arteries (LAD: n = 13, r = 0.59, p = NS; LCx: n = 11, r = 0.10, p = NS; RCA: n = 13, r = 0.59, p = NS; data not shown). Linear correlation between the square root of coronary calcium area values (x-axis) and the square root of lumen area values (y-axis) for each of the 723 coronary segments is shown in Figure 2B (r = 0.07, p = NS).

Average whole-heart, summed histologic lumen area was 235.4 ± 143.6 mm^2 (range 70.9 to 518.8). The average lumen coronary artery areas were 8.22 ± 61.9 mm^2 for the LAD, 5.81 ± 34.4 mm^2 for the LCx and 9.8 ± 91.34 mm^2 for the RCA.

To further analyze the relation between coronary artery calcification and corresponding lumen area stenosis, the 723 coronary artery segments were divided into two different
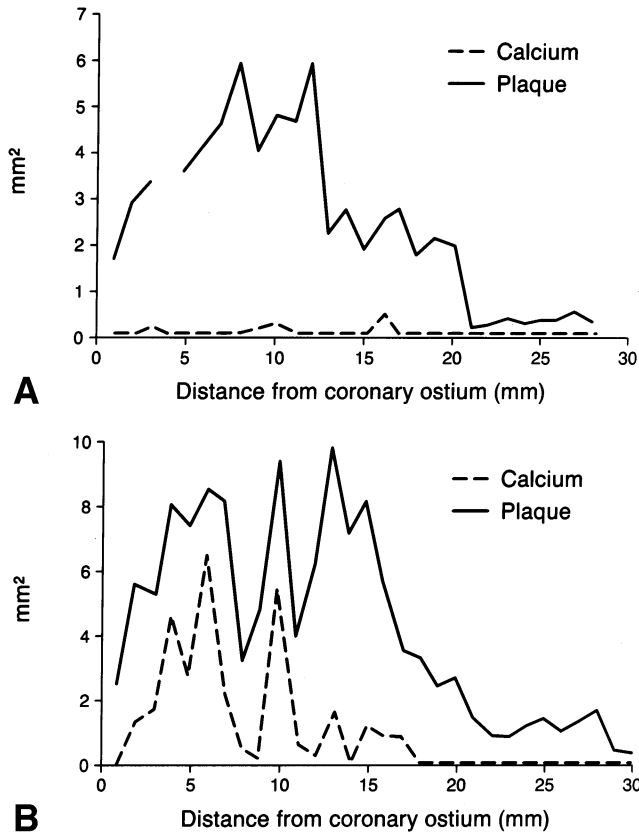
Figure 3. A, Graph showing the plaque area values and calcium area values along the entire length of a coronary artery. In this example there was diffuse segmental coronary plaque but not associated calcium deposition. **B,** In this graph diffuse segmental atherosclerotic disease was associated with calcific deposits within the atherosclerotic plaque.

Figure 4. Frequency distribution of noncalcified coronary segments by microradiographic analysis and corresponding decades of percent histopathologic stenosis. The mode of this distribution suggests that percent lumen area stenosis between 10% and 20% was the most frequently observed.

groups on the basis of the amount of calcium presence by microradiographic analysis. In total, of the 723 paired microradiographs and histologic sections, 69 (9.5%) had no detectable coronary artery calcification (0 mm^2 of calcium) and 654 (90.5%) had calcium areas >0 mm^2.

Figure 4 shows the frequency distribution of percent lumen stenosis in the noncalcified coronary artery segments. In this subgroup of segments the most frequently observed percent stenosis was between 10% and 20%. Figure 5 is a graph representing the polynomial regression analysis of calcium area values versus percent histologic stenosis in the coronary segments with a calcium area >0 mm^2 (n = 654, r = 0.44, p < 0.0001). Although there was a tendency for higher values of segmental calcium areas to correlate with higher percent stenosis, the relation was generally poor throughout the entire range.

Correlation between changes in EEL, lumen and plaque area values. A high correlation was present between coronary calcium area and plaque area on a segment by segment analysis, although no significant correlation existed between calcium area and lumen area. To evaluate whether atherosclerotic arterial remodeling might explain the poor correlation
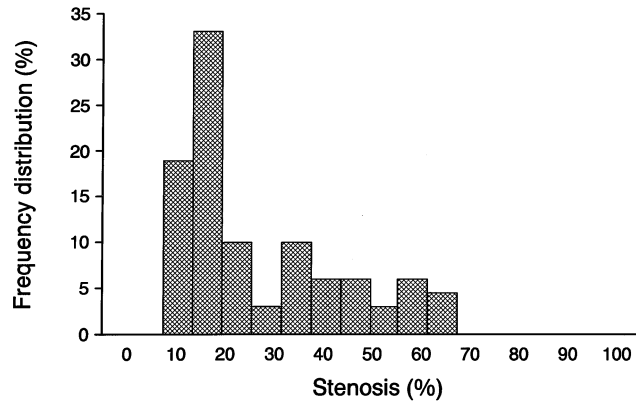
between calcium area and percent lumen stenosis, the longitudinal changes in lumen and EEL areas were compared with the same changes in plaque areas. Figure 6A shows the correlation between change in plaque areas and change in EEL areas (n = 723, r = 0.60, p < 0.0001), and Figure 6B shows the correlation between change in plaque area and change in lumen area (n = 723, r = 0.01, p = NS). These data show that the change in EEL area was strongly related with the change in plaque area (both positive and negative), whereas lumen area did not correlate with plaque size change.

Discussion

Principal results. The results from this detailed histopathologic study suggest the following conclusions regarding coronary artery calcification and the corresponding extent of CAD.

First, both whole-heart coronary atherosclerotic plaque area and whole-heart coronary calcium area increased with

Figure 5. Graph showing the polynomial regression analysis of the coronary calcium area (mm^2) detected by histopathologic and microradiographic analysis versus percent histologic stenosis for each of the 654 coronary artery segments with calcium >0 mm^2.
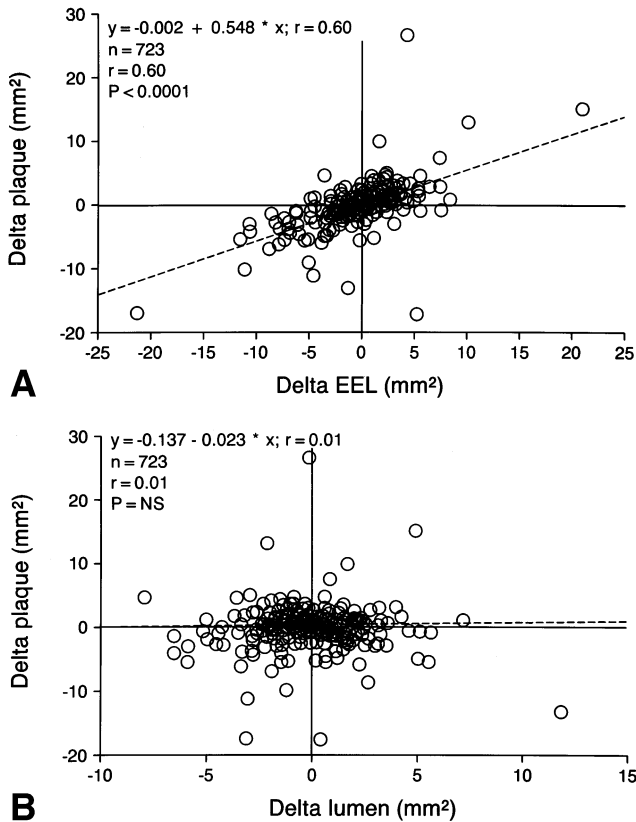

$y = -0.103 + 0.004 * x = 1.042E-4 * x^2$: $r = 0.35$
n = 654
r = 0.35
P < 0.0001
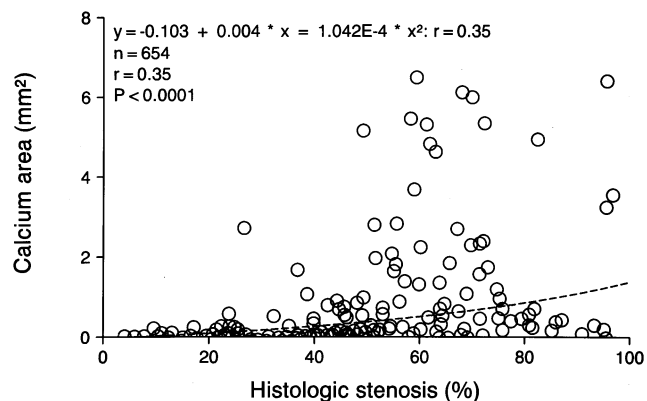
Figure 6. A, Graph showing the difference in consecutive plaque area values in mm^2 (delta plaque) versus the difference in consecutive EEL area values in mm^2 (delta EEL) along each coronary artery segment (n = 723). **B,** Graph showing the difference in consecutive plaque area values in mm^2 (delta plaque) versus the difference in consecutive lumen area values in mm^2 (delta lumen) along each coronary artery segment (n = 723).

advancing age. Second, coronary artery calcium area and coronary artery atherosclerotic plaque are directly correlated on the basis of whole-heart, individual coronary artery and segment by segment analysis (Fig. 2A). Third, the present investigation indicated that although coronary artery calcification can predict the presence of coronary atherosclerotic plaque, the absence of any coronary artery calcification on a segment by segment analysis does not exclude the presence of atherosclerotic plaque. In fact, as in the example shown in Figure 3A, on a segment-based analysis, there were several individual arteries with diffuse atherosclerotic plaque and little or no calcific deposits. However, on average, when there was no calcium, there was a low overall plaque burden or minimal lumen narrowing. Fourth, the lack of correlation between calcium area and lumen area (Fig. 2B) is probably due to the remodeling phenomenon (Fig. 6, A and B).

Calcium and atherosclerotic disease. The prevalence of calcification is a function of age and gender, ranging from 14% in young subjects to more than 70% in the elderly (27,28). As reported in previous studies from our laboratory (21,29) and others (30), these data demonstrate that the burden of coronary artery calcium with increasing age reflects a similar and parallel increase in the extent of coronary atherosclerotic plaque with advancing age. Although men and women have different degrees of calcification at a particular age, when matched for severity of obstructive atherosclerotic disease histologically (21,31) or angiographically (20), the amount of calcification is independent of gender.

Atherosclerotic plaques typically consist of a central necrotic core containing various amorphous material such as cholesterol crystals and calcific deposits bounded on the lumen side by a fibrous cap made of different cells type. Fitzpatrick et al. (14) demonstrated that calcium deposition in the form of hydroxyapatite was widely present within atherosclerotic plaques and that the messenger ribonucleic acid (mRNA) for osteopontin and osteonectin, proteins associated with normal bone calcification, was similarly present in cells within the plaque. Normal segments without evidence of atherosclerotic disease and calcification had no evidence of osteopontin expression, however. The presence of mRNA for osteopontin has been reported in different types of cellular populations that comprised human atherosclerotic plaque (32,33). Another study by Hirota et al. (12) established that osteopontin expression was related to atherosclerotic disease severity. In this latter study, conversely, osteonectin protein expression was found to be less in advanced atherosclerotic plaques. These data therefore suggest that the molecular basis of the coronary calcification process may not only be quite variable, but may also help to understand the assertion that although calcium area is a marker of plaque presence, not all plaques contain calcium.

Histologic findings, EBCT and coronary calcifications. EBCT currently permits rapid, accurate, noninvasive in vivo identification and quantification of coronary artery calcification (17), and thus this test has been suggested as an effective method of screening for CAD. However, a key question to expand the use of EBCT in the clinical arena centers on relations of coronary calcium area to lumen size and atherosclerotic plaque burden. Previous studies have shown variable results relating calcium to lumen and/or plaque distribution. Margolis et al. (34) performed an angiographic study of living patients and detected calcification in 250. Ninety four percent of those patients had angiographic stenoses >75% in one or more major coronary artery. Kragel et al. (35) found that atherosclerotic plaques associated with obstruction of the lumen contained greater amounts of calcium than those associated with lesser narrowing. Calcification was absent or minimal in 0% to 25% of lumen obstructive plaques, but increased with higher percentages of obstruction. In contrast, Clarkson et al. (36), in a histopathologic investigation in human and nonhuman primates, found that calcified plaques were larger and associated with larger coronary arteries compared with arteries without calcification. Furthermore, other investigators found that the correlation between coronary calcium and percent lumen stenosis at the same site was positive but nonlinear, with large confidence limits (26,37). Simons et al. (29) attempted to evaluate the relation between calcification detected by EBCT and histopathologic CAD using decalcified

sections. In this study, although coronary calcium deposition was highly predictive of the presence of atherosclerotic disease on a segment by segment basis, it did not predict lumen stenosis severity.

The results of the current histopathologic study confirm the findings of Simons et al. (29). As shown in Figure 2B, coronary calcium area was not correlated with lumen area. Furthermore, coronary artery calcification cannot quantify lumen stenosis severity on a segment by segment basis. As shown in Figure 5, in fact, the correlation between coronary calcium area and histologic percent stenosis was poor. However, the probability of obstructive coronary atherosclerotic disease is higher when the amount of calcium within the artery is greater, but there is not a one to one relation (21).

Atherosclerosis and vascular remodeling. Enlargement of atherosclerotic arteries (remodeling) is generally attributed to a reaction of increased flow and/or coincidental artery enlargement due to plaque progression with age (38). Recent evidence suggests that remodeling is an active process to maintain cross-sectional lumen area patency as atherosclerotic plaque area increases (22,36). Later, as the plaque continues to grow, the lumen then narrows when the plaque is of sufficient magnitude to be obstructive. The compensatory arterial enlargement is the likely reason for underestimation of lesion severity by angiography compared with histologic studies.

The present study indicates that coronary remodeling is the likely explanation for the poor correlation of calcium area with lumen area and/or percent stenosis found in this and in previous reports from our laboratory (20,29,31,39). As indicated in Figure 6A, on a segment by segment analysis, as the plaque enlarges, so does the EEL, indicating positive remodeling. As a result of this phenomenon, lumen area did not decrease (Fig. 6B). Another hypothesis is that the better correlation between higher calcium values and more severe histologic percent stenosis (Fig. 5) may be explained by greater deposition of calcium within an artery, making the arterial wall more stiff and less expandable, which can in a more advanced phase of atherosclerotic disease impair the ability of the vessel to remodel.

Clinical implications. Current clinical and angiographic data suggest that quantitation of coronary calcification does not accurately determine angiographic stenosis at the calcific site (40). Other data, however, suggest it may be useful to estimate the overall extent of CAD (39,41). The present study confirms this suspicion with quantitative, segment by segment analysis. This study also documents that in some atherosclerotic plaques, calcium deposition can be totally absent despite substantial plaque presence. However, the absence of calcification within a coronary artery, although not ruling out atherosclerotic disease, makes severe lumen obstruction improbable (Fig. 4). A clinical EBCT scan showing absence of calcification may thus have clinical utility in evaluating the patient with suspected CAD. Furthermore, our study unequivocally found that total plaque area in the coronary arteries of a given patient may be estimated if the calcific area is known. However, the clinical utility of this information remains to be

determined because little information is gained about either absolute lumen size or percent angiographic stenosis, and further studies are necessary to improve the understanding of the remodeling relation with lumen stenosis. Nevertheless, this finding may also have clinical significance, but only if it can be shown that patient clinical events and prognosis are related to overall atherosclerotic plaque burden. This may occur with the recognition that clinical coronary events are related to plaque rupture and thrombosis, usually occurring in lesions that are not obstructive (42–44).

Limited data are available on the prognostic significance of coronary artery calcifications. A multicenter EBCT and angiography correlative study published by Detrano et al. (45) evaluated the event rate in 501 patients symptomatic for CAD. The logistic regression analysis showed that of the other independent variables examined, only the calcium score was a strong predictor of coronary events in the follow-up period. A large series of asymptomatic patients evaluated by EBCT was recently published by Arad et al. (46). During 19 months of follow-up, 18 of 1,173 subjects examined had 27 cardiovascular events. Also in this study, EBCT coronary calcium score showed a correlation with cardiovascular events.

Although these studies suggest that the risk of having a main cardiovascular event is higher in subjects with coronary calcifications, further research is needed to better establish the relation between coronary artery calcification, lumen stenosis and risk of coronary events.

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