Natural History and Topographic Pattern of Progression of Coronary Calcification in Symptomatic Patients
An Electron-Beam CT Study

Axel Schmermund, Dietrich Baumgart, Stefan Möhlenkamp, Paul Kriener, Heiko Pump, Dietrich Grönemeyer, Rainer Seibel, Raimund Erbel

Abstract—Electron-beam CT may assess the progression of coronary atherosclerosis by visualizing changes in calcification. The present investigation analyzes (1) the rate of progression of calcification in symptomatic patients, (2) the topographic pattern, and (3) the influence of baseline plaque burden and risk factors. Progression of calcification during a mean (median) interval of 18 (15) months was measured in 102 symptomatic outpatients (aged 59±9 years, 80% male) with calcification. In 4 patient groups with a baseline total score (Agatston criteria) of 1 to 30, >30 to 100, >100 to 400, and >400, the median was 3.1, 26.1, 58.9, and 109.7, respectively, for absolute annual progression of the score (P<0.05) and 57%, 49%, 32%, and 15%, respectively, for relative progression (P<0.05). On the coronary segmental level, changes were largely restricted to typical predilection sites of coronary atherosclerosis. The presence of angiographically defined coronary narrowing influenced absolute, but not relative, progression. Of the risk factors, only low density lipoprotein cholesterol levels showed a trend, although not significant, for predicting progression. These data indicate that baseline plaque burden determines the rate of progression of calcification. This appears to be a coronary systemic process, reflecting the natural history of coronary atherosclerosis. (Arterioscler Thromb Vasc Biol. 2001;21:421-426.)

Key Words: progression ■ coronary atherosclerosis ■ calcium ■ electron-beam CT ■ coronary artery disease

Electron-beam CT (EBCT) has been in serial studies to determine the progression of coronary calcified plaque disease.1–6 The natural rate of progression of calcification has been described in healthy subjects in a community setting.5 It has been suggested that in asymptomatic high-risk patients, the influence of treating elevated lipid levels on the progression of coronary atherosclerotic disease can be evaluated by use of EBCT.3,5 If these reports are taken into consideration, EBCT may be of value in assessing the treatment of symptomatic patients. However, little is known about the rate of progression to be expected in symptomatic patients with modern pharmacological therapy. The progression of calcification may vary substantially between patients with or without established coronary artery disease (CAD) and may depend on the baseline amount of calcification.6

As calcification develops, the pattern of distribution among the major coronary arteries and the coronary segments has not been clarified. Only the changes in the overall amount of calcification have previously been reported. It was the aim of the present investigation (1) to analyze the rate of progression of calcification in symptomatic patients with modern treatment, (2) to establish the topographic pattern of progression, and (3) to determine the relationship of EBCT-derived and angiographic coronary findings and of risk factors with the rate of progression.

Methods

Patients
Outpatients followed in the Cardiology Department of the University Clinic Essen because of known or suspected CAD were considered for this investigation. Patients were included in a consecutive manner between January 1997 and December 1999 if they were males aged ≥40 years or females aged ≥45 years and if the scanner at a remote site was available. Exclusion criteria were body weight >300 pounds, possible or confirmed pregnancy, prior coronary stent implantation, plaque-debulking coronary interventions or bypass surgery, and arrhythmias interfering with the ability to perform ECG-gated triggering. Patients with previous percutaneous coronary angioplasty were accepted if the intervention was performed before and not during the follow-up period. It has been suggested that angioplasty does not alter EBCT calcium measurements.7 A total of 111 patients were included in the study. The minimum interval between the 2 studies was 6 months. The mean±SD interval was...
Electron-Beam CT

Nonenhanced EBCT scans were performed with a Siemens Evolution scanner (Imatron Inc) in the single-slice mode with an image acquisition time of 100 ms and a section thickness of 3 mm, as described previously. A 26-cm² field of view was used. Contiguous slices down to the apex of the heart were obtained.

For each study, including separate analyses of the major coronary arteries and 12 coronary segments as described below, a calcium score was determined by using the methods of Agatston et al. The calcium score is the product of the area of coronary artery calcium (at least 4 contiguous pixels with a CT density ≥ 130 Hounsfield units) and a factor rated 1 through 4 dictated by the maximum CT density within that lesion. Calcified lesions were encoded manually by a physician and were included in the analysis only if they were strictly in the trajectory of the coronary arteries. All studies were analyzed in this same fashion with the use of the original software provided with the scanner console. Because it has been suggested that for serial EBCT studies, the area of calcification provides for better reproducibility, calcium areas, which represent an inherent component of the Agatston score, were also computed for the major coronary arteries and the overall amount of calcification.

In our laboratory, scan-to-scan reproducibility was tested in 40 patients as part of a multicenter validation study that was independent of the present series. The median variability between 2 scans performed minutes apart in the same patient (only in patients with positive calcium scores) was 10% for the Agatston score and 8% for the calcium area and was not statistically different. In the present investigation, reproducibility was not as much a concern as in studies analyzing individual changes, because calcification was analyzed in groups of patients. Therefore and because calcium scores (which are more familiar to physicians than calcium areas) are usually reported, the present investigation gives calcium scores for the detailed population. Figure 1 shows that at baseline, calcification was seen most frequently in the proximal LAD, followed by the proximal LCx. Whereas in the left coronary artery (LCA), scores ranging between 1 and 400 (Table 2). The absolute progression was significantly less in the lowest total coronary artery (RCP, segments 1 to 4 according to the American Heart Association); the left main stem (segment 5); the proximal, mid, and distal portions of the right coronary artery (RCA) and the right posterior descending coronary artery (RPD, segments 1 to 4 according to the American Heart Association); the left main stem (segment 5); the proximal, mid, and distal left anterior descending coronary artery (LAD) and first diagonal branch (segments 6 to 9); and the proximal, mid, and distal left circumflex coronary artery (LCx, segments 11, 13, and 15). We and others have previously described the application of this segmental model to EBCT images. Only 12 of the 15 segments specified in the American Heart Association classification were considered because only they could be assessed reliably.

Statistical Analysis

The changes in coronary calcium area and score values between the 2 scans were annualized. Absolute changes in area and score were calculated as follows:

\[
\frac{(X_i - X_{i+1}) \times t_{\text{months}}}{12}
\]

where \(X\) is the value of calcium area or score, and \(t\) is the time interval between the 2 scans, measured in months. Relative (percent) changes were calculated as follows:

\[
\frac{(X_i - X_{i+1}) \times 12 \times 100}{X_i \times t_{\text{months}}}
\]

The distributions of coronary calcium area and score values of the complete coronary system (“total”), the major coronary arteries, and the coronary segments were skewed. Although the usual range was from 0 through 10 to 100, there were some extreme values. Therefore, for comparison of >2 unrelated groups, the nonparametric Kruskal-Wallis test was used along with post hoc Bonferroni-Holm analysis with correction for multiple comparisons to discern differences between 2 groups. For analysis of related samples (vessel scores and areas), the Friedman and Wilcoxon signed rank tests were used. To compare 2 unrelated groups, the Mann-Whitney test was applied.

To analyze the influence of different baseline total calcium scores on parameters of the progression of calcification, patients were classified into 4 groups according to suggestions by Rumberger et al. Total calcium score cut points of 30, 100, and 400 were used. Patients with a positive score of >30 had minimal coronary calcified atherosclerosis, whereas the extent and severity of the disease increased in patients with scores between 30 and 100, between 100 and 400, and >400. In modification of the suggestions by Rumberger et al, we used 30 instead of 10 as the cut point for minimal atherosclerosis because of the potential for artifacts confusing the topographic analysis in the very low score range. In recent reports, calcium scores >30 generally had an interscan variability <10%.

Usually, the median of calcium area and score values and their changes were computed. However, because most segmental calcium score values were 0, the 75th percentile was given for segmental calcium score values. A 2-tailed value of \(P<0.05\) was considered to indicate a significant difference.

Results

Patient Demographics

Characteristics of the 111 patients are listed in Table 1. Cardiovascular risk factors were highly prevalent among the patients, and multiple medications were used during the follow-up period. A positive total calcium score was found at baseline in 103 patients (93%) and at follow-up in 102 patients (92%). In 8 patients (7%), no calcium was detected at either of both examinations, and in 1 patient (1%), a positive total calcium score (2.6) was observed at baseline but not at follow-up. At baseline, the mean and median values were 434.3 and 134.1, respectively, for the coronary calcium score and 130.6 mm² and 46.2 mm², respectively, for the coronary calcium area. At follow up, these values were 527.5 and 206.1, respectively, for the calcium score and 143.6 mm² and 58.5 mm², respectively, for the calcium area. The detailed values for each major coronary artery are listed in Table 1 (please see online data supplement at http://atvb.ahajournals.org). Most patients had a baseline total calcium score >100 in this symptomatic population. Figure 1 shows that at baseline, calcification was seen most frequently in the proximal LAD, followed by the proximal LCx. Whereas in the left coronary system, the presence and the amount of calcification were much more prominent in the proximal coronary segments, the distribution was more even in the RCA.

Progression of Coronary Calcification

For the analysis of progression, only the 102 patients with a positive total score at follow-up were considered. The baseline total calcium score was 1 to 30 in 18 (18%) patients, >30 to 100 in 21 (21%) patients, >100 to 400 in 31 (30%) patients, and >400 in 32 (31%) patients. Within all subgroups, calcium score and area were greater at follow-up than at baseline, and this was significant for the 3 groups with scores ranging between 1 and 400 (Table 2). The absolute annual progression was significantly less in the lowest total calcium score group compared with the other groups, as shown in Figure 2. The relative progression of calcification
(calcium area and score) was greater in the lower than in the higher total calcium score groups, but the difference was much less pronounced than for the absolute values.

In the total group of 102 patients, mean and median relative annual progression of the total score was 51% and 32%, respectively, and mean and median relative annual progression of the total area was 42% and 27%, respectively (Table II; please see online data supplement at http://atvb.ahajournals.org). In the subgroups with baseline scores of 1 to 30, to 100, and 100 to 400, median relative annual progression of the calcium score was 57%, 49%, 32%, and 15%, respectively, and that of the calcium area was 36%, 39%, 27%, and 13%, respectively (Figure 2 and online Table II).

Overall regression of calcification was measured in 15 (15%) of 102 patients. The percentage of patients with regression was quite evenly distributed among the 4 baseline score subgroups, i.e., 3 of 18 (17%, lowest baseline score group), 2 of 21 (10%), 4 of 31 (13%), and 6 of 32 (19%, highest baseline score group).

Coronary angiographic status was known in 85 (83%) patients. At least 1 vessel showed luminal diameter obstruction ≥50% in 52 (61%) patients (partly treated by angioplasty, as shown in Table I). The median baseline total coronary calcium score in these patients was 353.8, which was significantly greater than that in patients without angiographically obstructive CAD (median 97.8, P<0.001 by Mann-Whitney test). The median absolute annual progression of the total calcium area and score was significantly greater in patients with versus patients without obstructive CAD: 15.6 and 43.8, respectively, versus 6.9 and 26.3, respectively (P=0.03 and P=0.04, respectively). However, the relative annual progression was similar in the 2 patient groups. The median values of relative area and score progression were 20.3% and 26.6%, respectively, in patients with obstructive CAD and 27.4% and 26.0%, respectively, in patients without obstructive CAD (P>0.8).

**Topographic Pattern of Progression of Calcification**

As shown in Figure 2 (and shown in online Table II), the changes in areas and scores in the major coronary arteries were very comparable, suggesting that the CT density of the lesions changed in the same direction and with the same magnitude as the lesion area. The difference in the rate of progression between the vessels did not reach significance.

Figure 3 shows the topography of progression of the segmental calcium scores. Clearly, those segments with the highest initial (baseline) calcium burden also displayed the greatest increase in calcification. Analysis according to the baseline total calcium score subgroups revealed that in the lower score subgroups, the most prominently calcified segments also displayed the greatest rate of progression. With higher total calcium scores, there appeared to be a shift toward greater relative progression in those segments that were less prominently calcified at baseline.

**Topographic Pattern of Progression According to Overall Changes in Calcification**

To analyze the topography of progression according to the overall change in total calcium score, patients were classified into quartiles of relative total calcium score change. The changes in the major coronary artery scores paralleled the overall calcium score changes. The progression of calcification was evenly distributed among the major coronary arteries (online Table II).
The changes in segmental calcium scores, demonstrated in Figure 1 (please see online data supplement at http://atvb.ahajournals.org), also paralleled the overall changes. The proximal left coronary segments and the RCA segments (more evenly distributed) displayed an increasing progression in scores with an increasing progression of total calcium scores.

Factors Influencing the Rate of Progression
Baseline overall coronary plaque burden (ie, calcium scores and areas) was an independent predictor of absolute and relative overall changes in calcium score ($P<0.05$, respectively, linear regression analysis). However, as judged by the $r^2$ values, only $\sim 5\%$ to $10\%$ of the variability in progression was explained by baseline calcium score or area. As described above, angiographic status predicted only absolute, but not relative, progression of calcification.

Of the risk factors listed in Table 1, only LDL cholesterol demonstrated a tendency, although not significant, for increased values in patients with greater progression of calcium area. LDL cholesterol in patients with relative progression above the median was $142 \pm 44$ mg/dL (median, $139$ mg/dL) versus $130 \pm 33$ mg/dL (median, $128$ mg/dL) in patients with relative progression below the median ($P<0.05$). Use of lipid-lowering medication was $80\%$ in patients with regression of calcification versus $62\%$ in the other patients ($P<0.05$). Use of lipid-lowering medications was also not different among the 4 baseline score subgroups, ie, $13$ of $18$ ($72\%$, lowest baseline score group), $11$ of $21$ ($52\%$), $22$ of $31$ ($71\%$), and $20$ of $32$ ($63\%$, highest baseline score group).

Discussion
The present data provide information on the rate of absolute and relative annual progression of calcification in symptomatic patients with risk factors and modern medical therapy (online Table II). Several observations deserve to be noted. It appears clinically relevant that opposite trends in absolute and relative (percent) measures of progression were seen (Figure 2). Patients with extensive calcification had the greatest absolute rate of progression, indicating an enhanced activity of atherosclerotic plaque disease despite medical therapy. This underscores the need to account for the initial extent of calcification. However, angiographically proven obstructive CAD per se did not appear to accelerate the progression of calcification.

Further observations pertain to the pathophysiology and natural history of calcifying atherosclerosis. Changes in calcium area and score were very consistent and indicated that calcified lesion density progressed along with lesion area (online Table II, Figure 2). There were no significant differ-
ences in the rate of progression of calcification between the major coronary arteries (LAD, LCx, and RCA). It appears only consequential that the most consistent and greatest progression of calcification was observed in the segments with the most prominent initial involvement. Consistent with previous pathological and angiographic studies on the natural history of atherosclerosis,19,20 the rate of progression of calcification was greatest in the proximal left coronary system and showed a more even distribution from proximal to distal in the RCA (Figure 3).

Greater relative progression of overall calcification was a result of uniformly greater relative progression of calcification in the coronary segments involved. Thus, the development of calcified atherosclerotic disease occurred simultaneously at different predilection sites in the coronary tree.19,20 This uniform pattern of change suggests that the development of calcified plaque disease is a coronary systemic process.

Rate of Progression of Calcification

The overall mean relative progression of calcification observed in patients with positive calcium scores was 51% for total calcium scores and 42% for total calcium areas. The median values were 32% and 27%, respectively.

Most previous reports on the rate of progression of calcification examined only asymptomatic patients. Maher et al4 reported a mean annual progression of coronary calcium scores in healthy adults (aged 46±7 years) of 24%. In asymptomatic patients with several risk factors, Budoff et al5 observed a mean annual progression of 33%, which was lower in patients on lipid-lowering therapy than in the total group. These 2 reports included patients with negative EBCTs.

Callister et al3 assessed the progression of a volumetric score essentially computed on the basis of calcium areas. In asymptomatic high-risk individuals, they observed a mean and median relative annual change of the volumetric score of 52% and 44%, respectively. Expanding on that work, they subsequently reported that successful pharmacological LDL cholesterol reduction led to a significant mitigation of progression of the volumetric score.3 In untreated patients with a mean LDL cholesterol level of 147 mg/dL, the mean annual progression was 52%. In patients treated pharmacologically but whose LDL cholesterol level remained >120 mg/dL (at a mean value of 139 mg/dL), mean annual progression was 25%. In patients with LDL cholesterol values <120 mg/dL, on average a 7% regression of the volumetric score was observed.3

In an early careful study, Janowitz et al6 compared the progression of total calcium area in 10 patients with angiographically proven CAD with that in 10 asymptomatic patients and found a significant difference of 48% versus 22%, respectively. This difference was not reproduced in our present series of 85 patients who underwent coronary angiography. This may partly be due to different patient characteristics apart from the angiographic data, inasmuch as we examined a selected referral population treated with modern pharmacological therapy. We believe that in stable angina pectoris, it is unlikely that luminal obstruction per se predicts accelerated progression of CAD. Rather, it would indicate an angiographically appreciable advanced stage of coronary atherosclerotic plaque disease and thus increased susceptibility to further endothelial injury and progression of disease in the absence of adequate treatment.

Regression of Calcification

It is yet unclear whether regression of calcification, observed in 15 (15%) patients in the present investigation, is more than simply a phenomenon within the range of interscan reproducibility. Callister et al3 found regression of the volumetric score in 63% of 65 patients with low LDL cholesterol levels. A possible explanation for regression of calcification has been derived from an animal model in rhesus monkeys, who after 3.7 years on a low cholesterol regression diet showed a slightly decreased area of calcified lesions, perhaps as a result of shrinkage and increased density of the lesions.21 The median changes of calcium areas and scores in patients with regression of calcification in the present investigation generally went in the same direction. It remains unresolved whether, indeed, “lesion consolidation” with decreased calcium area and increased density may account for the regression of calcification in some patients.

Topographic Pattern of Progression of Calcification

The topographic pattern of progression as reflected in the analysis of 12 coronary segments paralleled the overall changes in calcification seen with different baseline total calcium scores as well as with varying overall changes, ranging from regression of scores to annual progression >60%. Changes were seen predominantly at the typical predilection sites of atherosclerosis in the proximal left coronary segments.19,20 Of note, the distribution of disease progression was much more even in the RCA, with substantial progression found in the distal segments of that vessel. Accordingly, for studies of the progression of coronary calcification, it is likely useful to obtain sections through the cardiac apex instead of a limited set including only the proximal cardiac structures.22

Risk Factor Influences

Risk factor influences were moderate, and only LDL cholesterol appeared to modify the rate of progression. However, this did not achieve significance. The use of lipid-lowering drugs did not differ between patients with higher versus lower baseline amounts of calcification and thus cannot explain the different rates of progression between these groups.

Study Limitations

It has been mentioned that a recently validated volumetric calcium score appears to offer advantages for serial EBCT studies because of significantly improved reproducibility compared with the Agatston score,2,3 which is presently the most widely used.14 For the present investigation, volumetric calcium scoring, which depends on 3D-rendering capabilities, was not available. However, the calcium area has also been reported to yield improved reproducibility, because as with the volumetric score, calcium area does not take an arbitrarily assigned density factor into account. We computed calcium area and score (Agatston score) for the major coronary arteries and the complete coronary tree, which enabled us to compare the changes in both parameters.

It should be noted that recently published studies13,18 have demonstrated a better reproducibility of the EBCT-derived
Agatston score than earlier studies. This is partly due to improvements in the technique with the new scanner generation. For example, scanning can presently be completed in 1 breath-holding as opposed to the 2 breath-holdings required when the older EBCT scanners were used. The more recent publications have reported a median variability of the Agatston score ≤10%, which is clearly less than the median progression of 32% observed in the present investigation. These reassuring data notwithstanding, small amounts of calcium, especially on the segmental level, can certainly yield measurements with substantial variability. However, it should be noted that in the present investigation, groups of patients were analyzed. The consistent increase in calcium scores between the baseline and the follow-up scan in subgroups of patients and in the coronary segments indicates that our results are meaningful.

Because a selected referral population was examined, our data cannot be extrapolated without much caution to other symptomatic populations. Especially, ethnic groups other than whites (which made up the present population) may show different rates of disease progression. Our results are in agreement with previous reports also derived from predominantly white patients. Pathological investigations have demonstrated an impressive consistency in the predilection sites and axial distribution of coronary atherosclerosis among various ethnic groups and in both sexes. Hence, there is no reason to believe that the topographic pattern of disease progression will differ in other patient populations.

Conclusions

The present data appear to provide a useful basis for interpretation of the progression of calcified plaque disease in symptomatic patients with modern therapy. Patients with extensive calcification had the greatest absolute rate of progression, indicating an enhanced activity of atherosclerotic plaque disease despite medical therapy. Therefore, it appears critical to account for the initial extent of calcification. The topographic pattern of progression of calcification revealed uniform changes at the predilection sites of coronary atherosclerosis, consistent with the natural history of the disease. These uniform changes indicate that the mechanisms that influence disease progression affect the coronary tree in a systemic fashion.

References

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Table I: Coronary calcium scores and areas at baseline and after a mean (median) interval of 18 ± 12 (15) months in 111 patients.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Follow Up</th>
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<tbody>
<tr>
<td><strong>Left Main</strong></td>
<td><strong>LAD</strong></td>
</tr>
<tr>
<td>Score</td>
<td>Area</td>
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<tr>
<td>Mean</td>
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<tr>
<td>SD</td>
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<tr>
<td>Median</td>
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<tr>
<td>25th perc.</td>
<td>0.0</td>
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<tr>
<td>75th perc.</td>
<td>4.6</td>
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</table>

LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, “perc.” = percentile, RCA = right coronary artery, SD = standard deviation. Comparison between “Left Main”, “LAD”, “LCx”, and “RCA” at baseline and at follow up, respectively: * p < 0.05 vs. all other groups, † p < 0.05 vs. “Left Main”, “LAD”, ‡ p < 0.05 vs. “Left Main”, “LCx”
Table II: Annual progression of coronary calcium areas and scores in 102 patients with positive total calcium score.

<table>
<thead>
<tr>
<th>Baseline total score subgroups</th>
<th>Absolute Changes (Score/Area)</th>
<th>Relative Changes (%) (Score/Area)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Main</td>
<td>LAD</td>
</tr>
<tr>
<td></td>
<td>Score</td>
<td>Area</td>
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<td>1-30</td>
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<td></td>
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<td>&gt;100-400</td>
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<tr>
<td></td>
<td>Median</td>
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</tr>
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</table>

Abbreviations as in Table I