Prognostic Significance of Cardiac Cinefluoroscopy for Coronary Calcific Deposits in Asymptomatic High Risk Subjects

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Objectives. This research investigated the prognostic significance of radiographically detectable coronary calcific deposits.

Background. Coronary calcific deposits are almost always associated with coronary atherosclerosis. We investigated the association between fluoroscopically determined coronary calcium and coronary heart disease end points at 1 year of follow-up.

Methods. This prospective population-based cohort study was conducted in the suburbs of Los Angeles. Fourteen hundred sixty-one asymptomatic adults with an estimated ≥10% risk of having a coronary heart disease event within 8 years underwent cardiac cinefluoroscopy for assessment of coronary calcium at initiation of the study. Clinical status including angina, documented myocardial infarction, myocardial revascularization and death from coronary heart disease were determined after 1 year.

Results. The prevalence of calcific deposits was high (47%). A follow-up examination at 1 year was successfully completed in 99.9% of subjects. Six subjects (0.4%) had died from coronary heart disease and 9 (0.6%) had had a nonfatal myocardial infarction. Thirty-seven subjects (2.5%) reported angina pectoris, and 13 (0.9%) had undergone myocardial revascularization. Fifty-three subjects had at least one event during the 1-year period. Radiographically detectable calcium was associated with the presence of at least one of these end points, with a risk ratio of 2.7 (confidence limits 1.4, 4.6). The presence of coronary calcium was an independent predictor of at least one end point when controlling for age, gender and risk factors. However, three deaths due to coronary heart disease and two nonfatal myocardial infarctions occurred in subjects without detectable coronary calcium.

Conclusions. The presence of coronary calcific deposits incurs an increased risk of coronary heart disease events in asymptomatic high risk subjects at 1 year. This increased risk is independent of that incurred by standard risk factors.

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Coronary heart disease is the most common cause of death and disability in industrialized nations (1,2). Autopsy studies show that coronary atherosclerosis, the pathologic substrate of coronary heart disease, is present in up to 15% of older children and young adults who die of violent causes (3), and in almost 100% of octogenarians (4). Pathologic and clinical studies (5–9) indicate that coronary calcific deposits are rare when atherosclerosis is absent. Blankenhorn (10) performed histopathologic studies of 89 randomly selected hearts. Examining 3,500 arterial segments microscopically and radiographically, he found that all calcified radiopaque lesions were atherosclerotic. Until recently, the only in vivo method for evaluating coronary atherosclerosis has been coronary angiography. However, because of its risks and expense, this procedure cannot be applied to large numbers of asymptomatic persons. Therefore, assessment of the prevalence of coronary atherosclerosis has been subject to biases inherent in autopsy and angiographic studies (11,12). Cardiac cinefluoroscopy has been used as a diagnostic test for coronary atherosclerosis (13–21); however, its application as a prognostic tool in asymptomatic subjects has never been tested. This is a report of the association of coronary calcium detected by cinefluoroscopy with coronary heart disease events in asymptomatic high risk subjects.

Methods

Recruitment. The South Bay Heart Watch screening clinic evaluated 5,023 subjects between December 1990 and December 1992. These subjects were ≥45 years of age and had at least one coronary risk factor. They were recruited...
through newspaper, radio, television advertising and direct mail campaigns. A trained nurse (O.S.B.) administered an angina questionnaire and recorded cardiac history (prior myocardial infarction or revascularization), smoking (yes if currently smoking; no if not currently smoking) and hypertension and diabetes histories (yes if being treated with diet or medications, or both; no otherwise). The same nurse measured the height and weight and the systolic blood pressure twice after the subject had rested in a sitting position for 10 min. In addition, he performed a phlebotomy to obtain serum for analysis of total and high density lipoprotein cholesterol by a California Association of Pathology-certified laboratory. Twelve-lead electrocardiograms (ECGs), recorded by the nurse, were reviewed independently without knowledge of other data by three board-certified cardiologists who used the Minnesota code to exclude subjects with prior myocardial infarction and a Romhilt-Estes score \( \geq 4 \) to diagnose left ventricular hypertrophy. Differences were settled at quarterly meetings by majority rule. The angina questionnaire, adapted from that of Rose et al. (22), contained the following five questions: 1) Have you experienced chest pain or discomfort? 2) Is the discomfort provoked by exertion? 3) Is the discomfort relieved by rest or nitroglycerin? 4) Does relief of the discomfort occur within 10 min? 5) Does this discomfort ever last \( >30 \) min?

We excluded subjects (4%) who answered yes to at least three of these questions, as well as those whose ECG showed diagnostic Q waves (5%) by the Minnesota criteria (23). All subjects reporting a history of a prior myocardial infarction were also excluded.

The nurse used the risk factor information to calculate the risk of coronary heart disease events during an 8-year period according to the Framingham risk calculation algorithm (24) and excluded subjects found to have a \(<10\% \) risk. The remaining 1,461 subjects (29%), underwent cinefluoroscopy to detect coronary calcification and were invited to return for a follow-up visit after 1 year.

All subjects gave written informed consent as volunteer participants in this investigation, which had been approved by the Harbor-University of California, Los Angeles Human Subjects Committee on October 5, 1990.

**Fluoroscopic protocol.** We performed cinefluoroscopy using a 60° left anterior oblique projection in all 1,461 subjects. We also used a 30° right anterior oblique projection in the first 451 subjects until we ascertained that this procedure increased the number of subjects with detectable coronary calcium by \(<1\% \). The imaging utilized a Philips X-ray tube, image intensifier and digital cardiac imaging (DCI) unit with a \( 512 \times 512 \) pixel matrix format. Exposure factors included pulse width 16 ms, kilovolt (peak) (kVp) 50 to 80 and mA 50 to 90. The imaging unit adjusts kVp according to the output of the image intensifier so as to ensure optimal X-ray penetration of the chest. The image intensifier light output is amplified and subtracted. The results regarding the digitized images will be reported elsewhere. The average radiation dose was 800 mrad.

**Image interpretation.** Two observers (R.C.D., W.T.) reviewed the images without knowledge of each other's reading or the risk factor information. The distributions of the right coronary artery, the left main–left anterior descending coronary artery and the left circumflex coronary artery were evaluated. The two observers assessed these regions as to the presence of calcific deposits.

**Follow-up.** After 1 year, surviving subjects returned to the South Bay Heart Watch clinic. We assessed coronary heart disease status using questions concerning intervening hospital admissions, the angina questionnaire used for the initial visit and a 12-lead ECG recorded in fashion identical to that used 1 year earlier. The same three cardiologists using the same Minnesota criteria reviewed these tracings. This committee met quarterly to decide by majority rule on all cases for which at least one member had diagnosed a new silent myocardial infarction. Subjects who were unable or unwilling to return to the clinic were contacted by telephone by the nurse coordinator (O.S.B.) and either were visited in their home by staff personnel or were mailed a questionnaire to obtain information regarding angina and hospital admissions.

We obtained medical records for all subjects admitted to the hospital. We also obtained all medical records for non-surviving subjects after first contacting next of kin to obtain information about the circumstances of the subject's death. A committee of three board-certified cardiologists reviewed these records without knowledge of other data to determine the occurrence of myocardial infarction or myocardial revascularization (coronary artery bypass surgery or percutaneous transluminal coronary angioplasty).

**Definitions.** **Myocardial infarction** was defined as 1) prolonged chest pain prompting hospital admission with either evolutionary diagnostic ECG changes (ST segment elevation \( \geq 2 \) mm or evolving Q waves, or both), and/or elevation of serum creatine kinase to twice the upper limit of normal or a positive serum creatine kinase MB fraction; or 2) evolutionary, diagnostic ECG changes and the preceding enzyme elevations in the absence of prolonged chest pain.

**Coronary heart disease death** was determined by committee review of medical records as having occurred if proved by autopsy or if the subject died within 1 h after the onset of prolonged severe chest pain or during hospital admission for an acute myocardial infarction.

**Angina pectoris** was defined by a score of \( \geq 3 \) on the angina questionnaire.

**Coronary heart disease** was considered present if any of the following end points occurred during the 1-year period: coronary heart disease death, myocardial infarction (including silent), angina pectoris or myocardial revascularization.

**Statistical analysis.** We compared cardiac end points with the presence of coronary calcium using a likelihood ratio,
Prevalence (%)

Decade of Life

100
80
60
40
20
0

5th 6th 7th 8th 9th 10th

Figure 1. Bar graph showing the prevalence of coronary calcium in the indicated decade of life in the 1,461 subjects.

chi-square analysis or Fisher exact test when appropriate. We used multivariable logistic regression to determine independent contributors to the presence of one or more endpoints.

Results

Subject characteristics. Twelve hundred eighty-one men (88%) and 180 women (12%) were found eligible. Their mean age ± SD was 63.0 ± 7.8 years. Eighteen percent had diabetes mellitus (treated with diet or medications, or both), 52% reported a history of hypertension, 21% were smokers and 44% reported a history of coronary heart disease in a first-degree relative. The mean systolic blood pressure was 144 ± 18 mm Hg. The mean serum cholesterol and high density lipoprotein cholesterol was 241 ± 49 mg/dl and 44 ± 14 mg/dl, respectively.

Prevalence of coronary calcium. The prevalence of coronary calcium was 47%. The prevalence in individual vessels was 44.5% for the left main-left anterior descending coronary arteries, 18.1% for the right coronary artery and 12.0% for the left circumflex coronary artery. Twenty-seven percent of subjects had calcium in only one vessel, 13% in two vessels and 7% in all three vessels. Figure 1 shows the dependence of coronary calcium prevalence on age. There was a significant increase in coronary calcium prevalence from the 5th to the 9th decade of life (p < 0.001).

Interobserver discordance. A second independent observer reread the fluoroscopic studies in blinded manner. Disagreement concerning the presence of calcium arose in 7.7% of cases. These two investigators then reviewed the discordant studies in blinded fashion and made a consensus decision.

Completeness of follow-up. The research team successfully obtained follow-up information for 1,442 (99.9%) of the 1,444 survivors and for all 17 nonsurvivors. Thirteen hundred ninety-six participants (96.8%) returned to the South Bay Heart Watch clinic; of the remaining subjects, 35 (2.4%) were interviewed by telephone, 10 (0.7%) were interviewed in their home by staff personnel and 1 subject (0.1%) was followed-up by mailed questionnaire.

Seventeen subjects died in the year after their fluoroscopic examination. Medical records were obtained and reviewed for all 17. Six of the 17 deaths were ascertained to have been caused by coronary heart disease.

Prediction of events. Table I summarizes the coronary heart disease events that occurred in a 1-year period and their relation to the detection of coronary calcium. Fifty-three subjects (3.6%) experienced a coronary heart disease end point within 1 year after their cinefluoroscopic examination. Thirty-seven of these events occurred in subjects with detectable coronary calcium, and 16 in those without coronary calcium (p = 0.001). Six subjects (0.4%) died from coronary heart disease in this period. Of these, three had detectable coronary calcium on fluoroscopic study. Two of the six died suddenly within 1 h after the onset of severe prolonged chest discomfort, three died in the course of acute myocardial infarction and one died from congestive heart failure shortly after coronary artery bypass surgery. Of the 11 subjects who died from noncoronary causes, 4 died from a cerebrovascular accident and one from cardiomyopathy of undetermined etiology. Of the five subjects with a noncoronary but cardiovascular death, four had coronary calcium on cinefluoroscopic examination.

Nonfatal myocardial infarction (one silent) occurred in 10 subjects. These infarctions were more common among subjects with (1.2%) than among those without (0.3%) calcium (p = 0.03). Ten subjects underwent myocardial revascularization with either coronary bypass surgery or percutaneous transluminal coronary angioplasty. Ten of these had demonstrated coronary calcium on their initial visit (p = 0.03). Of 37 subjects reporting angina on follow-up examination, 27 had demonstrated coronary calcium during the initial cinefluoroscopic study (p = 0.001). Logistic regression using age, gender, coronary calcium status and risk factors

<table>
<thead>
<tr>
<th>Event†</th>
<th>Calcium (n = 691)</th>
<th>No Calcium (n = 768)</th>
<th>Risk Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (coronary heart disease death)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
<td>1.00</td>
<td>NS</td>
</tr>
<tr>
<td>II (nonfatal myocardial infarction)</td>
<td>8 (1.2%)</td>
<td>2 (0.3%)</td>
<td>4.00</td>
<td>0.03</td>
</tr>
<tr>
<td>III (coronary revascularization)</td>
<td>10 (1.5%)</td>
<td>3 (0.4%)</td>
<td>3.75</td>
<td>0.03</td>
</tr>
<tr>
<td>IV (angina)</td>
<td>27 (3.9%)</td>
<td>10 (1.3%)</td>
<td>3.00</td>
<td>0.001</td>
</tr>
<tr>
<td>I, II, III or IV</td>
<td>37 (5.4%)</td>
<td>16 (2.1%)</td>
<td>2.57</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Follow-up data were not obtained for 2 subjects (both in the survivor group) of the total study group of 1,461 subjects. Some subjects had more than one event.
revealed that only history of hypertension, left ventricular hypertrophy, family history and calcium status were independent risk predictors of at least one coronary heart disease end point. Detection of coronary calcium in at least one, two or three vessels incurred an overall event risk of 5.4%, 5.6% and 6.2%, respectively. Thus, the increase in risk incurred by more extensive calcium deposits was not high.

Table 2 shows mean values and frequencies as well as the risk ratios with 95% confidence intervals for each risk factor variable considered alone. The most powerful predictor of an adverse outcome was the presence of left ventricular hypertrophy on the rest ECG (risk ratio 3.2). Fluoroscopic calcium considered alone had a risk ratio of 2.7. A history of hypertension had a similar risk ratio, 2.6, and a history of coronary heart disease in a first-degree relative had a risk ratio of 1.8. Neither smoking status, family history, diabetes, systolic blood pressure nor serum lipids affected risk in this sample.

Table 3 shows the risk ratios calculated from the logistic regression coefficients for detectable calcium, age and gender and the three risk factors that were significant predictors by the bivariate analysis presented in Table 2. Left ventricular hypertrophy, hypertension, coronary calcium and family history were significant independent risk predictors with similar risk ratios (1.36 to 1.67). Age and gender were not significant predictors. The logistic equation, Risk = \text{logit}(f(x)) = \text{logit}(f(x_1)) = \text{logit}(f(x_2)) = \text{logit}(f(x_3)) = \frac{e^{0.012 \cdot \text{Age} + 0.32 \cdot \text{Male} + 0.45 \cdot \text{Hypertension} + 0.51 \cdot \text{Left ventricular hypertrophy} + 0.31 \cdot \text{Family history}}{(1 + e^{0.012 \cdot \text{Age} + 0.32 \cdot \text{Male} + 0.45 \cdot \text{Hypertension} + 0.51 \cdot \text{Left ventricular hypertrophy} + 0.31 \cdot \text{Family history})}

Discussion

Our results indicate that the cinefluoroscopic detection of coronary calcific deposits provides prognostic information in subjects at high risk for coronary heart disease events. This information is independent of that incurred by elevated levels of standard risk factors such as serum lipids, smoking and systolic blood pressure. Ample theoretic and experimental justification exists for such a predictive association (16,25,26).

However, coronary calcium was not detected in five subjects who died from coronary heart disease death or had a nonfatal myocardial infarction. The mean age of these five subjects was 61 years and four of them were men, making the age and gender distributions similar to that of the entire sample. Moreover, their risk factor profiles were not remarkable except that none were smokers and all had hypertension. We have noted an increased prevalence of coronary calcium in smokers and no significant relation between coronary calcium and history of hypertension (27). In view of the relatively high prevalence of coronary calcium in this population, the presence of these false negatives may limit the applicability of cinefluoroscopy as a screening tool.

Strengths and limitations of the study. The 1-year event rate in this cohort is likely to be accurate because of complete and comprehensive follow-up (>99%). Although the funding agency required that the fluoroscopic results be presented to the subjects, these were presented as research data whose meaning was to be determined and not as significant results requiring referral or further diagnostic evaluation. Thus, we do not believe that the knowledge of the results had great impact on the medical care of these subjects. Confirmation of this rests on the following facts. 1) Although reported smoking frequency decreased by 2%, there was no greater tendency for subjects with coronary calcium than for subjects without coronary calcium to quit smoking. 2) Mean systolic blood pressure did not change significantly in either group of subjects during the 1-year period. 3) If the presence of calcium had influenced the subjects with coronary calcium to report angina or undergo revascularization more frequently, we would have noted an especially high risk ratio for these "soft" end points. This was not noted.

For these reasons, we do not believe that the knowledge of the test results significantly influenced the coronary end points. The participants were all self-referred volunteers known to be at high risk for coronary heart disease. This
selection procedure was necessary to ensure an adequate number of coronary events in a relatively short period of time. However, the results for these subjects may not hold for subjects at lower risk chosen randomly from the general population.

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References


