Coronary Calcification

Relationship to Clinically Significant Coronary Lesions and Race, Sex, and Topographic Distribution

By Douglas A. Eggen, Ph.D., Jack P. Strong, M.D., and Henry C. McGill, Jr., M.D.

The need for methods to detect and measure atherosclerotic lesions in the coronary arteries before the onset of clinical manifestations of coronary heart disease is well recognized by clinicians and epidemiologists. Since coronary artery lesions are the principal factors in coronary heart disease, they should be more strongly correlated with clinical disease than are the commonly used risk factors such as serum lipid levels, blood pressure, smoking habits, family history, and glucose tolerance. In addition, if the prevalence and extent of coronary artery lesions could be determined in the living, the relationship of these “risk” factors to the arterial lesions could be examined more closely in epidemiologic studies. Although coronary angiography has been developed to measure coronary stenosis and is being used successfully for diagnosis, this method is not yet applicable on a large scale nor is it suitable for screening purposes.

Calcified lesions are the only lesions of atherosclerosis that can be detected in the living patient without significant risk. The possibility of assessing atherosclerosis in the living patient by detecting calcification in the arteries roentgenographically has been investigated by several workers. Clinical studies of calcified lesions in the coronary arteries by fluoroscopy and cinefluorography have shown that calcified lesions are strongly associated with clinical coronary artery disease. We have recently reported an association between abdominal aortic calcification and clinically significant coronary atherosclerotic lesions in necropsy material.

The present study of calcified coronary artery lesions in a large number of necropsied patients by analysis of x-rays of dissected arteries is an attempt to define more precisely the significance of calcified lesions in the coronary arteries in relation to clinically significant lesions of coronary atherosclerosis. The topographic distribution of calcified lesions in the coronary arteries is also described, and the prevalence and extent of calcified coronary lesions in white and Negro men and women in New Orleans are examined.

Materials and Methods

Source and Preparation of Material

The main series of coronary arteries in this report was collected from 1,242 consecutive necropsies performed between May 1960 and August 1963 on patients aged 30 to 69 years at Charity Hospital of Louisiana at New Orleans and Office of the Coroner, Orleans Parish. The axial distribution of calcified plaques was determined in 349 specimens collected from consecutive necropsies performed between June 1962 and June 1963 on patients aged 20 to 69 years. These two series of specimens are part of the material from an international cooperative project to survey the geographic pathology of atherosclerotic lesions.

A third sample of 47 sets of coronary arteries (from specimens collected prior to May 1960) was used to compare the area of calcified plaques with the chemically determined calcium content.

The method of dissecting and storing specimens has been reported previously and is described in more detail in the Standard Operating Protocol of the International Atherosclerosis Project.
CORONARY CALCIFICATION

Table 1

The Distribution by Race, Sex, and Age of the 1,242 Consecutive Necropsies in the Survey of Coronary Artery Calcification

<table>
<thead>
<tr>
<th>Age in years</th>
<th>White</th>
<th>Negro</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>30-39</td>
<td>59</td>
<td>32</td>
<td>76</td>
</tr>
<tr>
<td>40-49</td>
<td>101</td>
<td>47</td>
<td>94</td>
</tr>
<tr>
<td>50-59</td>
<td>170</td>
<td>46</td>
<td>106</td>
</tr>
<tr>
<td>60-69</td>
<td>125</td>
<td>52</td>
<td>88</td>
</tr>
<tr>
<td>Totals</td>
<td>455</td>
<td>177</td>
<td>364</td>
</tr>
</tbody>
</table>

Grand Totals | 632 | 610 | 1,242 |

ect. In short, the arteries are slit longitudinally, cleaned of excess tissue adhering to the adventitia, and fixed in a flat position with neutral formalin. After staining with Sudan IV, they are stored in plastic bags.

The distribution of the series of 1,242 cases by race, sex, and age is shown in Table 1.

Classification of Cases

In analyzing results, the 1,242 cases have been classified into four groups based on cause of death or presence of disease defined as follows:

1. Atherosclerotic—all cases in which the primary cause of death was ascribed to coronary atherosclerosis or its sequelae (myocardial infarction or coronary occlusion and sudden death without infarction);

2. Accidental—all cases dying of accidental death or trauma;

3. Related diseases—all cases not assigned to groups 1 or 2 with any of the following conditions: diabetes mellitus, hypertension, cerebral vascular disease, cardiovascular syphilis, disabling peripheral vascular disease, or coronary heart disease not causing death; and

4. Other natural—all remaining cases.

Evaluation of Lesions

Stenotic and complicated lesions (hemorrhage, ulceration, or thrombosis) in the coronary arteries were evaluated visually by a team of pathologists without knowledge of identity or source of specimen. “Stenosis” was defined as a reduction in lumen size by 50 per cent or more as estimated in longitudinally opened vessels. The presence of recent or old myocardial infarction or coronary occlusion causing sudden death without infarction was recorded on standardized data forms at the time of necropsy.

The area of calcified plaques was measured by an objective method in which a radiograph of the artery was scanned to generate an electrical (video) signal that was analyzed electronically to obtain an area measurement. A radiograph of two sets of coronary arteries is shown in Figure 1.

Since the coronary arterial system is inherently variable, the measurement of calcified plaques has been made on a standardized fixed length of the three main branches; viz., the proximal 5 cm. of the right coronary artery (R), the proximal 5 cm. of the common plus anterior descending branch of the left coronary artery, the proximal 3 cm. of the circumflex branch of the left coronary artery.

The mass of calcium in the calcified plaques of the coronary arteries from a series of 47 cases was determined chemically by a method previously described. A product-moment correlation coefficient of +0.88 was determined between the area of the plaque and the mass of calcium in the plaque for the 42 arteries with detectable lesions. This coefficient indicates that variations in the area measurements provide a reasonable approximation of the variations in calcium content of the calcified plaques.

Figure 1

A soft x-ray radiograph of two sets of coronary arteries as prepared for analysis by flying-spot scanner. The irregular light areas represent calcified plaques and the lighter gray areas correspond to regions with elevated fibrous plaque. The central rectangular areas are for control of photographic processing and for standardization during analysis.
to random factors; and, in survey data such as these when “statistically significant” differences are observed, the possibility must also be considered that unknown factors (bias) may be acting to cause these effects.

Results

Topographic Distribution of Calcified Lesions

The curves of figure 2 show the manner in which the frequency of involvement with calcified plaque varies with distance from the orifice along the right and the left anterior descending coronary arteries. In both branches calcified lesions are most frequently located about 2 cm. from the orifice; however, in the right branch this maximum is much less pronounced; i.e., the lesions are distributed in a more uniform manner.

Race and Sex Distribution of Calcified Lesions

Table 2 gives the prevalence of calcified lesions and the mean per cent of the surface involved with calcified plaques in each of the three main branches of the coronary arteries for each race-sex group. In table 2, cases dying of coronary atherosclerosis and cases with diseases related to atherosclerosis have been excluded. The left anterior descending coronary artery has a consistently higher level of involvement than the other two branches. The left circumflex and the right coronary artery have about the same degree of involvement. In both men and women, the white person

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcified Lesions in the Three Main Branches of the Coronary Arteries by Race and Sex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race and Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>284</td>
<td>129</td>
</tr>
<tr>
<td>Negro</td>
<td>234</td>
<td>130</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Branch* of coronary artery</th>
<th>Prevalence (%)</th>
<th>Mean % surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>45</td>
<td>3.5</td>
</tr>
<tr>
<td>LAD</td>
<td>67</td>
<td>7.3</td>
</tr>
<tr>
<td>LC</td>
<td>42</td>
<td>4.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race and Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>50.9</td>
<td>48.9</td>
</tr>
<tr>
<td>Negro</td>
<td>48.1</td>
<td>48.0</td>
</tr>
</tbody>
</table>

Note: Based on a sample of 1,242 consecutive autopsies, ages 30 to 69 years. The 465 cases dying of coronary atherosclerosis or with atherosclerosis-related conditions have been excluded.

*R, right coronary artery; LAD, common plus anterior descending branch of the left coronary artery; LC, circumflex branch of the left coronary artery.

Circulation, Volume XXXII, December 1965
has greater involvement than the Negro, and in both race groups the male is more involved than the female. The mean ages of the four race-sex groups are slightly different; however, the statistical analyses with adjustment for age indicates that the race and sex differences are statistically significant ($p < 0.05$).

**Calcified Lesions in Disease Categories**

Table 3 gives the results of the analysis for grouping into the four broad disease categories, and figures 3 and 4 show how these data vary with age. The atherosclerotic death group has much higher prevalence and mean percent surface involvement than do the other three groups. The prevalence and extent of surface involvement in the group with atherosclerosis-related conditions are also greater than for the other natural death or accidental death groups. These differences are consistent within the four race-sex groups. The age-adjusted differences in prevalence and in mean extent of involvement between the atherosclerotic deaths and the other three groups are statistically significant ($p < 0.05$), but the differences among the other groups are not statistically significant. Figures 3 and 4 show that there is a steady increase with age in the prevalence or extent of lesions in accidental, related, or other natural death groups. In cases dying of coronary heart disease, the prevalence of lesions approaches the limit of 100 per cent in the 40 to 49 year age group and the mean extent of lesions also

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Atherosclerotic deaths</th>
<th>Related diseases</th>
<th>Other natural deaths</th>
<th>Accidental deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td>214</td>
<td>251</td>
<td>416</td>
<td>361</td>
</tr>
<tr>
<td>Prevalence of calcified plaque (%)</td>
<td>93</td>
<td>72</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Mean % of area with calcified plaque</td>
<td>17.5</td>
<td>7.2</td>
<td>5.8</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*For definitions, see text.
Note: Based on the total sample of 1,242 consecutive autopsies including white and Negro of both sexes.

**Table 3**

**Calcified Lesions in the Left Anterior Descending Coronary Artery: Classification by Cause of Death or Disease Category**

**Figure 3**

Prevalence of calcified plaques in the left anterior descending coronary artery by disease category within decade of age, 1,242 cases, white and Negro, both sexes. Figures below each bar indicate number of cases.

**Figure 4**

Mean per cent of the surface of the left anterior descending coronary artery with calcified plaques. Same sample as in figure 3.
Table 4

Age Dependence of the Relationship between Calcification of the Coronary Arteries and the Prevalence of Advanced Coronary Atherosclerotic Lesions

<table>
<thead>
<tr>
<th>Maximum level of calcified lesions in R, LAD, or LC coronary artery</th>
<th>Prevalence of ischemic myocardial lesions*</th>
<th>Prevalence of complicated lesions</th>
<th>Prevalence of stenotic lesions</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>3%  7%</td>
<td>4%  7%</td>
<td>1%  1%</td>
<td>303  138</td>
</tr>
<tr>
<td>Greater than zero</td>
<td>24%  32%</td>
<td>26%  41%</td>
<td>19%  35%</td>
<td>212  589</td>
</tr>
<tr>
<td>Less than 10%</td>
<td>9%  14%</td>
<td>11%  18%</td>
<td>5%  10%</td>
<td>468  435</td>
</tr>
<tr>
<td>10% or more</td>
<td>40%  46%</td>
<td>36%  59%</td>
<td>39%  56%</td>
<td>47  292</td>
</tr>
<tr>
<td>All cases</td>
<td>12%  27%</td>
<td>13%  35%</td>
<td>8%  31%</td>
<td>515  727</td>
</tr>
</tbody>
</table>

*For definition, see text.

Calcified Lesions and Advanced Coronary Atherosclerosis

Table 4 gives the prevalence of (1) ischemic myocardial lesions, (2) complicated coronary lesions, and (3) stenotic lesions in the coronary arteries for the two age groups 30 to 49 years and 50 to 69 years in cases with different levels of calcified lesions in the coronary arteries. In this analysis myocardial ischemia was considered present if examination of the heart at autopsy revealed a recent or old myocardial infarct, or a recent occlusion causing sudden death without infarction. In both age groups there is a large difference in the prevalence of these advanced lesions between cases with and cases without calcified lesions. It is of greater interest, however, to consider relative increase in the prevalence of these lesions when the presence of a given level of calcified lesions is known. For example, in the age group 30 to 49 years, the prevalence of ischemic myocardial lesions is more than three times as great (40 per cent/12 per cent) in those cases having 10 per cent or more of the surface of any branch of the coronary arteries calcified than it is for the total sample (i.e., where level of calcification is not known). This ratio has been calculated for each lesion and for each decade of age and is given in table 5. From these results it is clear that the value of information concerning calcified coronary plaques in the differential diagnosis of clinically significant coronary artery disease is greatest in younger individuals.

Discussion

Comparison with Results of Other Studies of Coronary Artery Calcification

Blankenhorn has extensively reviewed the subject of coronary arterial calcification and has confirmed the fact, first reported by Faber in 1912, that calcified lesions of the coronary arteries are of atherosclerotic origin and are not due to Monckeberg's sclerosis. He has stressed the possibilities of antemortem detection of coronary artery calcification by cinefluorography as developed by Jorgens and co-workers. These latter authors have reported on a series of 803 examinations and in a smaller series of cases that came to autopsy reported an "exceptionally high correlation of coronary calcium seen in vivo with moderate to severe coronary atherosclerosis at post mortem."

More recently Oliver et al. have used fluoroscopy with image intensification to study the

Table 5

Proportional Increase in Prevalence of Advanced Coronary Lesions with the Determination That Calcification Exceeds 10 Per cent of the Surface for Any Branch of the Coronary Arteries

<table>
<thead>
<tr>
<th>Type of advanced lesion</th>
<th>Proportional increase in prevalence at age (yr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-39</td>
</tr>
<tr>
<td>Ischemic myocardial lesions</td>
<td>3.9</td>
</tr>
<tr>
<td>Complicated lesions</td>
<td>2.6</td>
</tr>
<tr>
<td>Stenotic lesions</td>
<td>5.0</td>
</tr>
</tbody>
</table>
incidence of coronary artery calcification in 500 patients. They conclude that in many patients, especially those below age 50, this method "may act as a useful adjuvant to a difficult differential diagnosis."

This necropsy study confirms the fact, reported in studies on living patients by Jorgens et al.\textsuperscript{2-5} and by Oliver et al.,\textsuperscript{6} that the proximal left anterior descending branch is the most prominent site for coronary calcified lesions. These latter studies observed a greater prevalence of calcified lesions in the right than in the left circumflex branch; however, we found plaques with approximately equal frequency in both branches. This difference in relative involvement of the right and the left circumflex branches, if not due to chance, may be due to differences in populations sampled but is more likely due to sampling bias or to differences in relative detectability of lesions in these two branches. In this necropsy study and in the necropsies reported by Oliver et al.,\textsuperscript{6} the prevalence of calcified plaques is higher than is observed in living individuals. This is undoubtedly due to considerably higher sensitivity when examining excised arteries.

Young et al.\textsuperscript{17} have examined coronary arteries from 143 hearts histologically and observed a distribution of calcification in the left anterior descending branch similar to that in figure 2.

\textbf{Relation of Calcified Lesions to Other Advanced Lesions}

The topographic distribution of calcified lesions observed in this series agrees well with the distribution of occlusive lesions reported by others. Rodríguez et al.\textsuperscript{18} recently reported a series in which two thirds of all occlusions were within 4 cm. of the ostia. They also observed that the occlusions ranged farther from the coronary ostium in the right than in the other branches. Pitt et al.\textsuperscript{19} also found 70 per cent of the occlusions within 4 cm. of the ostia and observed the highest incidence of occlusion a short distance from the ostia. Crawford et al.\textsuperscript{20} found that the occlusive lesions were concentrated in the proximal region of the left coronary artery and were distributed more uniformly along the right coronary artery. Fisher\textsuperscript{21} observed that occlusive lesions and intimal hemorrhages reached a maximum at a distance of 4 to 5 cm. from the origin of the coronary arteries. Blankenhorn and Stern\textsuperscript{2} also found sites of occlusion to be most frequent in the proximal portion of the artery. Young et al.\textsuperscript{17} showed that for the left anterior descending branch topographic variations in intimal thickness are similar to variations in the frequency of calcification.

The interartery distribution of coronary occlusion has been described by a number of authors. Schlesinger and Zoll,\textsuperscript{22} and Rodríguez et al.\textsuperscript{18} observed occlusion with about equal frequency in the left anterior descending and the right, and with lower frequency in the left circumflex branch. Pitt et al.\textsuperscript{19} found occlusion to be almost as frequent in the right and the left circumflex as in the left anterior descending branch. Crawford et al.\textsuperscript{20} and Fisher\textsuperscript{21} found occlusive lesions most often in the left anterior descending branch, less often in the right, and least frequently in the left circumflex. This disparity in the reports on the interartery distribution of occlusive lesions may result from undetermined sources of bias in the selection inherent in all autopsy studies. The consensus, however, would be that occlusive lesions are distributed among the three main branches in about the same manner as reported here for the calcified lesions.

In this study, the cases dying of coronary disease had a considerably greater involvement with coronary calcified plaques than the other cases. The increase in prevalence or extent of calcification in deaths due to coronary heart disease compared to that in accidental deaths is greatest in the youngest age group. Oliver et al.\textsuperscript{6} also observed that in the living there was a two-fold increase in prevalence of coronary calcification in men with clinical coronary heart disease and a three-fold increase in women with clinical coronary artery disease over the corresponding age-matched controls. Lieber and Jorgens\textsuperscript{4} found a much higher prevalence of clinical coronary heart
disease in patients with coronary calcification than in those without calcium.

Our data also show that ischemic myocardial lesions, complicated coronary artery lesions or stenotic lesions are strongly associated with calcified coronary lesions. This association is especially strong with stenotic lesions, confirming the suggestion of Oliver et al. that "calcified lesions are probably more closely related to stenosis than to any other functional impairment of the arterial lumen."

Most investigators have stressed the point that the significance of coronary calcification is much greater in the young patient than in the old patient. The values for the ratio of prevalence of calcification in living patients with coronary heart disease to the prevalence in the age-sex-matched control, calculated from table 2 of Oliver et al.,8 increase from 1.7 in the "over 65 year" age group to greater than 10 in the "less than 45 year" age group. Our data confirm this observation for calcification detectable by radiography of excised coronary arteries.

**Race and Sex Differences in Coronary Calcification**

The race and sex differences in prevalence and extent of coronary artery calcification generally parallel the rate of coronary heart disease in Louisiana.23 There is an exception in the relatively high level of calcification observed in the white female. This relatively high level in the white female suggests that although there are true sex and race differences in the formation of calcified plaques, there are other factors affecting the formation of calcified plaques that do not cause a parallel increase in the incidence of coronary heart disease.

**Conclusions**

The data in this report indicate an association between calcification of coronary arteries and clinically significant atherosclerotic lesions. This association is sufficiently strong that radiologic detection of calcification in the coronary arteries in the living should provide information of value in the differential diagnosis of advanced coronary atherosclerosis, especially in the young. It should also prove of value in selecting those younger patients with high risk of clinical coronary artery disease who should be subjected to the more drastic control measures. To the extent that the results of this study of necropsied cases from one population with high levels of coronary heart disease can be extended to other populations, radiologic detection of coronary calcification in the living should also be of value in the assessment of severity of atherosclerosis in epidemiologic investigations or in studying the geographic pathology of atherosclerosis.

**Summary**

Measurements of the per cent of the surface with calcified lesions have been made for the three main coronary arteries from 1,242 consecutive necropsies of whites and Negroes between the ages of 30 to 69 years.

Calcified lesions were most prevalent and most extensive in the left anterior descending branch and occurred with greatest frequency at 2 to 3 cm. from the orifice. Whites had greater involvement than Negroes and males had greater involvement than females. Prevalence and extent of calcification have been compared in four cause-of-death or disease categories; cases dying of coronary heart disease had greater involvement than the other three groups.

The prevalence of ischemic myocardial lesions, complicated coronary lesions, or stenotic lesions was greater for cases with calcified lesions, and this prevalence increases with increase in extent of calcified lesions. The significance of the presence of coronary calcified lesions for the diagnosis of advanced coronary atherosclerosis is greatest for younger individuals.

**Acknowledgment**

Drs. Robert Flair and James Long (as medical students) did the chemical calcium determinations. Mr. Robert Gary supervised the collection and preparation of the specimens. Miss Vivian Tabares, Mr. Howard Kavanaugh, Mr. Billy Chestang, and Mr. Melvin Bagget prepared and analyzed the radiographs. The statistical analyses were performed in the data-processing laboratories of the Department of Biostatistics at Louisiana State University School of Medicine.

_Circulation, Volume XXXII, December 1965_
References


The Enigma of Creativity

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Circulation. 1965;32:948-955
doi: 10.1161/01.CIR.32.6.948

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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