Coronary calcium: The good, the bad, and the uncertain

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Abstract
Background Coronary calcium deposits have been widely regarded to result from a passive process of encrustation or adsorption of mineral onto advanced, complex atherosclerotic lesions. Increasing interest has focused on noninvasive radiologic detection of these calcium deposits as a diagnostic and prognostic adjunct to clinical evaluation of coronary artery disease, particularly with the use of newer, high-resolution imaging techniques such as electron beam computed tomography.
Methods and Results We reviewed the literature on coronary calcium and its relation to pathologic atherosclerosis, angiographic stenoses, and clinical events. Clinical calcium detection studies have demonstrated an association between coronary calcium and both extent of coronary artery disease and risk of adverse events. These studies have in the past tended to reinforce the perception that calcific deposits result from a passive mineralization process, signify advanced coronary artery disease, and foreshadow future coronary events.
Conclusions Recent pathologic, genetic, clinical, and biochemical evidence reviewed in this article suggests that coronary calcium deposits are a manifestation of a complex, organized, and regulated process similar in many respects to new bone formation and may not be a reliable indicator of either the extent of coronary disease or the risk of a future event. These studies also suggest that atherosclerosis and calcific deposits may be distinct pathologic entities that frequently occur together and are related to each other in ways that are poorly understood. (Am Heart J 1999;137:806-14.)

Robert Browning
Nearly 3 centuries ago, Thebesius first observed calcium deposits in the coronary arteries, and these deposits were long thereafter regarded as the salient feature of coronary sclerotic pathology.1 By the middle of the 20th century, however, the prevailing view held calcific deposits to be merely an ancillary degenerative byproduct of advanced atherosclerotic disease, "...a terminal monumental deposit marking the sites formerly occupied by living tissue."1,2 This perception has in recent years undergone considerable change.

Nevertheless, many investigators recognized that noninvasive imaging of coronary calcium might be useful to identify patients with unsuspected coronary artery disease, and attempts were made to visualize calcific deposits with various radiologic techniques. Little success was met, however, until the advent of high-resolution techniques such as image intensifier fluoroscopy,3-5 and, more recently,
Clinical evidence: Is coronary calcium bad?
Detection of coronary artery calcium does indeed demonstrate promise as a diagnostic and prognostic adjunct to clinical evaluation. EBCT accurately detects calcium. Moreover, in symptomatic patients, EBCT appears to be moderately useful in predicting the severity of coronary artery disease compared with angiography or histopathology. A recent review of 7 studies that compared calcium detection by EBCT with angiographic findings of significant (50% narrowing) stenosis on coronary angiography reveals a range of sensitivities from 85% to 100%; however, the specificities were substantially lower, ranging from 41% to 76%. Positive predictive values ranged from 55% to 84%, whereas negative predictive values were somewhat more encouraging, ranging from 70% to 100%. Four published studies have directly compared radiographic (EBCT or fluoroscopy) evaluation of coronary calcium with exercise testing in the same asymptomatic patients who underwent coronary angiography. These studies also indicate that exercise testing and radiographic calcium detection have roughly comparable sensitivities (weighted averages of 4 studies involving 811 patients were calcium, 73%; exercise electrocardiography, 74%; thallium, 78%) and specificities (calcium, 83%; exercise electrocardiography, 72%; thallium, 83%) for detection of significant angiographic stenosis. These studies and others have clearly demonstrated a significant association between coronary calcium quantitated by EBCT and angiographically defined obstructive disease; however, these data are of limited value considering the well-known limitations of coronary angiography (incisively reviewed by Topol and Nissen). In addition, EBCT provides information that is primarily anatomic, whereas exercise stress testing provides information that is primarily physiologic, and although both may be used as clinical screening tests for the presence of disease, direct comparisons of EBCT and stress testing should be interpreted with caution. A more relevant issue is the relation of the quantity of coronary calcium to the quantity of atherosclerosis; from a clinical standpoint, however, the crux of the issue is the relation of both to the probability of a future coronary event.

Pathologic studies have demonstrated a clear relation between the quantity of coronary calcium and the quantity of atherosclerosis, giving rise to hopes that coronary calcium may be a reliable surrogate measure of coronary atherosclerosis. However, for a given degree of luminal narrowing or atherosclerotic plaque area, the quantity of calcium varies widely. Nevertheless, prospective studies have shown an association between the presence and quantity of calcium and the risk of a subsequent event.

Margolis et al performed angiography and cinefluoroscopy in 800 consecutive patients. The 5-year survival rate in patients with coronary calcium deposits was 58% compared with 87% in patients without calcium deposits (P < .001), and the predictive value of calcium was independent of age, sex, number of angiographically diseased vessels, results of exercise tests, or left ventricular function. These 5-year survival rates appear exorbitant by today's standards, suggesting that current clinical treatment of coronary disease is substantially improved compared with treatment at the time this study was undertaken. Nevertheless, the major findings of this study are indeed supported by more recent studies. Recent prospective digital cinefluoroscopic data indicate that asymptomatic subjects with coronary calcium are 3 times as likely to undergo myocardial revascularization or have new-onset angina, myocardial infarction, or sudden cardiac death when compared with asymptomatic subjects without coronary calcium. Furthermore, event risk increases significantly with the number of calcified coronary vessels: In asymptomatic subjects at high risk, the risk of a hard event at roughly 5 years' follow-up after digital cinefluoroscopy was 3% in subjects without calcium, 6% in subjects with 1 calcified vessel, 8% in those with 2 calcified arteries, and 10% in subjects with 3-vessel calcification. These differences were statistically significant, and the association between number of calcified vessels and probability of a subsequent event was true for both myocardial infarction and coronary heart
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disease death. After adjusting for risk factors, the risk of myocardial infarction or sudden cardiac death increased 1.4 times for every calcified artery. Similar results with the use of EBCT in both asymptomatic subjects33-35 and symptomatic patients undergoing angiography13 have also been obtained: There is a significant association between coronary calcium quantified by EBCT and the occurrence of subsequent coronary events.

These data clearly indicate that coronary calcium is associated with a “bad” outcome. Yet coronary calcium appears to have definite and perplexing limitations in predicting future events. For example, in a study of 1196 asymptomatic subjects, EBCT-detectable calcium did predict future events, but its predictive accuracy was not superior to that of standard risk factors.33 Prospective data in asymptomatic subjects with risk factors from our laboratory indicate that >45% (16 of 35) of deaths or infarctions occurred in patients with EBCT calcium scores <152; the remaining events occurred in subjects having calcium scores ranging from 152 to 4576.33,36 The significance of these findings is that a calcium score of 159 yields, by receiver operating characteristic curve analysis, the optimal sensitivity and specificity for predicting a maximal angiographic stenosis somewhere in the coronary arterial system of <Bild>80%.26 However, our data indicate that substantial numbers of those with lower calcium scores may have myocardial infarction and sudden coronary death. Furthermore, out of 13 infarctions and coronary deaths occurring in a cohort of 368 patients who underwent both EBCT and angiography, one of the fatal infarctions occurred in a patient with 3-vessel coronary disease who had a calcium score of zero, and 5 of the 13 events (infarctions and sudden coronary heart disease death) occurred in patients with low calcium scores (<Bild>104).14 Collectively, these findings would appear to be consistent with current American Heart Association guidelines,8 which emphasize that a negative calcium scan does not rule out the presence of atherosclerosis and of pertinence that unstable plaque may exist in the absence of calcific deposits anywhere in the coronary arteries. However, for a given quantity of atherosclerosis, why does there appear to be such variability in both the amount of calcium and the probability of an event?

Atherosclerosis and calcification are distinct yet related processes
Pathologic evidence
If coronary calcium deposits are a simple and direct consequence of the atherosclerotic process, one would predict that the distribution of atherosclerosis in the coronary arteries would be very similar to the distribution of calcific deposits; a given degree of atherosclerosis should result in a similar degree of calcific deposits at any given site. Accordingly, we reviewed the pathologic literature concerning the distribution of coronary atherosclerosis compared with the distribution of coronary calcium determined by pathologic postmortem analysis.

Mautner et al11 performed quantitative histomorphometric analysis on 4298 coronary artery segments stained with Movat stain and determined cross-sectional area stenosis and the area of calcific deposits for each section. Average percentage of stenosis and average percentage of total calcium in each artery (right, left circumflex, left main, and left anterior descending) were plotted as a function of distance from the ostium (Fig 1).

Fig. 1. Average percentage of stenosis (left y-axis) and average percentage of total calcium (right y-axis) of each major coronary artery plotted as function of distance in centimeters from ostium. Circles indicate calcific deposits; squares indicate stenosis. Top, Right coronary artery; middle, circumflex coronary artery; bottom, left main and left anterior descending coronary arteries. Data from reference ; n = 28 patients for right coronary artery and circumflex coronary arteries; n = 35 patients for left main and left anterior descending coronary arteries.
The left main artery was depicted as the proximal portion of the left anterior descending artery.

The left main artery demonstrated a high amount of calcific deposits. In the left anterior descending (which includes the left main artery as its proximal portion) and circumflex coronary arteries there was a greater proportion of calcium proximally, whereas in the right coronary artery, calcium was distributed relatively more evenly and at greater distances from the ostium. For all 3 arteries, the greatest amount of calcium appeared to be within the proximal 5 cm, with the highest amount at approximately
2 cm for the right coronary artery, 1.5 cm for the circumflex, and approximately 2 cm for the left main and left anterior descending arteries. All 3 arteries appeared to have a second small distal increase in calcium, at approximately 9 cm for the right coronary artery, 5 cm for the circumflex artery, and 7 cm for the left anterior descending artery (Fig 1).

We analyzed these data in more detail for the left main and left anterior descending arteries. We compared the number of segments with a cross-sectional area narrowing of >75% (n = 222 segments) with the number of segments with calcific deposits (n = 383 segments). We then plotted the frequency distributions of stenotic segments and calcified segments as a function of distance from the origin of the artery (Fig 2).

Fig. 2. Frequency distribution of calcified segments (circles and bold line) and stenotic segments (open squares and open line) plotted as function of distance from origin of left main/left anterior descending coronary artery. Origin is defined as ostium of left main coronary artery; left main is included as most proximal portion of left anterior descending artery. Stenotic segments are defined as segments (n = 222) with >75% narrowing in cross-sectional area. Calcified segments are those that contained any calcium (n = 383). Bold vertical line at 3.4 cm represents expected distance of calcified segment from origin; open vertical line at 4.8 cm represents expected distance of stenotic segment from origin. Expected distance of calcified segment is significantly more proximal than expected distance of stenotic segment (P = .001; t test for matched data). Data adapted with permission from the Radiological Society of North America: Mautner GC, et al. Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. Radiology 1994;192:619-23.

For the most proximal 3.5 cm of the left anterior descending artery (including the left main as its most proximal portion), there was a higher frequency of calcified segments compared with stenotic segments. Between 3.5 cm and approximately 6 cm, the frequencies were equivalent. However, distal to 6 cm there was a higher frequency of stenotic segments compared with calcified segments. The expected distance of a calcified segment from the ostium was calculated to be 3.4 cm, whereas the expected distance of a stenotic segment from the ostium was 4.8 cm (Fig 2). This difference was statistically significant (P = .001; Student’s t test for matched data).

These data are consistent with previous work. Young et al also found that for a given degree of atherosclerosis, there was much more calcium in the proximal portion of the left anterior descending artery than the distal portion (Fig 3).

Fig. 3. Atherosclerosis and calcific deposits plotted as function of distance from origin of left anterior descending coronary artery. Left y-axis is degree of sclerosis, defined as intimal area (I) divided by total cross-sectional area (E), with the subscript c indicating coronary artery. Frequency of calcification (right y-axis) is defined as number of sections with calcified area of <5 m2 divided by total number of sections. Data are based on analysis of 1670 coronary artery sections. Adapted from The American Journal of Cardiology: Young W, et al. The quantitation of atherosclerosis, I: relationship to artery size. 1960;6:288-93. Copyright © 1960 with permission by Exerpta Medica, Inc.

Image not available
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The distribution of calcific deposits in the left anterior descending artery appeared to be different from the distribution of atherosclerosis, which suggests that the underlying processes leading to atherosclerosis and calcium deposition may be distinct. Very recent pathologic evidence from Sangiorgi et al,29 who used a unique nondecalcifying histopathologic methodology, also indicates significant correlations but wide variabilities between the quantity of atherosclerosis and the quantity of coronary calcium.29

Evidence from animal atherosclerosis regression models also supports the concept that atherosclerosis and calcification are related yet distinct. For example, it has been observed that calcium content in arterial wall increases as lesions regress.38 More recently, Strong et al39 examined regression of lesions and radiographically evaluated calcium in the abdominal aorta, carotid sinus, and the iliofemoral artery in a rhesus monkey model. These investigators found that more animals in the regression group had calcium than animals in the progression group. These data suggest that calcification and atherosclerosis may not always be directly correlated. Furthermore, they also suggest that attempts to track the progression or regression of atherosclerotic disease by serial evaluation of calcium may result in misleading conclusions, particularly in individuals undergoing aggressive lipid-lowering therapy.

Genetic evidence

Several lines of genetic evidence support the concept that atherosclerosis and calcification are distinct but related processes. First, a familial syndrome of aortic calcium deposition without evidence of aortic or coronary atherosclerosis has been reported.40 Second, phenotypic expression of coronary calcium deposition in asymptomatic but high-risk adult human subjects is dependent on ethnic origin.41,42 Black subjects had a significantly lower prevalence of coronary calcific deposits when compared with nonblack (white or Asian American) subjects. Phenotypic expression cosegregated with race even after controlling for coronary artery disease risk factors.41,42 Third, autopsy studies have demonstrated a lower prevalence of coronary calcium in black subjects when compared with white subjects with similar extent of atherosclerosis.43-45 Although these ethnic differences do not negate the possibility that calcium is only “bad,” they do suggest that both calcium deposition and atherosclerosis may be expressed dissimilarly in distinct ethnic groups. Fourth, Qiao et al46 examined atherosclerosis and calcium deposition in strains of inbred mice maintained on an atherogenic diet or a standard chow diet. Advanced atherosclerotic lesions developed in several strains, but both advanced atherosclerotic lesions and increased incidence of aortic and coronary calcium deposition, which was partially independent of atherosclerosis, developed in mice targeted for a null mutation in the apolipoprotein E gene. Genetic cross-analysis indicated that aortic calcium appeared to be determined by 2 or more genetic factors. However, although multifactorial models could not be completely excluded, coronary calcium deposition appeared to be determined by 1 major gene exhibiting incomplete penetrance. Collectively, these data suggest (1) genetic determinants of atherosclerosis and calcium deposition are distinct yet related and (2) genetic factors underlying aortic calcium deposition may be different from those underlying coronary calcium deposition.

Calcium and plaque rupture: Is calcification good?

Compelling evidence has implicated plaque rupture and subsequent thrombosis as the pathophysiologic event precipitating the clinical syndromes of unstable angina, myocardial infarction, and sudden death.47-52 Plaque volume or mass appears to have little bearing on the likelihood of rupture.49,51 However, plaque structure and composition appears to be a major determinant of the propensity of a plaque to rupture.49,51,53,54 Ruptured plaques tend to have high lipid and macrophage content54-56 and contain less collagen, smooth muscle cells, and calcium55,57 than nonruptured plaques. Importantly, areas of low tensile strength within the plaque are particularly vulnerable to rupture.51,53 Lipid-filled plaques exhibit diminished load-bearing capabilities, resulting in increased stress elsewhere in the lesion, particularly at the lateral edges,52,53 and it has been demonstrated that local variations in circumferential stress are associated with sites of plaque rupture.58 This may help explain why plaques frequently rupture at their edges,53 although it should be noted that the shoulder region of plaques is also where inflammatory cells such as activated mast cells (which secrete metalloproteinasases and other proteolytic enzymes) tend to accumulate.49,59-64 In vitro biomechanical data indicate that calcified plaques are much stiffer than either cellular or hypocellular plaques and are highly resistant to rupture.53,65,66 This is supported by data obtained in vivo by intravascular ultrasound that also indicate the relative stability of calcified lesions.67-69
We have proposed that calcium deposits may tend to impart stability to an atherosclerotic lesion and decrease the probability of plaque rupture. Luminal narrowings are believed to reflect in part past plaque ruptures and remodeling. The quantitative histomorphometric data just mentioned (Fig 2) and the pathologic data of Young et al suggest that these events occur more frequently in distal noncalcified rather than in proximal calcified segments.

One may argue that because morbidity and mortality is a consequence of plaque rupture and thrombosis rather than atherosclerosis per se, the perspicacious issue would be the relation between the distribution of the sites of plaque rupture and the distribution of calcium deposits: Is a calcified plaque less likely to rupture than a noncalcified plaque? Johnson et al examined 297 carotid arteries with real-time B-mode ultrasonography in asymptomatic patients. Plaques were classified as soft, dense, or calcified, and the degree of stenosis was quantified by cross-sectional area calculations and spectral analysis. Patients were followed-up for 3 years, and symptomatic events (transient ischemic attacks and strokes) were recorded. Regardless of the severity of stenosis, patients with calcified plaques were much less likely to have a symptomatic event than patients with soft or dense plaques. More recent studies have also shown an association between carotid artery plaque composition or echogenicity determined by real-time ultrasonography and symptomatic cerebral ischemia. Hypoechoic plaques were strongly (odds ratio 3.00, P = .005) associated with transient ischemic attacks, whereas densely echogenic plaques were not.

Black subjects demonstrate a significantly lower prevalence of calcific deposits that is independent of coronary artery disease risk factors or extent of atherosclerosis. Despite having significantly less coronary calcium, black subjects nevertheless had more coronary heart disease events (new-onset angina pectoris, myocardial infarction, or death from coronary artery disease) than non-black subjects with similar risk factors (clinical follow-up period of 45 ± 10 months; 99.9% follow-up). One possible explanation is that plaque composition, particularly quantity of coronary calcium, varies with ethnicity, and atherosclerotic plaques in black subjects may be more susceptible to rupture compared with plaques in nonblack subjects. Taken together, these data suggest that coronary calcium may tend to be associated with diminished probability of plaque rupture; calcification, in other words, may be "good."

Calcification is similar to bone formation: The uncertain

Recent studies have highlighted our ignorance regarding the pathophysiologic mechanisms leading to coronary calcium deposition and suggest that calcium deposition is a complex, active process similar in many ways to bone formation. Pathologic data indicate that coronary calcium deposition begins as early as the second decade of life and may precede the development of complex lesions. Matrix vesicles, typically found in developing bone, have been observed in calcified coronary lesions. Many proteins involved in bone formation have been found in calcified lesions. A novel smooth muscle cell subtype (calcifying vascular cell) has been found in calcified lesions that can assume an osteoblastic phenotype in vitro. These cells spontaneously form nodules, express osteopontin and bone morphogenetic protein (BMP)-2 mRNA, secrete alkaline phosphatase, osteonectin, osteocalcin, and collagen type I, generate hydroxyapatite mineral, and respond to osteogenic factors such as transforming growth factor-1 and BMP-2.3-8 Recently, Shioi et al have shown that bovine vascular smooth muscle cells are similarly capable of forming both diffuse and nodular hydroxyapatite deposits when cultured in the presence of glycerophosphate, ascorbic acid, and insulin. Calcification was associated with a time-dependent increase in expression and activity of alkaline phosphatase (generally considered a hallmark of the osteoblast phenotype) and was not detected in control fetal smooth muscle cells.

Pathologic studies indicate that atherosclerotic calcification may appear indistinguishable from fully formed lamellar bone, consisting of trabeculae, lacunae, and even marrow. Interestingly, implantation of BMP into skeletal muscle of mice results in bone formation, complete with hemopoietic marrow. Clearly, calcium deposition is a complex, organized, and regulated process, whose details we have only begun to ascertain.

Do we call the chessboard white—or black?

Data reviewed here have shown a definite association between atherosclerotic calcium deposition and both severity of disease and poor prognosis; calcification, then, appears to be "bad." On the other
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Hand, clinical and biomechanical studies suggest that calcific deposits tend to diminish vulnerability to plaque rupture; calcification, then, appears to be "good." We suggest that both may be true—the chessboard is white and it is black, and either descriptor alone is misleading. Calcium deposits indicate the presence of atherosclerotic disease, and in general, the more calcium deposition, the more extensive atherosclerosis. A subset of atherosclerotic lesions, specifically unstable lesions, tend to cause coronary events. However, unstable lesions may tend to be uncalcified, whereas stable lesions may more frequently be calcified.

Calcium is bad because the quantity of calcific plaque roughly reflects the total sum of atherosclerotic areas in segments of the coronary tree. However, what determines the probability of a coronary catastrophe is not only the amount of atherosclerosis but the propensity of individual plaque segments to rupture and collect blood elements that obstruct the arterial lumen. Here calcification may be good and connote a protective effect. The following mathematical diversion clarifies this point.

Here, P(t) denotes the probability of plaque rupture somewhere in the coronary tree at time t, and dl is an infinitesimal segment length in that tree. P(t) will be related to the plaque areas as follows:

\[ P(t) = \int A(l,t) p(l,t) \, dl \]

The argument between the integral sign and dl is a product of 2 factors. The plaque area, \( A(l,t) \), changes with location, l, in the coronary tree, and changes with time (progresses or regresses). This plaque area is related to the amount of calcium ("bad"). The second factor in the argument, \( p(l,t) \), is the plaque vulnerability function. This is the probability that a plaque at location l will rupture at time t. This probability increases with the size of the lipid core54 but decreases with the thickness of the fibrous cap54 and with the amount of calcium deposited in the plaque.58 Thus this factor will contribute to an inverse relation between the probability of coronary death or infarction and the measured amount of deposited calcium ("good").

Cities are occasionally buried by volcanic eruptions. The chance that a city will be buried depends not only on the number of nearby peaks but also on the volcanic activity of each one. Some cities with many surrounding mountains may never experience a volcanic eruption. However, residents of ancient Pompeii, as it turned out, could take little solace in the fact that Vesuvius was the only large mountain in the vicinity.

Whether perceived as "good" or "bad," however, it is increasingly evident that atherosclerotic calcification is a complex, regulated, and active process distinct from yet related to atherosclerosis. However, there is substantial lingering uncertainty, and much remains to be learned regarding the details of this process, its relation to atherosclerosis, and its pathologic and prognostic implications.

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