

Imaging of Coronary Artery Calcification

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Abstract

Coronary artery disease is a leading cause of morbidity and mortality among Americans. The traditional methods of evaluating coronary artery disease rely on the evaluation of the patient's symptoms and the presence of advanced disease. Until recently there was no method of early screening for coronary atherosclerosis in an asymptomatic population. However, calcification is a recognized marker for disease and is sometimes a component of the atheromatous plaque. With the advent of electron-beam computed tomography and subsecond helical computed tomography, a method of screening for and quantitating the amount of coronary calcification has been developed. The coronary calcium score is based on both the area and density of the calcification. This methodology can identify patients at risk for coronary artery disease, so that risk factor modification and preventive therapy can be initiated early in the course of the disease.

Key Words: Coronary artery disease, atherosclerosis, electron-beam computed tomography, computed tomography, coronary artery calcification.

Introduction

CORONARY HEART DISEASE (CHD) is the leading cause of death among Americans. American Heart Association statistics (1) document more than 459,000 deaths from CHD in 1998. Of these deaths, 220,000 occurred before the victims could be hospitalized; they were often sudden deaths. It is estimated that this year 1,100,000 Americans will have a coronary event (myocardial infarction or fatal CHD). A 1995 study calculated that primary prevention of myocardial infarction could prevent more than 100,000 deaths in the United States each year (2). Therefore, the detection of coronary heart disease early in its course is of great potential importance. Yet, established risk factors fail to predict approximately one-third of

future deaths due to coronary heart disease (3). Moreover, the current noninvasive methods of detecting CHD due to coronary artery disease (CAD), such as exercise treadmill testing and myocardial single-photon-emission computed tomography (CT), depend on the presence of advanced stenoses within the coronary arteries.

Calcification is closely associated with atheromatous plaque, and is a recognized marker for coronary artery disease (4–7). In recent years, a new generation of CT scanners was developed that can acquire images very rapidly. These scanners, called electron beam scanners, can eliminate motion artifact from the heart and clearly image the coronary arterial tree and possible coronary calcification. This type of scanner is highly sensitive, making it an excellent tool for detecting coronary atherosclerosis, so that preventive strategies and risk modification can be implemented to decrease morbidity and mortality.

Pathophysiology of Coronary Artery Atherosclerosis and Calcification

The etiologic mechanism of coronary artery atherosclerosis has been studied in detail in re-

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cent years. As a result, our knowledge of the process has grown considerably. The most widely held theory is based on the "response to injury" hypothesis (8). The essential element of this hypothesis states that injury to the endothelial cells, which induces a chronic inflammatory response, leads to atherosclerosis. This response of the endothelial cells leads to the various types of atherosclerotic lesions (9, 10).

The earliest lesions begin in childhood and are known as fatty streaks. They consist predominantly of macrophages that have migrated into the intima of the vessel. However, a variable amount of smooth muscle cells can also be found in the lesions. Both cell types in these lesions are rich in lipid content; calcium can be detected within the lipid core. Fatty streaks are sessile and cause no obstruction to the artery. They have no clinical sequelae. In fact, these lesions are found in all young adults, including those who do not develop occlusive atherosclerotic disease.

The formation of fibrous plaque is the next step in the progression of atherosclerosis. It is characterized by the migration and proliferation of smooth muscle cells into the intima. These cells form a fibrous cap over the deeper layer of lipid-laden macrophages by depositing connective tissue matrix as well as intracellular and extracellular lipids. Again, calcium can be found in these lesions. The fibrous plaque is an elevated lesion of the arterial wall and protrudes into the lumen. Therefore, it can have clinical sequelae.

The more advanced lesion of atherosclerosis is sometimes called the complicated lesion. The fibrous cap becomes vascularized. In addition, the lipid-rich core enlarges and often calcifies. These lesions can be complex due to hemorrhage of the fibrous cap as well as its calcification. If the cap fissures or ruptures, an intense thrombogenic cascade can ensue that may lead to occlusive coronary disease.

Until recently, it was believed that the calcium in atherosclerotic plaques was simply calcium phosphate, which precipitated in a passive manner. Instead, it has been shown that the calcium in coronary arteries is in the form of calcium hydroxyapatite and is deposited in a process similar to that of active bone formation (11). Fitzpatrick et al. used undecalcified post-mortem coronary arteries to study mineralization (12) and found that calcification was present in all atherosclerotic plaques. In addition, they identified a cell attachment protein (osteopontin), a protein associated with calcification (osteonectin) and a gamma-carboxylated protein that regulates mineralization (osteocalcin).

Bostrom et al. identified bone morphogenic protein 2a in calcified atherosclerotic plaques (13). These studies show that calcification in atherosclerotic lesions is an active process, regulated in a manner similar to that of bone mineralization.

Coronary Artery Calcium-Imaging Techniques

Coronary artery calcification can be detected by multiple imaging modalities. Plain radiography, fluoroscopy, computed tomography, ultrasound and magnetic resonance imaging (MRI) have been used. Fluoroscopy and CT are the methods most commonly used today.

Chest radiography can detect coronary artery calcifications. However, it is limited by overlying shadows as well as by the amount and density of the calcifications. One study reported an accuracy rate of only 42% (14).

Fluoroscopy is frequently used to detect coronary calcifications, since it is a component of coronary angiography. Both conventional fluoroscopy and, more recently, digital subtraction fluoroscopy are being utilized. In a study of asymptomatic male air-crew members who underwent coronary angiography because of one or more abnormal screening tests, coronary artery calcification had a 66.3% sensitivity and a 77.6% specificity for predicting angiographically significant (greater than 50% diameter narrowing) stenosis (15). The authors concluded that the absence of fluoroscopically detectable coronary artery calcification indicated a low likelihood of significant coronary artery disease, while its presence raised the likelihood.

While fluoroscopy is relatively inexpensive and widely available, it does have disadvantages. One major limitation is that it is often unable to detect small calcium deposits. Agatston et al. (16) found that only 52% of calcium deposits seen on electron-beam CT (EBCT) could be detected fluoroscopically. The mean attenuation value for the EBCT-detected calcifications was +99 Hounsfield units (HU), whereas that for the fluoroscopically detected calcifications was +546 HU. This study demonstrated that only the larger, more heavily calcified deposits were detectable with fluoroscopy as compared with EBCT. Another disadvantage is its inability to provide a clear image in some patients with unusual body habitus, as well as in those with overlying anatomic structures and other cardiac calcifications (valve annuli, myocardial and pericardial calcifications). In addition, fluoroscopy is heavily de-

pendent on the skill and experience of the operator as well as the number of views obtained.

CT is sensitive for detection of calcifications, due to its ability to differentiate calcium from adjacent soft tissues (Fig. 1). A study was performed comparing CT, fluoroscopy, and angiography in a group of patients with angina (17). CT revealed calcified plaques in 62% of patients with significant stenosis at angiography, compared to 35% detected with fluoroscopy. In a group without angina, CT found coronary calcification in only 4%, none of whom had significant stenoses at angiography. Overall, CT showed calcifications in 50% more vessels than did fluoroscopy. In this study, CT detected calcification in all patients in whom fluoroscopy detected calcified plaques and in all patients in whom angiography showed stenosis. In another study of patients with suspected coronary artery disease, CT showed a 65% sensitivity and an 87% specificity for coronary artery calcification (18). Of 108 patients with calcification detected by CT, 90% had significant stenosis (greater than 75% narrowing), whereas 80% of 121 patients with significant stenosis on angiography had calcification on CT.

The main disadvantage of conventional CT is its long scan time. This leads to motion artifacts, volume averaging and breathing misregistration. Helical CT has faster scan times, of approximately 1 sec. Faster scanning reduces the artifacts associated with conventional CT, but cardiac motion still blurs calcium deposits, and small calcifications may be missed (19). However, a recent study showed that images acquired with an electrocardiogram-gated subsecond helical scanner correlated well with those acquired by EBCT (20). In addition, Becker et al. re-

ported that data acquired by EBCT correlated with that obtained by the newest generation of CT scanner, the multirow detector CT (21).

Electron-beam computed tomography (EBCT) is the main instrument involved in cardiac calcification imaging (Fig. 2). The physics of this new type of scanner is different from that of a helical scanner (22). With a helical scanner the x-ray source rotates around the patient while the detectors are stationary. An EBCT scanner has no moving parts. A high-energy electron beam originating from a structure behind the gantry is steered around the patient electronically and strikes a tungsten ring which encircles the patient. The resultant x-rays are focused onto detectors approximately 180° opposite. The major advantage of this technology is rapid scan times on the order of 100 milliseconds (increased temporal resolution compared to helical scanners). The main disadvantage is that fewer photons are used to produce an image. Thus, the images are less sharp (increased noise).

Ultrasound, frequently used to image the heart, is sensitive for the detection of calcification. Transthoracic echocardiography (TEE) is limited in usefulness for detection of coronary artery calcifications, due to poor external acoustic windows. While TEE can often identify the proximal coronary arteries (23, 24), it does not image the entire coronary tree well. Intravascular ultrasound (IVUS), a newer modality for evaluation of the coronary arteries, is most often used during coronary angiography. The ultrasound provides information about the vessel wall thickness and tissue characteristics. Calcification is depicted as a hyperechoic area with posterior shadowing; noncalcified fibrous plaques are hyperechoic without



Fig. 1. Helical CT scan showing calcification (arrow) along the proximal left anterior descending artery (arrow).

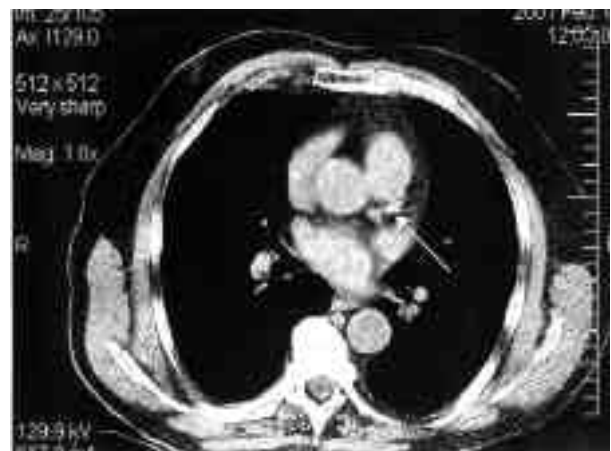


Fig. 2. Electron beam CT scan demonstrating calcification (arrow) in the left anterior descending artery (arrow).

associated shadowing (25). Recent studies (25, 26) comparing IVUS and angiography show angiography to be less sensitive at detecting calcification at the site of an atherosclerotic plaque.

The disadvantage of IVUS is that it is invasive and is, therefore, usually performed at the same time as selective coronary angiography. Also, because of the size of the catheters, it can only visualize the proximal coronary arteries. Therefore, it has a limited role in screening for coronary artery disease (CAD). Its importance lies in the fact that it can depict atherosclerotic lesions in patients with normal angiograms (27).

Magnetic resonance imaging does not excel in detecting small quantities of calcification, such as those found in early atherosclerotic plaques, and therefore plays little if any role in the early detection or screening of CAD.

Coronary Artery Calcium-Scoring Technique

In 1990 Agatston and colleagues published a report of a method of quantifying or scoring the amount of coronary artery calcification using EBCT (16). This EBCT study was electrocardiogram-gated with each slice triggered at 80% of the patient's R-R interval, so that images were obtained at the same point in diastole. Each image was obtained with 100-millisecond scan time and 3-millimeter slice thickness. Twenty slices were acquired in this study, although today 40 slices are usually acquired, to include the entire epicardial coronary system. Each slice was examined for calcium deposits. When a focus of calcium was detected, a region of interest was drawn around it. The area of the calcium deposit and its peak density were then determined. A deposit had to have a density measurement of at least +130 HU and an area of at least 1.0 mm². A density of 130 HU was chosen because this amount is well above the density of unenhanced myocardium and soft tissues (30–50 HU). The area measurement was used to try to discriminate noise from true calcium. An area of 1.0 mm² corresponds to at least 2 contiguous pixels at the usual scanning parameters. Noise usually comprises only one pixel. The calcium deposits that met these criteria were then scored. The Agatston score is a weighted score, calculated by multiplying the area of the calcification (in mm²) by a factor determined by the peak density within the area of interest. A factor of 1 was used for densities from 131–199; 2 for 200–299; 3 for 300–399; and 4 for 400 or

greater. The score for each calcification was determined and added to calculate the total calcium score for each coronary artery or for the entire epicardial arterial system. At about the same time, the Japanese developed a calcification scoring system using conventional CT, based on the length of calcifications (28), but it did not gain widespread acceptance.

Calcification and Coronary Artery Disease

As stated previously, it has been shown that calcification is associated with atherosclerotic plaque. The cardinal question remains, is calcified plaque associated with significant luminal stenosis? Mautner et al. conducted a study correlating EBCT-detected calcification and histologic plaque (29). They found that EBCT-detected calcification was present in 54% of coronary segments with stenosis of greater than 75%, in 41% of segments with 51–75% stenosis, in 23% of segments with 26–50% stenosis and in 6% of segments with 0–25% stenosis. Their data also showed that there was detectable calcification in 93% of segments with greater than 75% stenosis, but it was present in 20% of those with less than 50% stenosis and only 4% of those with less than 25% stenosis. It should be noted that this study used histologically determined stenosis of arteries, using the area of plaque central to the internal elastic lamina, and not the angiographic narrowing based on luminal diameter. Another study demonstrated that although calcified plaque is associated with atherosclerosis, the calcified plaque does not always correlate with the exact site of luminal stenosis (30, 31). In fact, some high-grade lesions and many smaller ones lack calcification altogether (29, 32). Rumberger et al. found that the total calcium area was roughly 20% of the total atherosclerotic plaque burden (32).

Coronary artery calcification is accepted as a marker of atherosclerosis. However, there is still controversy over what constitutes a vulnerable plaque. Some believe that calcification is an attempt by the body to protect weakened myocardium by strengthening the atherosclerotic plaque prone to rupture (33). The calcification may represent a stabilization attempt by the body to prevent plaque rupture. It has been shown that calcified areas are unlikely to be associated with sites of plaque rupture (34). However, the stiffened calcified area can induce stress at the junction of the calcified and noncalcified sections, a common site of plaque rupture (35). On the other hand, others believe that a mildly or mod-

erately stenotic plaque is more likely to rupture and lead to a coronary event (36). The reasoning is that the presence of calcium implies the presence of unstable and vulnerable lipid-rich plaques. This correlates with Rumberger's finding that only 20% of a plaque is calcified (32).

Studies have also correlated EBCT-detected calcification with known CAD risk factors. Goel and colleagues found an increased prevalence of coronary calcification associated with diabetes, smoking, hypertension, and a history of chest pain or previous myocardial infarction in men and hypercholesterolemia and smoking in women (37). Wong et al. performed a similar study in asymptomatic subjects (38). They found a higher prevalence of calcification in men with hypertension, diabetes, smoking, hypercholesterolemia, infrequent exercise and obesity; in women the association only held with hypercholesterolemia. Guerci et al. compared calcium scores with conventional risk factors in a group undergoing coronary angiography for clinical indications (39). For significant obstructive coronary disease, the calcium score had a higher odds ratio than most other risk factors, such as lipid profile, hypertension, smoking history, diabetes, family history of CAD, age, and gender.

Age and gender have been the risk factors with the most interesting trends concerning coronary calcification. In a large study by Janowitz et al. (40), 1,898 men and women aged 20–80 years were studied using EBCT. Their data show that while the prevalence of coronary artery calcium increased with age, the prevalence of coronary artery calcium was lower in women compared to age-matched men until about the seventh decade. Moreover, the 10-year lag in the prevalence of calcification in women in comparison to men narrowed in the first decade after menopause. Therefore, EBCT-detected calcification seems to follow the epidemiological pattern of atherosclerosis.

Numerous studies have shown an association between coronary artery calcification and coronary artery disease, as proven angiographically. In Agatston's study (16), in which he described the scoring method, 584 patients underwent EBCT. Of these, 109 had coronary artery disease, as established by a history of myocardial infarction or more than 50% luminal stenosis on angiography. The other 475 patients had no history of CAD. Those with CAD had more calcified plaques compared to aged-matched individuals without CAD. A calcification score of 300 had a sensitivity of 74% and a specificity of 81% in the detection of obstructive CAD.

The negative predictive value of a calcium score of zero was 98%. In another study (41), 100 patients aged 23–59 years were evaluated with EBCT and coronary angiography. Sensitivity and specificity for detecting calcified plaques in subjects with angiographically significant stenosis (greater than 50%) was 100% and 47%, respectively.

The largest multicenter study involved 710 subjects with symptoms of CAD and a mean age of 56 years (42). There were 456 men and 254 women. Each subject underwent both EBCT and coronary angiography. Significant stenosis was defined as narrowing greater than 50%. The sensitivity of the coronary calcium score in patients with significant stenosis was 95% (404 out of 427 patients). The specificity was 44% (124 out of 283 patients). The negative predictive value was 84%. As these studies show, there is high sensitivity for the association between significant CAD and detectable calcifications using EBCT. The specificity is low. This probably relates to the fact that only 20% of atherosclerotic plaque is calcified. However, the absence of calcification seems to indicate a lack of significant luminal stenosis. In a study of 150 patients, Stanford et al. found only one patient with a stenosis of greater than 50% and no coronary artery calcium (43).

Recently, He et al. studied a group of 3,895 mostly asymptomatic patients with EBCT (44), 411 of whom had myocardial single proton emission computed tomography (SPECT) studies shortly thereafter, i.e., within a median period of 17 days. No patient with a calcium score of less than 10 had an abnormal SPECT. On the other hand, 2.6% with a score of 11–100, 11.3% with a score of 101–399 and 46% with a score greater than 400 had a SPECT showing ischemia. They concluded that the calcium score can identify a high-risk group with silent myocardial ischemia within a low-risk population.

More recently, Raggi et al. studied the coronary calcium score as a predictor of unheralded myocardial infarction (45). They studied 632 asymptomatic patients as well as 172 patients who had an acute myocardial infarction with no previous manifestations of CAD. The asymptomatic group was followed for the development of myocardial infarction or cardiac death for approximately 32 months. The groups were compared using sex- and age-matched cardiac score percentiles. They found that 70% of patients who had a myocardial infarction or who died had coronary calcium scores greater than the 75th percentile.

Another important aspect of a test to detect early coronary artery disease is the ability to follow its progression or regression over time. Information on the reproducibility of coronary artery calcium scoring is not consistent. Janowitz and associates calculated calcium scores twice for plaques in 25 asymptomatic and symptomatic patients, 406 days apart (46). There was a 48% increase in the calcium score in the patients with proven obstructive CAD compared with 22% in the asymptomatic group. Also, the patients with proven CAD had 55 new calcified deposits versus 18 in the asymptomatic cohort. The authors concluded that coronary artery calcium scores could be used to follow the natural history of CAD. However, they did not take into account that the differences might be due to interscan measurement error. Another study showed that when a repeat EBCT scan was performed after the patient had gotten off the table and walked around the room, many small calcifications were not seen (47). Deposits of less than 2 mm² were missed up to 50% of the time. Other investigators have demonstrated that large increases in the calcium score are needed before the change can be attributed to disease progression rather than to measurement error (48–50). The variability between scans is usually due to misregistration resulting from patient motion. Increasing the slice thickness to 6 mm has been shown to decrease the interscan variability (50).

Calcification and Prognosis

It has been established that the coronary artery calcification score is an indicator of the overall atherosclerotic plaque burden (32). Furthermore, the greater the plaque burden, the more likely it is that one of the plaques may be unstable and lead to a cardiovascular event. The event data in turn (angina, myocardial infarction, need of coronary angioplasty or revascularization, and death) are essential to determining the clinical significance and utility of the coronary artery calcification score.

Detrano et al. conducted a study of survival in asymptomatic, high-risk subjects with coronary artery calcium detected at fluoroscopy (51). They followed 1,461 subjects with a greater than 10% risk of having a coronary event (defined as angina, documented myocardial infarction, myocardial revascularization, or death from coronary heart disease). At one year, events occurred in 5.4% of the subjects with coronary calcification versus 2.1% of those without calcium. One-

vessel calcification had a risk of an event of 5.4%, two-vessel calcification had a risk of 5.6% and three-vessel calcification incurred a risk of 6.2%. They concluded that the presence of fluoroscopically detectable coronary artery calcification identified an increased risk of cardiac events in asymptomatic, high-risk subjects and that this risk was independent of the risk incurred by standard risk factors.

Several studies have been conducted utilizing EBCT-detected calcification and event outcomes. Detrano and colleagues also performed an EBCT study involving 491 patients with a mean age of 55 years who were referred for coronary angiography (52). There were 13 coronary-heart-disease-related deaths (12 sudden cardiac deaths and 1 fatal myocardial infarction) and 8 nonfatal myocardial infarctions during the 30 ± 13 month follow-up period. One patient in the first quartile had an event, 2 patients in the second quartile, 8 in the third, and 10 in the fourth. The odds ratio for cardiac events in patients with calcium scores above the 75th percentile versus those below the 35th percentile was calculated at 10.8. In addition, the event-free survival rate was significantly greater for patients with a calcium score below 100 than for those with scores above this level.

Arad and co-workers monitored 1,173 asymptomatic patients (mean age 53 years) with no known CAD for 19 months following an EBCT exam (53). Eighteen (18) subjects had 26 cardiovascular events: 1 death, 7 nonfatal myocardial infarctions, 9 coronary angioplasty procedures, 8 revascularization procedures and 1 nonhemorrhagic stroke. The coronary artery calcification scores were divided into three threshold groups: greater than 100, greater than 160, and greater than 680. The sensitivities for these groups were 89%, 89%, and 50% respectively. The specificities were 77%, 82%, and 95% respectively. The negative predictive values were greater than 99% for all groups. The odds ratios were 25.8, 35.4, and 20.0 respectively. This study has now been carried out for a total of 3.6 years of follow-up (54). The odds ratio for a baseline calcium score of greater than 160 remain significant at 23.

Agatston and associates studied 367 asymptomatic patients with a mean age of 52 years who were followed for 36–72 months (55). A total of 26 events occurred, consisting of the development of angina, myocardial infarction, or coronary angioplasty, or need for revascularization. The mean calcium score for those with an event was 399, while those without events

had a mean score of 76. The authors also calculated an odds ratio of 6.9 for the development of symptomatic CAD for those with a calcium score of greater than 50 versus 2.7 for those with a score below 50.

Conclusion

Coronary artery calcification is intimately associated with atherosclerotic plaque. It can be detected with EBCT *in vivo* in a noninvasive manner, and the amount of calcification can be quantitated. This calcium score is related to the total atherosclerotic plaque burden within the coronary system. Whereas the total calcified area may represent roughly 20% of the overall plaque area, the calcified plaque does not necessarily correspond to the site of luminal stenosis in a patient with obstructive coronary artery disease. A negative or very low (0–10) calcification score generally excludes the possibility of significant coronary artery stenosis, but not the presence of an unstable atherosclerotic plaque that can lead to a cardiac event. Identifying patients early in the course of coronary artery disease would be a major public health advance, since multiple studies have shown benefit following the use of lipid-lowering agents in patients with known or asymptomatic CAD (56–59). The role of EBCT scanning as a screening tool to reduce the morbidity and mortality from CAD, the leading cause of death in the United States, has not been established. However, this technique is useful for evaluating patients with atypical chest pain syndromes. If the patient has no detectable calcium, the source of the chest pain is not likely to be due to CAD. If there is moderate-to-severe calcification present, then the patient can be scheduled for more traditional tests for cardiac ischemia. Another possible role for EBCT could be in following the progression or regression of CAD in patients on medical therapy (60). However, interscan measurement variability needs to be addressed before this can be a practical application.

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