Clinical utility of coronary calcification scanning in primary prevention

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The role of lipid-lowering drug therapy in secondary prevention of coronary events and stroke is well established. Virtually all persons with known atherosclerotic cardiovascular disease, including coronary, cerebrovascular or peripheral vascular disease, should be treated with a lipid-lowering drug. However, decisions about which patients to treat with drugs in primary prevention are considerably more difficult. Certainly, diabetics, patients with multiple traditional risk factors and those with substantially increased low-density lipoprotein (LDL) cholesterol levels should be approached aggressively and are in most cases candidates for drug therapy. The West of Scotland Coronary Prevention Trial demonstrated the safety and efficacy of drug therapy with pravastatin in a relatively high-risk cohort of hypercholesterolemic men (1). However, many persons develop premature atherosclerotic vascular disease despite lacking major traditional risk factors or having exceptionally high cholesterol levels. It has been estimated that only about half of the variation in coronary artery disease (CAD) can be explained by known traditional risk factors. Furthermore, the majority of persons who develop CAD do not have elevated cholesterol levels and approximately one third have total cholesterol levels less than 200 mg/dL. The indications for lipid-lowering drug therapy in primary prevention became even more complex with the publication of the Air Force Coronary Artery Prevention Study (AFCAPS)/Texas Coronary Artery Prevention Study (TexCAPS) (2). In this primary prevention study, individuals were not exceptionally high risk and had LDL cholesterol levels in the average to slightly elevated range. Only 17% of the subjects in this trial would have qualified for drug therapy based on current National Cholesterol Education Program guidelines. Nevertheless, treatment with lovastatin to reduce LDL cholesterol reduced the risk of first acute coronary events by 37% over 5 years. If everyone who meets the entry criteria for AFCAPS/TexCAPS were treated, a substantial portion of the adult United States population would qualify for drug therapy. Better methods for identifying asymptomatic persons at high risk of developing future clinical CAD are needed so that we can target preventive therapies, such as lipid-lowering drug therapy, to those most likely to benefit from such therapies in a cost-effective fashion.

Detection of subclinical atherosclerosis

The use of multivariate risk algorithms enhances our ability to predict risk and make decisions about drug therapy (3). These algorithms include known risk factors, but it is highly likely that unknown factors also contribute to the development of clinical CAD. Detection and quantitation of subclinical atherosclerosis could theoretically provide a method of integrating all risk factors, both known and unknown, and thus provide more precise information about the likelihood of developing future clinical CAD. It is this intuitive appeal that has generated tremendous interest in the use of noninvasive modalities to detect and quantify subclinical atherosclerosis. Given the clinical and economic importance of decisions such as the use of lipid-lowering drug therapy in primary prevention, the interest in this area is likely to grow.

Methods for detecting subclinical atherosclerosis can be grouped into physiologic and anatomic methods. Physiologic methods require some functional impairment of blood flow or other arterial vascular function, such as vasodilation. They include procedures such as the ankle/brachial ratio, stress testing and coronary positron emission tomography scanning. They also include procedures like brachial artery ultrasound imaging of flow mediated vasodilatation as a test for endothelial dysfunction. Because acute coronary events are frequently caused by lesions that represent less than 70% stenosis of the vessel, the goal in identifying persons at high risk of coronary events is not to identify those with flow-limiting coronary stenoses (as does stress testing) but rather to identify persons who are at higher statistical risk of having or developing vulnerable coronary lesions. Therefore, the most promising methods are likely to be those that sensitively and specifically detect and quantify atherosclerosis rather than stenosis. Although physiologic tests clearly have a role in symptomatic
Coronary artery calcification

Coronary calcification is a specific marker for coronary atherosclerotic plaque (4), and its presence indicates the definite presence of coronary atherosclerosis. Arterial calcification occurs relatively early in atherosclerotic plaque evolution and denotes an active process of plaque development. Recent data indicates that plaque calcification is not a passive end-stage process but an active process involving extracellular bone matrix proteins, such as osteopontin, osteonectin, osteocalcin and bone-morphogenetic protein 2 (5). The hydroxyapatite mineral found in calcified arteries is also similar to that found in bone. Calcification does not appear in the earliest fatty streak lesions, but by the time lesions have progressed to a 50% stenosis, at least 95% of them have some detectable calcification (4), making calcification a useful target for identifying plaque in asymptomatic patients.

EBCT for detection of coronary artery calcification

The presence of calcification in arteries has long been recognized with standard x-ray films. However, x-ray films lack the sensitivity and specificity needed to accurately identify calcified plaque in arteries of the moving heart. Coronary calcification can be sensitively detected and quantitated using electron beam CT (EBCT) (6). EBCT was first introduced commercially in 1983 to improve calcium imaging through reduction of motion artifact of the heart. Conventional CT imaging involves rotation of a single imaging x-ray source in conjunction with a collimator-detector around the patient. EBCT uses a rotating electron beam to generate x-rays that sweep across a tungsten target that is situated below the patient. The fan of x-ray photons allows for 100 ms scans and sharp, accurate images that can be stored in less than 1 minute. The procedure is relatively short, lasting approximately 10 minutes; no contrast is necessary. The amount of calcium is measured by quantifying the number of pixels with a density greater than 130 Hounsfield units. Typically, a coronary calcium score is reported and is derived from the product of the area of calcification and a factor rated 1–4. The factor is derived from the maximum calcium CT density within a coronary artery segment. Most studies report a computer score that is the sum of the calcium scores throughout the entire coronary artery system (left main, left anterior descending, left circumflex and right coronary arteries). Recent upgrades in spiral CT equipment have renewed interest in using this multipurpose imaging machine in measuring coronary artery calcification. However, there are no studies to date that have compared EBCT with spiral CT for determination of coronary calcification across a wide range of coronary calcium scores.

Coronary calcification and angiographic disease

Coronary calcification as assessed by EBCT is highly correlated with extent of histologic atherosclerotic disease on autopsy (7). Some cross-sectional data demonstrate that coronary calcification is higher in persons with symptomatic clinical coronary disease than in asymptomatic persons, although these do not represent population-based samples. The issue of the relationship between coronary calcification by EBCT and extent of angiographic coronary disease has been studied extensively. Importantly, there is a relatively poor correlation between quantity of calcification at a specific coronary site and stenosis at the same site (7). Therefore, site-specific calcification has no value in helping to identify the specific site of a functional coronary stenosis. However, when the total global coronary calcification score is correlated with the overall probability of having at least one coronary stenosis somewhere in the coronary bed, a highly significant correlation has been noted by several investigators (6,8) (6,8). The coronary calcification score on EBCT provides information about the probability of having a functional stenosis and may, therefore, be useful as an aid to clinical judgment, for example in patients with atypical chest pain and a nondiagnostic exercise tolerance test prior to progressing to coronary angiography. A recent study suggests that coronary calcification by EBCT is better at predicting the presence of angiographic coronary disease than traditional risk factor analysis (9). No randomized controlled trials of cholesterol reduction or other risk factor modification have been performed using serial EBCT scanning to monitor progression of coronary calcification. However, a recent observational study indicated that the rate of progression of coronary calcification is slower in individuals who have lower levels of LDL cholesterol (10).
Coronary calcification and clinical events

Some prospective data exist with regard to the predictive ability of coronary calcification by EBCT to predict future coronary events. However, the numbers are relatively small, the samples are not population-based and the follow-up periods are relatively short. Secci et al. (11) examined the relative prognostic value of coronary calcium for predicting coronary heart disease (CHD)-related events in 491 high-risk patients referred for angiography who also underwent EBCT scanning. Thirteen documented CHD-related deaths and eight nonfatal myocardial infarctions (MIs) occurred over a period of 30 ± 13 months. The EBCT calcium score significantly predicted the probability of a coronary event, and this was independent of the severity of disease determined by angiography alone. Furthermore, there was a significantly greater event-free survival during follow-up for patients with a calcium score below the median (i.e., 50th percentile) value of 100 compared with those with a calcium score of 100 or greater. Detrano et al. (12) recently reported a cohort of 1,196 asymptomatic high-risk subjects who underwent risk-factor assessment and EBCT. At 41 months of follow-up, there were 17 coronary deaths and 29 nonfatal infarctions. The receiver operating curve area calculated from the coronary calcium score was 0.64, indicating a modest ability to predict events, but was no better than the receiver operating curve area based on a Framingham risk formula (0.69, p = NS). This study included a select population of very high-risk subjects with a mean age of 66 years. Another prospective study by Arad et al. (13) involved 1,173 asymptomatic persons (average age 53 ± 11 years) who underwent EBCT coronary scanning and were followed for an average of 19 months. A total of 18 persons had coronary events (including CHD death, nonfatal MI and revascularization); the magnitude of the coronary calcium score at the time of the index EBCT scan was highly predictive of subsequently developing symptomatic cardiovascular disease during follow-up. A longer follow-up period, averaging 3.6 years, of these same subjects included a total of 40 persons with a cardiovascular event, and the difference in coronary calcification scores between those with and without events remained highly significant. Based on the longer follow-up data, the odds ratio for having a coronary event if the coronary calcification score was greater than 80 was determined to be 14.3 (95% CI 4.9–42.3). Overall, these combined data are consistent with the concept that the amount of coronary calcification may be useful in identifying asymptomatic persons who may be at a higher risk of having a future cardiovascular event and therefore have an indication for more aggressive risk-reduction therapy (14). However, population-based studies in larger numbers of persons followed for longer periods of time are required before general guidelines can be established regarding use of coronary calcification scanning in asymptomatic patients.

Clinical case

A 42-year-old man whose father had an MI at age 53 went for risk assessment and cardiovascular risk reduction. At the time, he was already eating a healthy diet and exercising three times per week. His total cholesterol was 198 mg/dL (triglycerides 70 mg/dL, high-density lipoprotein cholesterol 38 mg/dL and LDL cholesterol 146 mg/dL) after adhering to an American Heart Association Diet. He was otherwise healthy and had no other traditional cardiovascular risk factors. An EBCT scan was obtained, and the coronary calcium score was 179, placing him within the 90th percentile for his age. The patient was counseled on these results, and a statin drug and antiplatelet therapy were prescribed to reduce his cardiovascular risk.

Summary

Coronary calcification scanning is a conceptually attractive method of stratifying selected asymptomatic persons according to CHD risk as a guide to more informed decisions regarding individualized preventive measures, such as drug therapy for cholesterol reduction. As such, this approach should be viewed as enhancing but not replacing clinical judgment regarding cardiovascular risk. The existing data suggest coronary calcification is a quantitative marker of coronary atherosclerosis and, when combined with clinical risk factor assessment, may predict future clinical events with greater precision than risk factor assessment alone. The clinician who understands the test and its limitations could elect to make clinical use of the test for selected patients. This is especially true in those patients for whom a clinical decision, such as institution of cholesterol lowering drug therapy, is uncertain. However, more prospective data is required before broad recommendations or general guidelines can be made regarding the clinical use of coronary calcification scanning as a guide to medical management.

References and Notes


