Title
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Journal
Circulation, 92(3)

ISSN
0009-7322

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Publication Date
1995-08-01

DOI
10.1161/01.cir.92.3.632

Circulation
circ.ahajournals.org

Circulation. **1995;** 92:**632-636**
doi: 10.1161/01.CIR.92.3.632

Articles

Coronary Artery Screening by Electron Beam Computed Tomography

Facts, Controversy, and Future

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Key Words:
atherosclerosis
coronary disease
tomography
calcium

There are two things: science and opinion; the first leads to knowledge, the second to ignorance. Hippocrates

There has been a dramatic increase in the use of electron beam computed tomography to screen for coronary calcium phosphate deposits. This radiographic procedure, available at increasingly numerous centers in the United States and abroad, can detect small amounts of these deposits. The test costs about $400 (technical fee, including professional interpretation), takes 15 minutes to perform, involves little radiation (similar to that of a barium enema or chest radiograph series), and is noninvasive, not requiring injections or drugs to perform the procedure and obtain results.

Advocates of universal coronary calcium screening state that since coronary calcium signifies atherosclerosis, a potentially deadly disease, its detection is important, and a positive screen is reason for aggressive management of risk factors or even further evaluation with exercise testing or angiography. They argue that asymptomatic persons whose coronary status is unknown would benefit from the test, since those with positive scans can be treated more aggressively than those with negative scans and thereby be prevented from suffering myocardial infarctions or cardiac death.

Others are not as convinced regarding the value of this new procedure. A recent science advisory published by the American Heart Association[1] concluded that the "clinical use of ultrafast computed tomographic imaging to screen patients for coronary artery disease is not justified at this time." Major reasons given were (1) the lack of a precise correlation between the degree of atherosclerosis and coronary calcium and (2) the unknown prognostic significance of calcification detected by this technology.

We summarize in this review the strength of the evidence linking coronary calcium to atherosclerosis and coronary events. We then propose a paradigm on which the future development of this technique can be modeled. On the basis of these arguments, we try to explain the varying consensus concerning the implications of the findings on coronary calcium scans as well as that concerning indications for screening.

Evidence Linking Coronary Calcium to Atherosclerosis

Autopsy evidence[2 3 4 5 6] supports the contention that coronary calcium generally signifies coronary atherosclerosis.[2 3 4 5 6 7] Blankenhorn[6] performed radiographic and histopathologic studies of 89 randomly selected hearts and examined 3500 arterial segments. Simons et al[7] used electron beam tomography and careful histopathologic sectioning to study 13 hearts for coronary calcium deposits. Neither Blankenhorn nor Simons et al found one calcified radiopaque lesion that was not associated with an underlying atherosclerotic plaque, although a wide range of plaque area or percent lumen stenosis appears to be associated with a given calcium burden.[7] This suggests that the prevalence of atherosclerosis is at least as high as the prevalence of coronary calcium and probably higher, since not all atherosclerotic plaques are calcified.

Angiographic studies also support an association between calcium and luminal stenoses in symptomatic populations. Gianrossi and colleagues[8] performed a meta-analytic review of the relation between fluoroscopically detectable coronary calcium and angiographic disease. The studies reviewed used conventional image intensifier fluoroscopy in symptomatic subjects undergoing angiography for clinical indications. It was found that accuracies for cardiac fluoroscopy approached those of exercise ECG and exercise thallium scintigraphy. Similar investigations comparing electron beam tomography for calcium and coronary angiography for stenoses in symptomatic subjects have produced sensitivities and negative predictive values approaching 100% but specificities and positive predictive values of lower magnitude (ie, 47% and 62%, respectively).[9 10 11] A high percentage of arteries with significant compared with mild stenoses are seen to contain calcium,[12] and those patients with symptomatic coronary artery disease are most likely to show coronary calcium.[13] Although specificity may be enhanced by a more stringent definition for defining a positive test (eg, a greater area, score threshold, or number of calcified vessels) by electron beam computed tomography, this comes at the expense of reduced sensitivity.[14 15 16]

Coronary Calcium as a Predictor of Coronary Events in Asymptomatic Populations

Properties essential to any test result are their sensitivity and specificity for predicting pathology, defined by accepted standards. Highly prevalent diseases of various severities will require less sensitive and more specific tests. Diseases that are less common but almost always fatal require very sensitive tests at the expense of specificity.

For better or worse, coronary angiographic luminal narrowings are accepted standards of pathology. Loecker et al[17] performed a prospective fluoroscopic evaluation of 613 asymptomatic aircrew members undergoing conventional coronary fluoroscopy and coronary angiography. These authors found that angiographic narrowing was present in 17% of subjects, and found a sensitivity of 66% and a specificity of 78% for the ability of fluoroscopy positive for calcium to predict at least one angiographic luminal narrowing of at least 50%. We know from epidemiological data that at least 95% of healthy men can expect to remain free of coronary events for ≥10 years.[18] Even so, as many as 20% had fluoroscopic coronary calcium, and 17% of those undergoing angiography had at least one obstruction >50% of the normal luminal diameter. Their findings suggest that although fluoroscopically detectable coronary calcium or a positive angiogram signifies the presence of atherosclerosis, the mere presence of either of these findings may not be a sufficient predictor of prognosis.

The prevalence of coronary artery calcium detected by electron beam computed tomography is even higher and rises dramatically with age; >60% of asymptomatic women and 80% of asymptomatic men >60 years old have at least some detectable calcium by this method.[19 20] Since a much smaller proportion of these individuals will eventually develop clinical coronary events,[18] effective risk stratification requires that a certain threshold amount of calcium be present for a calcium screen to indicate "high risk." Sensitivity and specificity with respect to subsequent events in asymptomatic populations, who have recently been targeted for calcium screening, remain unknown, but the high prevalence of simple "positive" scans[21] suggests that specificity is low for disease that is likely to become clinically manifest. The amount of disease that can be detected is so small as to greatly limit the predictive value of the simple detection of coronary calcium. For this reason, we suggest that accurate quantification of coronary calcium will be necessary to find useful thresholds above and below which the detection of calcium is of prognostic value.

There is preliminary direct evidence of an association between coronary artery calcium, risk factors, and prognosis. The presence (or number) of selected coronary risk factors, including reported hypertension, smoking, diabetes, male sex, and hyperlipidemia, corresponds to a higher prevalence (or quantity, based on total calcium score) of calcium among asymptomatic populations.[19 20 22 23] After adjustment for coronary risk factors, the presence of coronary artery calcium is an independent indicator of prior history of coronary artery disease[24] as well as angiographically obstructive disease.[25] Furthermore, preliminary findings have linked calcium detected by fluoroscopy[26] or electron beam tomography[27] to an increased risk of future coronary events or revascularization.

A Paradigm for Future Research

The potential problem of oversensitivity of coronary calcium screening might be resolved if the following conditions are met: (1) electron beam computed tomography can accurately quantify the mass of calcium precipitated in coronary arteries; (2) the mass of calcium corresponds to the amount of atherosclerosis; and (3) the amount of atherosclerosis correlates with risk of coronary events.

If these three conditions are met, reliable thresholds for a positive test can be found such that specificity and predictive value are high enough to be clinically useful.

Accuracy in Quantifying Calcium Mass

Although limited work has been done to validate calcium measurements in coronary arteries, an arbitrary scoring system has been used for several years.[28] Important physical limitations of this scoring algorithm have been identified, and work toward the development of more accurate methods, including those that accurately correspond to total calcium mass, is in progress.[29 30 31 32] A recent report[12] showed that both calcium score and area of calcified deposits assessed by electron beam computed tomography correlated highly (r=.95 to .96) with histomorphometric calcium area. Investigators have also begun to demonstrate high reliability for identifying calcified foci of a given area on repeat scanning,[33] and concordance of a positive test based on a given number of calcified pixels[34] has been reported by some investigators.

Relation of Mass to Pathology

Recent studies[21 35] show an imperfect relation between the amount of calcium and atherosclerosis. Whereas the absence of coronary calcium at any site is highly specific for the absence of obstructive disease, nonobstructive disease (<75% stenosis) is still common in most such segments. Others show a closer correlation between calcified plaque volume (r=.84 for individual coronary arteries and r=.94 for whole-heart calcium volumes) and histological plaque volume.[36] The percentage of coronary artery surface area with calcified plaque from autopsy subjects with accidental deaths also tracks closely with coronary calcium prevalence in a large, asymptomatic sample.[19] In addition, the mass of calcium may track progression or stabilization of atherosclerosis,[37] and such progression is measurable and may predict prognosis.[38] Also, retest reliability may be sufficient for tracking of coronary calcium or atherosclerotic progression, particularly in research studies.[34] Pathological comparison studies and further prognostic data are needed to confirm these reports, however. More importantly, the relation between clinical plaque stability and amount, morphology, or changes in coronary calcium is not clear. More research, including studies evaluating longitudinal changes in coronary calcium with atherosclerosis assessed by methods such as coronary angiography and intravascular ultrasound, is needed to examine the relation of calcium mass and morphology with volume, morphology, progression, and stability of atherosclerotic plaque.

Relation of Pathology to Risk

Although it is plausible that a direct and strong relation between amount of atherosclerosis and risk exists, the available evidence to support this is limited. Neither has it been proved that calcified atherosclerosis is more malignant than noncalcified atherosclerosis,[39 40 41] although persons with identified coronary artery calcium appear to have a graver prognosis,[26 27] possibly because such persons have correspondingly more atherosclerosis in general. There is, however, some evidence that calcified atherosclerosis may be associated with greater stability.[39 40 41 42 43] One study[40] showed that calcified plaques may be less likely to rupture. Studies using intravascular ultrasound before and after interventions[42 43] also have shown that calcified plaques are less likely to be associated with arterial restenosis than are noncalcified plaques.

Reasons for the Controversy

Electron beam computed tomography is a noninvasive tool that can detect even small amounts of coronary calcium (which may or may not be associated with clinically significant lumen stenosis). However, atherosclerosis is detected in many individuals who may never suffer from its clinical consequences. This is not the only example of the dilemma of widespread potentially malignant pathology that, if left unknown and untouched, usually runs a benign course. Harach et al[44] estimated that almost everyone >50 years old would have a diagnosis of thyroid carcinoma if sufficiently thorough biopsies were performed, although thyroid carcinoma is a relatively uncommon clinical malignancy. Fortunately, routine biopsy of the entire population has not been seriously proposed. The advantages and disadvantages of coronary calcium screening of large segments of the asymptomatic population, in particular, which could also uncover pathology likely to remain clinically nonmanifest, needs to be weighed in a similar light.

At present, identification of coronary calcium may serve to confirm the presence, or even relative extent, of atherosclerosis, but not necessarily the clinical severity of disease. For the large number of asymptomatic individuals with coronary calcium, however, there are no established guidelines for referral for either an exercise treadmill test, angiogram, or even more aggressive medical treatment. Therefore, at present, acceptable medical decisions may be difficult to make on the basis of the results of coronary calcium screening. The presence of coronary calcium, however, might alert the patient to a potential emerging problem and encourage him or her to better manage his or her risk factors by making important lifestyle changes. This is currently under investigation as a potential benefit of coronary artery screening by electron beam tomography. However, this supposed beneficial effect must be balanced against the potentially detrimental effects of negative labeling, anxiety, and the cost to society for additional and potentially unwarranted diagnostic and invasive procedures.

There are, however, possible scenarios in which electron beam computed tomography may be helpful in clinical decision making. For example, we must evaluate whether an abnormal exercise treadmill test in an asymptomatic subject with a negative coronary calcium screen might assist the clinician in determining whether the exercise test is a false-positive due to hyperventilation,[45] medications, or an estrogen effect.[46] Conversely, whether a positive exercise test might confirm the significance of a positive coronary calcium screen as an aid to effective risk stratification[47] needs consideration. Also, a positive screen in an individual with chest pain could provide evidence that such chest pain is in fact linked to coronary atherosclerosis. Furthermore, persons in extremely high-risk occupations, such as airline pilots and emergency response workers, might benefit from coronary calcium screening in that a negative result, together with a negative history, might indicate a low likelihood of a cardiac catastrophe. One must, however, use caution in interpreting positive results, and one must be willing to remove from these high-risk positions some able persons whose likelihood of cardiac events is not much higher than that of their colleagues with negative coronary scans. Investigations are also needed to determine whether asymptomatic persons with elevated risk factors who have significant coronary calcium are at greater risk of coronary heart disease events and could benefit from further diagnostic evaluation or intervention beyond risk factor control.

Summary

Coronary calcium as detected by electron beam computed tomography always signifies at least some atherosclerosis, appears to be correlated with coronary risk factors, cardiac history, and overall angiographic severity of disease, but is inconsistently related to degree of atherosclerotic lesion stenosis in a given artery. Increasing evidence, however, suggests an association between coronary artery calcium, atherosclerosis, and coronary risk. But atherosclerosis is a very common condition, its prevalence increasing with age. No fully validated method for determining the quantity of coronary calcium is available, and we do not know whether the amount of calcium is a consistently accurate reflection of the amount of atherosclerosis or whether the amount of atherosclerosis reflects the degree of risk. Furthermore, the prognostic significance of coronary calcium in any given atherosclerotic lesion is not yet established. What is clear from cohort studies, however, is that at least three quarters of asymptomatic individuals, at least half of whom would have “positive” coronary calcium electron beam computed tomographic scans, will live for at least 10 years without cardiac problems of any kind.[18 48] Investigation is needed to determine whether medical intervention may impact the clinical outcome of the rest of those identified with a positive scan but destined to suffer future clinical events.

Despite lack of validation, this test has widespread appeal, both to the public as a means of being able to find out the condition of their coronary arteries “without injections or dye” and to hospitals and private medical groups who view this both as an innovation in cardiovascular diagnosis and as a potentially profitable diagnostic procedure. Physicians asked to explain the results of the test must clearly delineate to patients the meaning of their results. Since the clinical value and cost-effectiveness of identifying individuals at risk over and above the existing methods of risk-factor evaluation are not known, it is not possible to recommend universal screening at this time. However, active research and emerging findings by many investigators may soon make it possible to recommend whether specific risk subgroups of individuals might benefit from coronary calcium screening.

Footnotes

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