Atherosclerosis imaging and coronary calcification

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Abstract

Recently published data have greatly expanded the applicability of electron beam tomography and electron beam angiography. Guidelines and policy towards these modalities have shifted, with increased recognition of their importance among experts in cardiology, lipidology and preventive medicine. Given the high sensitivity of coronary calcification for the presence of obstructive coronary artery disease (CAD) (95–99%), exclusion of coronary calcium may be useful as a filter prior to invasive diagnostic procedures or hospital admission.

The prognostic power of coronary calcium has been recognised to be superior to risk factor assessment in summary data from nine studies. The presence of coronary calcification was associated with a 10-fold increased risk of cardiovascular events. Several trials have demonstrated slowing of the calcification process under the influence of statin therapy. Data suggest that change in calcium score can be used to assess the efficacy of lipid-lowering therapy and is currently being used as a surrogate end point for a host of pharmaceutical studies.

Electron beam angiography provides non-invasive visualisation of native coronary arteries and bypass grafts. Some current clinical uses include: following non-diagnostic stress tests; for any person with an intermediate likelihood of CAD (where the step to coronary angiography might be premature); for symptomatic persons post-angioplasty and possibly post-stent; for evaluating graft patency post-coronary artery bypass graft (CABG); and for early detection of obstructive CAD in the high-risk person.

Key words: computed tomography, electron beam, prognosis; review, coronary artery calcification, atherosclerosis, non-invasive angiography.

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Introduction

Atherosclerosis is the primary cause of morbidity and mortality in every industrialised nation.[1] The initial manifestation of CAD is a myocardial infarction (MI) or death in up to 50% of patients.[2] Identification of people at high risk for cardiovascular events is the major focus of primary prevention efforts, since lifestyle changes and certain pharmacological interventions have been shown to increase the life expectancy of high-risk persons.[3] Unfortunately, traditional risk factor assessment fails to identify a large portion of patients at risk for CAD.

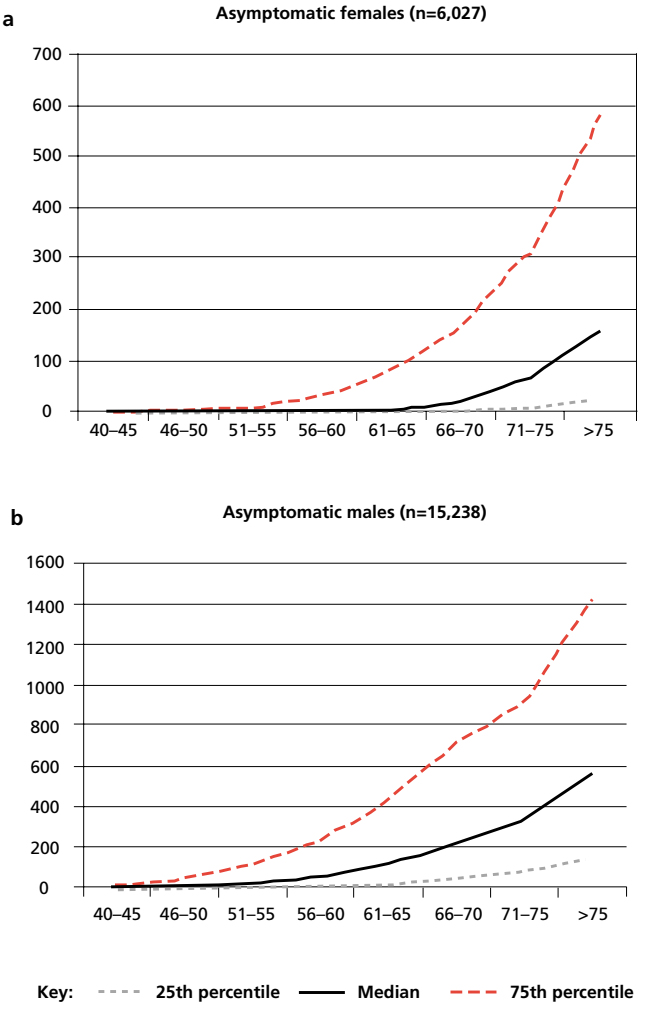
Multiple trials have now demonstrated that a vast majority of heart attacks occur at the site of a non-obstructive plaque.[4] Coronary occlusion and MI most frequently evolve from mild to moderate stenoses.[5,6] Studies of patients dying from either acute MI or sudden cardiac death have demonstrated that the extent of coronary atherosclerosis, rather than the severity of stenosis, is the most important predictor.[7] Thus, the need to measure atherosclerosis burden has become paramount to risk stratification.

Coronary artery calcification and atherosclerosis

Calcific deposits in coronary arteries are pathognomonic of atherosclerosis.[8,9] Histopathological[10] and intravascular ultrasound[11-13] studies confirm the close correlation between atherosclerotic plaque burden and extent of coronary artery calcification (CAC). Electron beam tomography (EBT) can accurately and non-invasively quantitate the amount of CAC ($r > 0.90$).[14,15] Other non-

Figure 1. Dense calcification in a 50-year-old man. White arrow represents left anterior descending; black arrow is calcification in diagonal branch

Figure 2. Graphs representing nomogram of calcium scores among asymptomatic persons. Graph **a** and graph **b** show the 25th percentile, median and 75th percentile of scores in asymptomatic women and men respectively.



Data from Wong *et al*.[17]

invasive modalities to diagnose CAD focus on physiological consequences of coronary obstruction, while EBT coronary calcium represents an anatomic measure of plaque burden. Accurate and non-invasive measures of atherosclerosis in the high-risk person could allow better assessment of the processes associated with disease progression, as well as of therapies to prevent the progression or even induce regression of atherosclerosis and clinical CAD.[16]

Electron beam tomography

EBT is a fourth-generation computed tomography (CT) imaging process, which is able to obtain thin slices of the heart and coronary arteries to evaluate for CAC. Rapid image acquisition – due to the absence of a moving X-ray source – allows approximately five times greater imaging speed than conventional multislice CT, limiting respiratory and cardiac motion artifacts (figure 1). Usually 30 to 40 axial images are obtained to include the full length of the myocardium. The entire coronary artery tree is imaged during a single 20 to 30 second breathhold. Published nomogram tables of the calcium score distribution in asymptomatic people have been published.[17] In men, there is a rapid increase in the prevalence and extent of coronary calcification after age 45; in women, this increase is delayed for 10 years (figure 2).

EBT as a diagnostic tool in symptomatic persons

Detection of coronary calcium by EBT has been demonstrated to be highly sensitive for the presence of significant CAD. A recent report of 1,764 persons undergoing angiography and EBT similarly showed a very high sensitivity and negative predictive value in men and women (>99%).[18] Thus, a score of 0 (no coronary calcium) can virtually exclude those patients with obstructive CAD.

While a positive EBT study (presence of CAC) is nearly 100% specific for atheromatous coronary plaque,[19] the ability of EBT to predict significant stenosis in a highly specific manner has been challenged. Recent guidelines support the use of EBT in symptomatic persons, stating that EBT is "sufficiently accurate for predicting the presence of angiographic stenosis".[20] Since both obstructive and non-obstructive lesions have calcification present in the intima, CAC is not specific to obstructive disease.[21] Rumberger *et al*.[22] demonstrated higher calcium scores are associated with a greater specificity for obstructive disease at the expense of sensitivity; for example, a threshold score of 368 on

Table 1. Characteristics and risk ratio for follow-up studies using electron beam tomography

Author	Number	Symptoms	Mean age (years)	Sex (% male)	Follow-up duration (years)	Cut-off for risk assessment	Risk ratio
Detrano[28]	491	Yes	57	64	2.5	Top quartile	10.8
Arad[29]	1,173	No	53	71	3.6	CAC >160	22.1
Detrano[30]	1,196	No	66	89	3.4	CAC >44	2.3
Raggi[31]	676	No	52	51	2.7	Top quintile*	15.4
Agatston[32]	367	No	52	68	6.0	CAC >50	16.9
Wong[33]	928	No	54	79	3.3	>270-Top quartile	8.8
Georgiou[26]	221	Yes	53	54	4.2	Median†	13.1
Keelan[34]	288	Yes	56	77	6.9	Median (>480)	3.4
Total	5340		55	69	3.5	------	10.1

Key: *Using age- and gender-matched cohorts, representing the top quintile; †using age- and gender-matched cohorts, representing top quartile

EBT was 95% specific for the presence of obstructive CAD. EBT has been shown to be comparable to nuclear exercise testing in the detection of obstructive CAD.[21,23]

The accuracy of EBT is not limited by concurrent medication, the patient's ability to exercise, or baseline ECG abnormalities. Further evidence suggests that EBT may be more cost-effective at diagnosing CAD than traditional non-invasive testing, especially in women.[24]

Three studies have documented that EBT is a rapid and efficient screening tool for patients admitted to the emergency department with chest pain and non-specific ECGs.[25-27] These studies demonstrate sensitivities of 98-100% for identifying patients with acute MI and very low subsequent event rates for persons with negative tests. The high sensitivity and negative predictive value may allow early discharge of those patients with non-diagnostic ECG and negative EBT scans (scores = 0). Exclusion of coronary calcium may therefore be used as an effective filter prior to invasive diagnostic procedures or hospital admission.

EBT and prognostication

The most powerful and important data for this modality relates to its ability to predict future coronary events in both symptomatic and asymptomatic persons (table 1). Risk factors have been demonstrated to be suboptimal predictors of future events, failing to predict one-third of future deaths due to CAD.[35] In a symptomatic patients' study by Kennedy,[36] EBT-detected CAC was a stronger independent predictor of disease and future events than a sum of all of the traditional risk factors combined.

Three prognostic studies have been reported in the symptomatic population. A multi-centre study[28] of 491 patients undergoing coronary angiography and EBT scanning found that higher calcium scores were associated with an increased risk of coronary events over the next 30 months as compared to patients in the lowest quartile of score (odds ratio 10.8, 95% confidence interval 1.4 to 85.6). In multivariate analysis, the only predictor of a hard cardiac event was log calcium score. The ability to predict future events was greater with EBT calcium scores than with measures of angiographic severity, reinforcing the idea that plaque burden, and not stenosis severity, is a more important marker of disease.[5]

Keelan *et al.*[34] followed 288 symptomatic persons who underwent angiography and EBT calcium scanning for a mean of 6.9 years. They found age and CAC score were the only independent predictors of future hard coronary events. Importantly, no conventional coronary risk factors (other than age) predicted events. This study confirmed the previous findings of Detrano *et al.*[28] that CAC extent determined by EBT provides more prognostic information than angiography or risk factors in symptomatic patients. Another recent study[26] reported a 50-month mean follow-up of a chest pain population. Multivariate logistic regression analysis demonstrated CAC score to be the strongest predictor of future cardiovascular events (OR 27.8, 95% CI 1.88, 815, p=0.02).

Arad *et al.*[37] initially reported a 19-month follow-up of 1,173 patients over 19 months, finding CAC to be the strongest predictor of future cardiac events. This prospective study now has been carried out for a total of 3.6 years of follow-up, maintaining the strong power of this technology to predict future cardiac events (odds ratio 22.3, CI 5.1–97.4).[29] Agatston *et al.*[32] reported the longest follow-up data. There was a significant difference in the mean coronary calcium scores for patients with cardiac events (399 $\pm$ 424), versus those without (76 $\pm$ 207), demonstrating an odds ratio of 21.2 for coronary events in patients with CAC scores of >26, and 16.9 for scores above 50 (hard events). However, caution should be used in screening an older population. Our group published an analysis in an older population (1,196 patients, 89% male, mean age 66 years).[30] This study demonstrated that while CAC was a significant predictor of future cardiac events, it did not have great power over tradition-

al risk factors to discriminate who will develop CAD events. Unfortunately, we utilised a scanning protocol (6 mm thick slices) that has proved not to be as sensitive as the standard protocol (3 mm), and a definition of a calcific focus that was 16 times greater than other studies (>8 mm^2).[38] However, this study did demonstrate great prognostic potential in the population most likely to benefit from screening for heart disease (ages 45–62); the relative risk of developing a cardiac event was 6.3 ($p<0.001$).[39]

In a recent study of 676 asymptomatic patients prospectively followed for 32 $\pm$ 7 months,[31] calcium scores significantly outperformed risk factors in cardiac event prediction, and demonstrated the incremental benefit of adding calcium scores to conventional risk factors. A meta-analysis[40] of five studies (two abstracts and three manuscripts) involving 4,348 subjects found that a calcium score above a median score was associated with an increased risk of a combined outcome of non-fatal infarction, death, or revascularisation (risk ratio 8.7, 95% CI 2.7 to 28.1), and of a hard event, i.e. death or infarction (risk ratio 4.2, 95% CI 1.6 to 11.3).

Similarly, in a recent publication by Wong *et al.,*[33] 928 asymptomatic men and women (mean age 54 years) followed for an average of 3.3 years, with an absolute calcium score in the upper quartile, showed a relative risk for cardiovascular events of 8.8 ($p<0.001$) times that of patients in the lowest quartile, with risk factors adding no incremental prognostic information.

Progression

Reproducibility was initially a concern for repeated testing, but hardware and software improvements have lowered inter-scan variability to a median of 4–8%.[41] With excellent inter- and intra-observer variability (1%), this test can measure plaque burden and follow atherosclerosis over time. Intuitively, documenting slowing of the atherosclerosis process would be more effective than just documenting a change in lipid values. EBT studies have consistently shown that statin therapy significantly slows progression of coronary calcification from approximately 40% per year down to 10%.[42,43] Two studies demonstrate that the vast majority of events (>95%) occur in those patients who exhibit rapid CAC progression (>20%/year),[44,45] suggesting that these patients are at increased risk and warrant more aggressive therapy.

Spiral CT

It is the speed of acquisition (temporal resolution) which greatly differentiates EBT from the results of the slower images from helical (or multi-row-detector spiral) CT.[46,47] The only studies demonstrating similar results between EBT and spiral CT consisted of elderly symptomatic men with very high plaque burdens.[48,49] A recent comparison study in 70 asymptomatic patients undergoing both EBT and spiral CT concluded: "Spiral CT has not yet proved to be a feasible alternative to electron-beam CT for coronary artery calcium quantification".[47] These differences in scores may prove a major difference in prognostic ability. Since there is no improvement of temporal resolution with newer multi-row-detector spiral CT scanners (each slice is still obtained in 250–330 msec), it is unlikely that closer correlations with EBT will be obtained. Furthermore, with images obtained over a longer time (i.e. the scanner is 'on' for 500 msec per rotation, even if these data are not used), the radiation doses to the patient with multislice CT are 6–38 fold greater than EBT.[50] Only the long-term studies now underway (such as the ongoing Multiethnic Study of Atherosclerosis [MESA]) will be able to demonstrate if spiral CT has a role in prognostication.

Cost-effectiveness

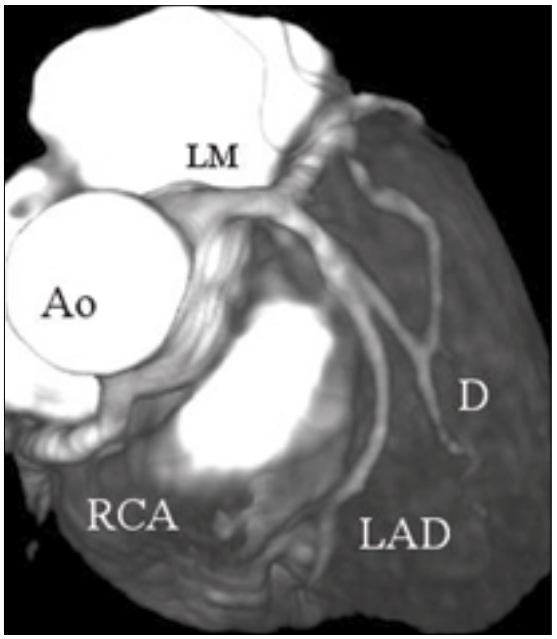
The use of EBT to better risk stratify patients could greatly reduce costs and better direct therapy. Recent European joint society guidelines[51] recommend employing aggressive risk reduction therapy in asymptomatic patients if their absolute risk approximates that of patients with coronary heart disease. Drug therapy, while very effective, entails significant expense. The average cost of statin therapy in the United States is approximately 720 US $ per patient per year,[52] not including physician visits or laboratory tests. With the recent withdrawal from the marketplace of one statin due to safety concerns (cerivastatin), the need to identify those people who would benefit from these medications is even greater. In one model, coronary artery screening with EBT was demonstrated to be a cost-effective screening test in asymptomatic individuals between 45 and 65 years of age.[53] Combining the power of this non-invasive tool with the effectiveness of statin drugs, aspirin and other therapies, will allow physicians to focus aggressive preventative treatment on those individuals with underlying atherosclerosis who are at highest risk of having future heart attacks and coronary death. Furthermore, Wong *et al.*[54] demonstrated that people with CAC have been reported to be more likely to undertake preventive health measures, including beginning cholesterol- or blood-pressure lowering medications, starting aspirin, initiating an exercise programme, following a low-fat diet or quitting smoking. However, this algorithm has not yet been tested prospectively and many physicians remain sceptical.

The absence of CAC on coronary screening identifies a group of patients at very low risk of events over the next three to five years.[19,20] Raggi demonstrated an annual event rate of only 0.36% for patients with scores of zero.[31] Both the American College of Cardiology/American Heart Association writing group and the Prevention V Conference agreed that the negative predictive value of EBT is very high for short-term events.[20,55] Whether a score of zero will allow physicians to withhold therapy also remains to be prospectively tested. However, since most cardiac events occur in individuals at intermediate risk, it seems appropriate to concentrate screening efforts on this group of patients.

Limitations

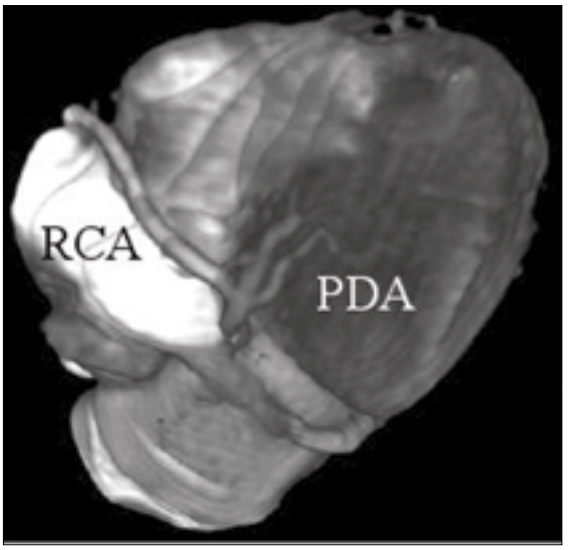
The presence of CAC does not allow for reliable identification of the unstable or vulnerable plaque. However, CAC quantification appears to identify those people at increased risk. The available data suggest that while we cannot identify the vulnerable

Figure 3. Electron beam angiogram in a 54-year-old man with chest pain. Results showed no significant stenosis in any large epicardial artery



Key : Ao = aorta; D = diagonal branch; LAD = left anterior descending; LM = left main; RCA = right coronary artery

Figure 4. Electron beam angiogram in a 66-year-old woman with abnormal thallium scan (reversible inferior defect). Distal right coronary artery (RCA) and posterior descending artery (PDA) demonstrated no stenosis



plaque, by measuring overall plaque burden, EBT can identify the vulnerable patient.[19] A positive EBT demonstrates that advanced atherosclerosis exists in this person, and appropriate therapies should be applied.[20,55] Given the discrepancies as to the prognostic ability of this tool (ranging from odds ratios of 2.3 to 22), longer and larger studies are underway to define the subgroups who will benefit most from measurement of CAC. Current guidelines suggest intermediate-risk patients would benefit most from further risk stratification.[20,56] Furthermore, since CAC is not specific for obstructive CAD, other testing may be necessary to confirm high-grade stenosis prior to angiography.

Caution in the widespread application of EBT has been voiced. Direct patient advertising without physician interaction, inappropriate cardiac catheterisation after detection of CAC in asymptomatic persons, and limited data on cost-effectiveness have been deemed the largest shortcomings in this technology.

Key messages

- Electron beam tomography can accurately and non-invasively measure the extent of coronary artery calcification
- Coronary artery calcification is highly sensitive for the presence of significant coronary artery disease
- Higher calcium scores in symptomatic patients are associated with an increased risk of coronary events. In asymptomatic patients, calcium scores significantly outperform risk factors in cardiac event prediction
- Calcification can be slowed by statin therapy. The use of electron beam tomography can help risk stratify patients and thus better direct therapy and reduce costs
- Electron beam angiography provides non-invasive visualisation of native coronary arteries and bypass grafts

Non-invasive angiography: the promise of electron beam angiography

Electron beam angiography (EBA), with three-dimensional (3-D) capabilities, is an emerging technology with the potential for obtaining essentially non-invasive coronary arteriograms (figures 3-4). This procedure requires intravenous contrast to opacify the lumen and is completed within 20–30 minutes. Recent studies have reported this modality could be used to identify significant coronary lumen narrowing (>50% stenosis) with the sensitivity of 74–92%, specificity of 79–100% and accuracy of 81.2–93.4%, as compared to invasive coronary angiography.[57-60] Selective use of EBA might prove both cost-effective and provide a safer, less invasive method to assess for luminal stenosis.

Using EBA in patients post-CABG or post-stent demonstrated sensitivities of 92–100% and specificities of 91–100% for establishing patency, as compared to conventional coronary angiography.[61-63]

Conclusions

The prognostic studies of EBT, alone or in combination, provide consistent and supportive evidence that EBT-detected CAC carries significant prognostic weight. The presence of CAC in asymptomatic individuals predicts the occurrence of acute coronary events with greater accuracy than other screening tests, including risk factors.[29,31,33,36,39] Two ongoing trials (the MESA trial in the US and the Heinz Nixdorf Recall Study in Germany) will examine the value of EBT-derived CAC in the general population; they will also provide more answers in relation to the role of CAC in primary prevention.

Editors' note

An editorial discussing electron beam tomography in the UK can be found on pages 373-6.

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