Electron-beam CT scanning for detection of coronary calcification and prediction of coronary heart disease

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Summary

Electron-beam or ultrafast computerized tomographic (CT) scanning provides a convenient and sensitive means of detecting coronary calcification, which is an early index of atherosclerosis. The procedure has strong negative predictive power for the presence of coronary artery disease, but a limited ability to predict disease severity. However, preliminary indications are that it is as good or better than conventional risk factors in this respect. Although further validation is needed before electron-beam CT can be regarded as an established method of detecting presymptomatic coronary atherosclerosis, the procedure has potential in this context.

Introduction

Primary prevention of coronary heart disease (CHD) is a more controversial and less cost-effective endeavour than secondary prevention. For example, the reduction in the number of deaths from CHD by simvastatin in the Scandinavian Simvastatin Survival Study (4S), a secondary prevention trial, was fourfold greater than was achieved by pravastatin in the larger West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention trial. One of the main reasons for this difference must have been the frequency in WOSCOPS of asymptomatic individuals who were able to tolerate their hypercholesterolemia without developing CHD prematurely. Thus the ability to detect by non-invasive means the presence of clinically silent coronary atherosclerosis in persons at risk is attractive, in that it offers the possibility of targeting therapeutic intervention to those in whom the likelihood of future CHD is greatest.

Coronary calcification on fluoroscopy

Used alone, exercise testing is not a good means of screening asymptomatic patients for CHD, but its predictive value is markedly increased in those shown to have coronary calcification on fluoroscopy. In one series, all individuals who were positive on both tests were shown to have coronary artery disease (CAD) on angiography, of whom almost half developed clinical CHD within 3 years. However, the frequency of CHD events in subjects without any coronary calcification on fluoroscopy limits the usefulness of this technique as a screening tool, and raises the question as to whether more efficient methods of detecting calcium might have greater prognostic power. Electron-beam computed tomographic (CT) scanning may prove to be just such a tool. This review attempts to evaluate the evidence that this technique might have a major role in screening for CHD.
Electron-beam CT scanning for coronary calcification

Electron-beam CT scanning, which was first developed in 1979 and was originally known as ultrafast CT, enables high-resolution images of the heart to be acquired in less than 100 ms. Using a commercially available scanner (Figure 1) Agatston et al. demonstrated that electron-beam CT was almost twice as sensitive as fluoroscopy in detecting coronary calcification, the presence of which was defined as an area \( \geq 1 \text{ mm}^2 \) with a CT density of \( \geq 130 \) Hounsfield units. Acquisition of 20 contiguous, ECG-triggered CT slices, each 3 mm thick, enabled individual areas of calcification to be quantified and a total coronary calcification score to be computed (Figure 2). The whole procedure takes only 10 min and the radiation exposure is approximately 0.3 mSv in men and 0.5 mSv in women, equivalent to less than one quarter of the annual background.

Electron-beam CT has been claimed to detect coronary calcification in 96% of those with angiographically-proven CAD, whereas absence of calcium means that significant disease is unlikely. However, the prognostic significance of these findings for clinical events has been questioned. A potential drawback is that electron-beam CT is so sensitive that it detects atherosclerosis in many who may never suffer any clinical consequences. As discussed below, this presumably reflects the poor correlation between the extent of calcification and degree of luminal narrowing, although serial examinations show that progressive calcification is more marked in patients with obstructive disease.

Figure 1. Patient positioned in Imatron C-100 electron-beam CT scanner (from reference 31).

Figure 2. Electron-beam CT scans showing anterior descending branch of left coronary artery without (top left) and with calcification (top right) and right coronary artery and circumflex branch of left coronary artery without (bottom left) and with calcification (bottom right).
Reproducibility and temporal change

The interobserver error for calcification scores in 88 subjects averaged 2.5%, with a standard deviation of 5% for two observers.\textsuperscript{10} In a smaller series of subjects, three observers obtained nearly identical scores for any one patient and each of them obtained nearly identical results for the same patient on repeat analysis.\textsuperscript{14} The authors concluded that the reproducibility of scoring is such that only one observer is required for this purpose.

The reproducibility of the procedure itself was assessed recently by performing repeat scans 24 h apart in 91 subjects,\textsuperscript{15} 43% of whom had nil scores on both occasions and 11% on only one occasion. The variability of the calcification score in the remainder averaged 49 ± 45% and was inversely related to the magnitude of the score. In that study calcification was regarded as present if a focus with a density of >130 Hounsfield units was detected in four contiguous pixels (1 mm\textsuperscript{2}) overlying the coronary arteries. However, an earlier study concluded that a focus with twice that area (2 mm\textsuperscript{2}) would provide a more reproducible criterion of whether coronary calcification was present.\textsuperscript{16}

Repeat electron-beam CT scans performed 1 year apart showed an appreciable increase in log-transformed calcification scores with time, especially in patients with known CAD, whereas those without coronary calcification on the initial study remained free of calcium.\textsuperscript{17} Interestingly, one patient showed a decrease in calcification score over this period, coincident with therapeutic reduction of his serum cholesterol.

Pathological correlates

When perfusion-fixed hearts obtained post mortem were scanned by electron-beam CT,\textsuperscript{18} the detection of calcification was predictive of the presence but not the extent of CAD. However, lack of calcification indicated the absence of any lesion which was more than 75% stenosed.

Hoeg et al.\textsuperscript{19} used electron-beam CT to detect calcification in the aorta and coronary arteries of patients with homozygous familial hypercholesterolaemia. Calcified lesions were found in all patients over the age of 13 years and were strongly correlated with the product of serum cholesterol and age. Calcification became detectable in these patients once the cholesterol (mmol/l) \times age (years) score exceeded about 260. If one extrapolates this score to subjects without familial hypercholesterolaemia and with only a moderate increase in serum cholesterol (6.5 mmol/l), the estimated time of development of coronary calcification would be 40 years. This is corroborated by CT observations made in patients aged 30–39 with and without CHD.\textsuperscript{15}

Recent pathological studies have identified the presence of both calcium and osteopontin in atheromatous plaques.\textsuperscript{20,21} The latter is a sialic-acid-rich bone-matrix protein which binds strongly to hydroxyapatite and plays an important role in the calcification process.\textsuperscript{22} mRNA for osteopontin is expressed by both smooth-muscle-cell-derived\textsuperscript{22} and monocyte-derived foam cells.\textsuperscript{23} Osteopontin therefore appears to play a causal role in atherogenesis. Taken together these various lines of evidence suggest that calcification is an integral feature of atheromatous lesions which occurs at an earlier stage in their development than had been thought.

Electron-beam CT compared with angiographic or clinical evidence of CHD

Several studies have examined the relationship between coronary calcification on electron-beam CT and angiographic evidence of CAD. In a series of 100 patients below the age of 60 studied at the Mayo Clinic,\textsuperscript{24} all those with at least one lesion which was >50% stenosed on angiography had coronary calcification on CT. However, in a similar-sized but younger series of patients, one-sixth of those with CAD on angiography, all of whom were aged <50, had a negative CT scan.\textsuperscript{25} This was not a problem in the slightly older patients of both sexes reported by Rumberger et al.\textsuperscript{26} in whom a negative calcium score was strongly correlated with the absence of any angiographic evidence of CAD. The negative predictive power of electron-beam CT for severe CAD has recently been confirmed, but in both studies its ability to predict disease severity was relatively low.\textsuperscript{26,27} In contrast, Agatston et al.\textsuperscript{28} found a close correlation between the amount of coronary calcification on CT and the extent of CAD on angiography.

Electron-beam CT scans in 584 subjects with or without either a previous myocardial infarction or angiographic evidence of CHD showed that calcification scores increased with age, the rate of increase being much steeper in those with CHD (Figure 3). After logarithmic transformation, calcification scores in 30–39-year-olds with CHD were similar to those found in 60–69-year-olds without CHD.\textsuperscript{10} An even larger series was reported by Wong et al.\textsuperscript{29} who studied more than 1200 men and women, just over 10% of whom had historical evidence of CHD. As in most previous studies the predictive value of a negative result was high but the predictive value of a positive test was <40%.
Figure 3. Distribution of coronary artery calcification scores in patients (n = 584) as a function of age and absence or presence of CAD. Asterisks indicate p < 0.01 for CAD vs. no CAD; data are means with standard deviations. UFCT, ultrafast computed tomography (from reference 9).

Estimates of the sensitivity and specificity of electron-beam CT differ little between studies, irrespective of whether the diagnosis of CHD is based on clinical grounds or on angiographic criteria, e.g. presence of a lesion \( \geq 50\% \) stenosed. Using a calcium score of \( > 1 \) as the cut-off, the sensitivity of electron-beam CT (i.e. positive for calcium in the presence of CHD) ranges from 85–100\%, the lower values relating to women and to men <50 years old. Specificity (i.e. negative for calcium in the absence of CHD) ranges from 43–72\%, with the lowest values in men >60 years old. If a higher cut-off value for the presence of calcification is used, namely a calcium score of \( \geq 50 \), sensitivity decreases to 71–91\% and specificity increases to 70–81\%. The improved specificity is highly desirable but occurs at the expense of a slight loss in the sensitivity of the procedure in women and younger men. Lacking at present, however, are prospective data on the relationship between coronary calcification and clinical events.

Electron-beam CT in asymptomatic subjects

Megnien et al. undertook CT scans for coronary calcification and ultrasound scans of the aorta, carotid and femoral arteries in 111 hypercholesterolaemic men. Coronary calcification was detected in 65\% and extracoronary plaque in 72\% of these subjects; these abnormalities were significantly correlated. Interestingly the coronary calcification score was also correlated with the serum triglyceride level but not with serum cholesterol.

Another study examined the relationship between the coronary calcification score and the presence of risk factors for CHD, as gauged by questionnaire.

In contrast to the French study alluded to previously, presence of hypercholesterolaemia was independently correlated with the coronary calcification score, together with age, hypertension, diabetes, smoking and obesity.

The largest study of asymptomatic subjects to date is that of Janowitz et al. who undertook electron-beam CT in almost 2000 men and women. The prevalence of coronary calcification in women was half that in men up to the age of 60, after which the gap narrowed. The authors surmised that the usefulness of this test might be even greater in women than in men because other non-invasive methods of detecting CHD, such as exercise testing, are less accurate in women.

Conclusions

Electron-beam CT scanning provides a convenient, safe and sensitive means of detecting coronary calcification, the presence of which is an integral constituent of atheromatous plaques. However, only one centre in Britain possesses the requisite Imatron scanner, which is a reflection of its purchase price; the cost of each procedure varies from $400 in the USA to just over £100 in this country. The variability of the calcification score on repetition of the scan, especially scores of \( < 100 \), is another drawback, but against this must be set the evidence that absence of coronary calcification on a single CT scan virtually excludes significant CAD, except perhaps in subjects below the age of 40. Despite conflicting evidence as to the role of coronary calcification in predicting the severity of CAD, it appears to be more than twice as good as a conglomerate of conventional risk factors in this respect.

The likelihood of a raised coronary calcification score increases with age and male sex, but the influence of risk factors on coronary calcification has not yet been adequately investigated. Nor are there sufficient data as to the relationship between a raised coronary calcification score and future clinical events. In this context it is important to establish whether therapeutic reversal of risk factors, for example by lipid-lowering drugs, can lead to a reduction or stabilization of coronary calcification. Until such studies have been performed it is impossible to assess properly the future role of electron-beam CT scanning as a means of rationalizing the primary prevention of CHD. Nonetheless, both the need and the potential are there.

References


