Electron beam computed tomography for the diagnosis of cardiac disease

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Electron beam computed tomography (EBCT) of the heart is a new modality which will alter the way cardiology is practised. It allows for the detection of early coronary artery disease (CAD) in asymptomatic individuals, regardless of their level of risk as assessed by traditional risk factor analysis. Compared with risk analysis based on risk factors alone, an assessment which also utilises quantitative measurements of coronary artery plaque by EBCT allows for more precise determination of the need for medical therapy. Non-invasive intravenous contrast EBCT coronary angiography can identify significant obstructive CAD, and should reduce the need for conventional coronary angiography. Incorporation of EBCT into routine medical practice is more cost-effective than other modalities currently available.

This paper reviews relevant original articles on EBCT and preventive cardiology published in peer-reviewed medical journals, and assesses the implications of EBCT for preventive cardiology.

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Limitations of traditional evaluation of coronary heart disease

Coronary artery disease (CAD) is the leading cause of death in developed countries. Despite marked progress in the diagnosis and treatment of CAD, its detection is limited by the high incidence of silent, preclinical disease. In up to 50% of patients the first symptom of atherosclerotic cardiovascular disease is either an acute myocardial infarction (MI) or sudden death.[1] Furthermore, although subjects with a higher degree of obstruction may subsequently be more likely to suffer a cardiac event, angiography shows that half of those with a first or a fatal MI have less than 50% coronary obstruction. This apparent paradox is due to the much larger number of potential patients with less extensive disease. The correlation

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between the pathological and angiographic estimates of the extent of CAD is also adversely affected by the variance of the baseline (pre-disease) vessel size, vascular remodelling and underestimation of disease in reference vessels[2] (Fig. 1).

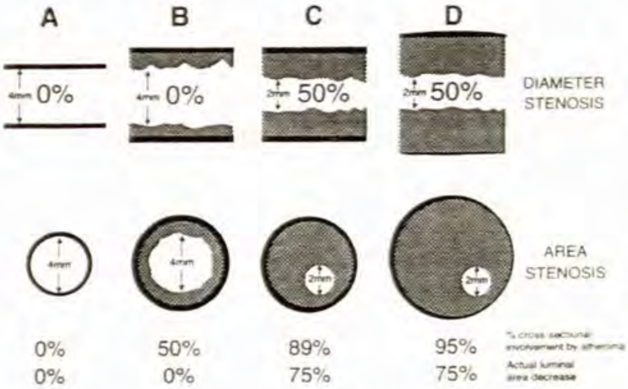

Fig. 1. The effect of vascular remodelling on angiographic analysis. The ability of vessels to dilate in response to ischaemia downstream allows for retention of near-normal lumen size despite progressive plaque build-up. This process not only affects the assessment of disease in the culprit artery, but may also affect the assessment of stenosis in the reference vessel, resulting in a gross underestimation of the degree of stenosis. (Adopted with permission from the American Heart Association.[2])

Approaches to detection of CAD based on cholesterol concentrations are hampered by extensive overlap in the distribution of total cholesterol between those destined to develop symptomatic coronary heart disease and those who remain disease-free.[3] In fact, the majority of patients with coronary disease have normal, or only mildly elevated, cholesterol levels.[4] Measurements of cholesterol concentration, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol[5,6] or apolipoprotein concentrations[7,8] only slightly improve the discriminative value. Other recently identified risk factors, such as homocysteine, lipoprotein A and fibrinogen, have not been shown to improve our discriminating powers substantially.

Stress testing is also of limited usefulness in apparently healthy middle-aged subjects, since the majority of positive stress tests in such populations are falsely positive, and a negative test result (i.e. no evidence of ischaemia) adds just one percentage point to prognostic power (from a pre-test probability of remaining event-free of 0.96 to a post-test probability of 0.97).[9,10] For this reason, a recent statement from the combined task force of the American College of Cardiology and the American Heart Association has concluded that there are no indications for the use of stress testing in asymptomatic people (class I) and that such routine screening may in fact be harmful (class III). The task force has concluded that efficacy of stress testing is debatable even for people with multiple CAD risk factors (class IIB).[11] Newer forms of stress testing, utilising either radionuclide imaging or echocardiography, are expensive and time-consuming and therefore ill-suited for use as screening tests for CAD.

Recent studies, such as the Asymptomatic Carotid Artery Progression Study (ACAPS)[12] and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries investigation (PLAC II),[13] suggest that risk-stratification based on non-invasive anatomical definiton of carotid artery atherosclerosis can be helpful in identifying subjects likely to benefit from therapy, and may allow for relatively easy and inexpensive sequential tracking of CAD over time. Because of the limited correlation of coronary and carotid disease,[14-16] however, direct, non-invasive quantification of coronary disease would be preferable to carotid ultrasonography.

Electron beam computed tomography (EBCT) and coronary calcium

Electron beam (ultrafast) CT (EBCT) is a relatively recent technology which provides the needed tools for non-invasive screening and quantification of coronary disease. The efficacy of EBCT is due to the speed of data acquisition. In contrast to conventional and helical CT which use a mechanically moving cathode-ray tube, EBCT utilises an electron gun which shoots an electron beam toward a series of four semicircular tungsten rings. The beam is focused and swung around the tungsten rings using a magnet. Since no mechanical movement is required during the acquisition of a single slice, the process is extremely quick. Thus only 50 - 100 milliseconds are required per image, allowing for precise ECG triggering and synchronisation, and resulting in a freeze-motion image of the beating heart. The most commonly used protocol generates 40 3 mm slices during a single breath-hold, minimising breath artefacts. Using newer software it is possible to obtain as many as 120 images per run, allowing for thinner slices, more overlap between slices, and a wider scan window (top to bottom). For routine screening, actual scanning time is less than a minute and the complete procedure can be done in 5 - 10 minutes.

Coronary EBCT is most commonly used to screen for unsuspected CAD by measuring calcium deposition in the walls of coronary arteries. The quantity of coronary artery calcium in postmortem specimens, measured by chemical or histological assays, is a marker for the presence of atherosclerotic plaque and correlates with plaque volume, as documented in autopsy studies (six studies, 2 500 hearts), with correlation coefficients ranging from 0.75 to 0.94.[17-22] EBCT-derived coronary artery calcium (CAC) scores accurately measure coronary calcium mass[23] and plaque mass as documented by autopsy.[24] In addition, EBCT-determined CAC scores correlate with the extent of coronary obstruction documented by coronary angiography in symptomatic subjects. A recent report performed a Receiver Operating Characteristic (ROC) analysis for the ability of EBCT-derived CAC scores to predict coronary disease in men and women undergoing angiography. It found an area under the curve of 0.92 for the prediction of any disease and 0.83 and 0.88 for the prediction of 50% or greater stenosis in women and men, respectively.[25] Budoff *et al.*[26] studied 710 patients undergoing angiography and found a sensitivity to detect obstructive CAD of 95% and an area under the ROC curve of 0.82. Specificity was only 44%, but they used the presence of any calcium as a cut-off point, which is probably too inclusive. Most studies comparing coronary calcium scores with angiographic measurements of CAD in symptomatic people have found sensitivities and specificities of 74 - 86% and areas under the ROC curves of 0.8 - 0.9. This relationship holds for asymptomatic patients as well. In a study of 36 asymptomatic subjects, Guerci *et al.*[27] reported a correlation of 0.85 between coronary artery calcium scores and the worst stenosis in any major coronary artery segment, as determined by computer-assisted quantitative coronary angiography at a blinded remote site. The utility of CAC as a marker for the quantity of atherosclerosis and the extent of coronary obstruction is therefore well established. Specific risk analysis can be used to identify optimal CAC scores (maximal accuracy) for a desired degree of stenosis.[28] Further details as to the risk of segment-specific significant CAD may be gained by analysing the character of the calcific deposit. Thus Kajinami *et al.*[29] defined lesions as 'spotty,' 'long,' 'diffuse' or 'wide'. The positive predictive values for significant stenosis and all atherosclerotic lesions increased progressively from 0.04 and 0.17 for no calcification to 0.18 and 0.59 for spotty calcifications, 0.32 and 0.87 for long lesions, 0.40 and 0.84 for wide lesions and 0.56 and 0.96 for diffuse lesions.[29]

Consistent with the limitation of angiography described above, recent studies using intravascular ultrasound have confirmed that occult coronary disease is often present in sites of angiographically 'normal' coronary arteries,[30] and that coronary calcium, quantified with intravascular ultrasonography (IVUS), is predictive of the total plaque burden, although not of site-specific plaque volume.[31] In fact, EBCT can identify IVUS-confirmed CAD in angiographically normal vessels[32] (Fig. 2). It is therefore not surprising that coronary EBCT can differentiate patients with very early coronary artery wall irregularities from those with perfectly smooth walls,[33] and that even in subjects with normal coronary angiography, the presence of coronary calcification still imposes a threefold higher risk of a subsequent cardiovascular event.[34]

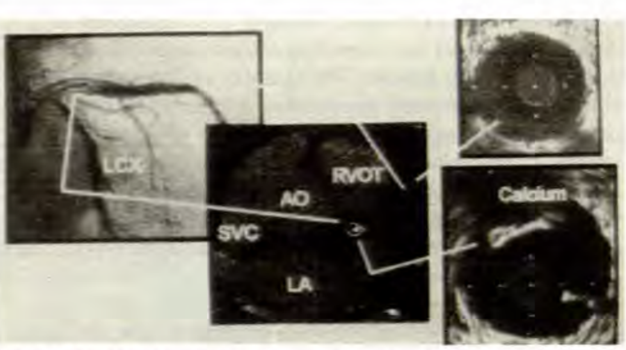

Fig. 2. Comparison of coronary angiography, intravascular sonography and EBCT-determined calcium deposition. Shown are two segments of a coronary artery laden with plaque. One segment (distally) is normal by all three methods. The proximal segment shows a plaque by sonography and EBCT but is normal by angiography. (Reproduced with permission from the American College of Cardiology.[32])

EBCT-derived CAC scores compare favourably with thallium stress testing (TST) for the prediction of obstructive disease in symptomatic subjects. Kajinami *et al.*[35] studied 251 subjects with suspected coronary disease with EBCT, TST and angiography. They showed an overall accuracy for predicting obstructive CAD of 0.85 for EBCT-derived CAC, compared with 0.71 for either TST or ECG stress testing, and 0.77 for TST and ECG stress testing combined. This finding was confirmed by Spadaro *et al.*[36] showing overall accuracy of 0.79 for EBCT versus 0.63 for TST for the prediction of angiographically documented coronary artery disease.

More importantly, EBCT-derived calcium scores predict future cardiovascular disease events. The only full follow-up report on asymptomatic subjects evaluated the predictive value of CAC scores in 1 173 subjects with no known CVD, as well as a negative Rose Angina Questionnaire on presentation. During an average follow-up of 19 months (range 14 - 23 months), EBCT-derived CAC scores above 160 denoted an odds ratio for future events of 35.[37] ROC analysis for the ability of EBCT to predict cardiovascular events showed an area under the ROC curve of 0.91 (Fig. 3).

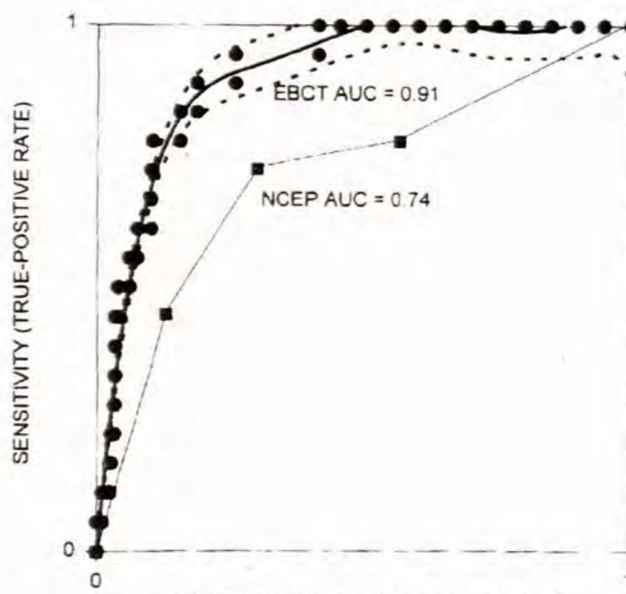

Fig. 3. The ROC curve for prediction of future cardiovascular events in asymptomatic subjects. For an average of 19 months 1 173 people with no history or symptoms of CVD were screened and followed up. Eighteen subjects had 26 events (1 cardiac death, 7 non-fatal MIs, 1 spontaneous thrombo-embolic stroke, 8 coronary artery bypass procedures and 9 coronary angioplasties). Indications for all angioplasties and bypass surgery operations were deemed justified by onset of new symptoms and/or new positive stress tests, and all stress tests were done because of new symptoms. The ROC analysis counts each patient only once. A perfect test would have an area under the curve (AUC) of one. The curve for the NCEP II guidelines (triangles) is based on analysis of the 12-year follow-up data from the Lipid Research Clinic Prevalence and Follow-up Studies.[6] (Reproduced with permission from the American Heart Association.[37])

Furthermore, while the overall risk for a future CVD event in this asymptomatic population was 1.5%, those with scores above 160 had a 5% event rate and those with scores above 680 had a 14% event rate. The conclusion that EBCT is the best screening method for preclinical CAD is supported by five other preliminary reports on asymptomatic subjects undergoing EBCT[38-42] (with follow-up ranging from 1 to 5 years) and by a follow-up study using fluoroscopy,[43] as well as by a study of subjects with a history of CAD.[44] In addition, EBCT-derived CAC scores predict the risk of restenosis following angioplasty, with mean pre-procedure CAC of 92 in patients with subsequent restenosis versus 228 for patients in whom there was no restenosis.[45]

As expected, there is a positive correlation between CAC and other known risk factors for atherosclerosis.[46] It is therefore essential to compare the predictive value of CAC with that of other risk factors, and to determine whether CAC offers an incremental value to any combination of known risk factors. Spadaro *et al.*[47] compared the predictive value of CAC with traditional risk factors in subjects without a history of MI who presented for first angiography. In multiple logistic regression analysis incorporating lipid and traditional non-lipid risk factors, EBCT-derived CAC scores were the most accurate predictors of the presence of either any CAD or obstructive CAD. Furthermore, for any number of risk factors, a CAC score above 170 doubled or tripled the likelihood of either any CAD or obstructive CAD, regardless of the number of risk factors (Fig. 4).

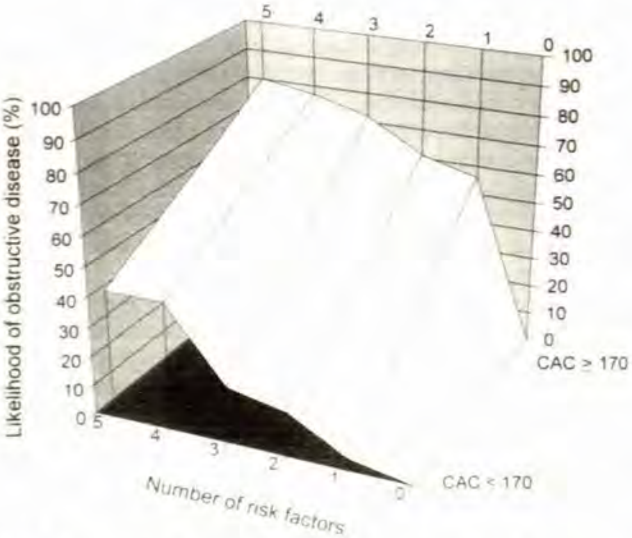

Fig. 4. Incremental predictive value of coronary calcium scores for coronary obstruction. The likelihood of angiographically documented obstructive CAD (Y-axis) is plotted against the number of traditional risk factors (X-axis) for 264 subjects with coronary calcium scores below (in front) or above (in back) 170. (Arad *et al.* — unpublished observation.)

The utility of coronary calcification as a screening test for occult CAD is hampered by the positive correlation between CAC and age and male gender.[48] EBCT has been criticised for poor sensitivity (due to universally lower scores) in women and young males and poor specificity in older subjects, males in particular (due to the high prevalence of high scores). In fact, these differences in CAC score distribution reflect actual differences in plaque burden between these groups.[25] Nonetheless, the use of raw CAC, uncorrected for age and gender, may result in treating an inordinate number of men and the elderly, while under-treating women and younger persons.

There is no general consensus at this time regarding these last two matters. However, a general approach can be proposed. First, although the CAC score correlates with the anatomical extent of atherosclerosis and is not a risk factor *per se*, it seems logical, on the basis of the data presented above, to adjust the NCEP-based risk analysis according to CAC scores. Second, each patient's CAC should be evaluated with reference to the distribution of CAC in subjects of the same age and gender.[9] Such an approach may be used as follows: a CAC score of zero could be considered as two negative risk factors; and a CAC score between zero and the 25th percentile for age and gender may be considered as one negative risk factor. A CAC score between the 25th and the 50th percentile may be considered as neutral. A CAC score between the 50th and the 65th percentile may add one risk factor; a CAC score between the 65th and the 80th percentile may add two risk factors; and a CAC score above the 80th percentile for age and gender may be considered evidence of obstructive CAD.

It can be concluded that EBCT-derived CAC scores are currently the best predictors of the presence and extent of coronary artery disease, and of the likelihood of future cardiovascular events in both symptomatic and asymptomatic persons, and that EBCT-derived coronary artery calcium measurement is therefore the best screening tool for CAD. Moreover, routine use of EBCT for detection of CAD can result in substantial health savings. For example, early detection and treatment with diet or drugs of subjects with elevated CAC scores will prevent future expenditures associated with hospitalisation for angina, MI or congestive heart failure (CHF), as well as those associated with worker's disability. Conversely, a very low calcium score in subjects with isolated hypercholesterolaemia or with relatively few risk factors is probably a good indication that expensive cholesterol-lowering medications are not required. Two preliminary analyses suggest that screening for CAD with EBCT is cost-effective.[49,50] The latter analysis concluded that using CAC screening to target lipid therapy, rather than using a cholesterol level of 6.73 mmol/l, would prevent 179% more events, at the same total cost. A more recent analysis compared EBCT-derived CAC scores with ECG-based stress testing, stress thallium, stress echocardiography, and conventional angiography.[51] Using a theoretical model based on previously published ROC curves for the correlation of CAC with angiographically measured CAD, the authors concluded that EBCT is the most cost-effective test for screening for CAD in high-risk patients, or patients with chest pain syndrome with no history of CAD (Fig. 5).

Intravenous contrast coronary angiography

The value of EBCT is not limited to determination of coronary calcifications. The most exciting and rapidly evolving modality of EBCT is intravenous (IV) contrast EBCT for imaging of the ventricles, valves and coronary arteries. New, sophisticated software programs have vastly improved the applicability of IV contrast EBCT. Studies can be

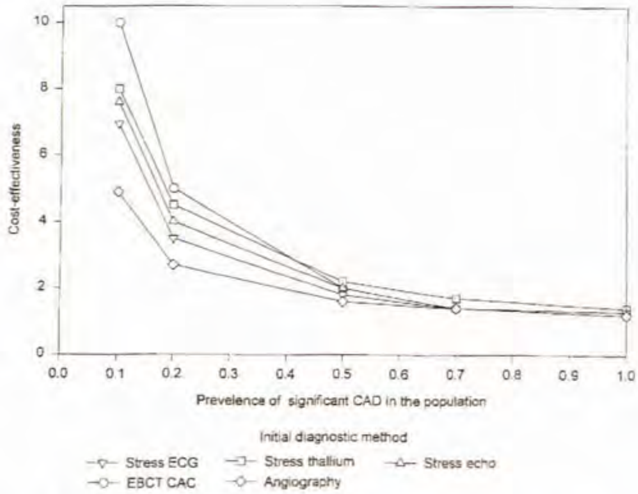

Fig. 5. The cost-effectiveness of EBCT versus other diagnostic modalities, including stress ECG, stress thallium, stress echocardiography and coronary angiography. The authors used a theoretical model to predict cost-effectiveness for subjects with various pre-test likelihoods of CAD, based on previously published ROC curves. (Reprinted with permission from Springer-Verlag.[51])

performed in the cine mode or the single-slice mode. In the cine mode, 18 images per second are obtained at eight contiguous levels, with the table stationary, allowing for real-time assessment of ventricular wall and valve function. Cine EBCT, which can be presented in four dimensions (3-D in real time) or reconstructed in any plane of interest, generates images of superior quality to those obtained with echocardiography, and produces excellent images of the right side of the heart. Very precise analyses of myocardial function, as well as of regional myocardial perfusion by time-density curves, are now also possible.[52,53] Another exciting new approach involves wall motion analysis before and during infusion of dipyridamole[54] or dobutamine[55] to detect wall motion abnormalities. The high resolution of EBCT for both the right and the left side of the heart, combined with the ability to reconstruct the image in any plane as well as in four dimensions, permits precise evaluation of regional wall abnormalities.[56-58]

In addition, in the single-slice mode and with new software, using shaded surface display, continuous volumetric (moving slab) reconstruction, or curvilinear space reconstruction methods, precise imaging and assessment is achieved. The patency of the proximal and middle portions of the three major coronary arteries and their branches,[59,60] as well as of bypass grafts,[61] stents[62] and post-angioplasty vessels,[63] can be assessed with accuracies of nearly 90% for native coronaries and 97% for bypass grafts. Since most errors are due to technical problems, such as slice gaps,[60] it is expected that with improvement in technique accuracy will soon approach 100%. Imaging of plaques and assessment of stenoses and complete obstructions, as well as stent patency, is rapidly performed in several minutes of on-line time (Fig. 6). Perspective rendering even allows for virtual reality, real-time, fly-through imaging of the coronary arteries.

The ability to analyse coronary and valve anatomy, regional wall motion abnormalities and myocardial perfusion

Fig. 6. EBCT coronary angiography. Intravenous contrast EBCT coronary angiography can be performed in several minutes and the images are reconstructed using one of several software options. (Courtesy of Dr John Rumberger, Professor of Medicine, Mayo Clinic, Rochester, Minn.)

in one sitting is unique to EBCT. Comparable complete evaluation of cardiac function and disease currently requires a combination of echocardiography, radio-isotope-based perfusion imaging and angiography, and is much more expensive and time-consuming. Work-up of chest pain of unknown aetiology is another example of the versatility of EBCT. Coronary disease, pulmonary embolism, pericardial disease and a variety of gastro-intestinal and pulmonary aetiologies are investigated simultaneously, rather than with a series of separate tests. Thus, EBCT presents a real potential for saving in health care.

Some remaining limitations of EBCT include incomplete visualisation of the distal portions of coronary arteries or small branches, and artefacts associated with imperfect breath-holding or beat-to-beat variation in the length of the cardiac cycle. Despite these limitations, the capacity of EBCT as a 'one-stop shop' to diagnose coronary disease already surpasses other available technologies. Expected improvements in hardware and software capabilities such as multi-array detectors, increased scanning speed and slice number which allow for thinner slices and more overlap between slices, as well as better reconstruction algorithms, should improve its utility even further.

Other technologies, such as helical CT, MRI and dichromatic angiography with synchrotron radiation, can potentially compete with EBCT. Helical CT can assess the presence of coronary calcifications[64] and has also been used for assessment of bypass graft patency,[65] but it is limited by its slower acquisition time and lack of ECG synchronisation. No studies with helical CT have reported efficacy in assessing the *degree* of bypass graft stenosis or the evaluation of native coronary arteries. Its slower acquisition time also limits the usefulness of helical CT for cine studies. MRI is limited by slower acquisition time and poor spatial resolution, although recent improvements in techniques might overcome some of these problems. In addition, MRI cannot be used for early CAD screening at the present time. Dichromatic angiography requires a particle accelerator and is not practical for routine medical use.

EBCT is currently the only technique with proven ability to perform the full spectrum of cardiac diagnoses, including screening for early atherosclerosis, predicting the risk of future cardiovascular events, visualising myocardial anatomy, function and perfusion in real-time and in three dimensions, and assessing coronary anatomy and obstruction. Its routine use for the medical evaluation of cardiac disease will result in more accurate and economical detection and treatment of heart disease.

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