Electron beam computed tomography: on its way into mainstream cardiology?

The recent surge of interest by both cardiologists and patients in electron beam computed tomography, an imaging technique developed in the 1970s, stems from reports about its excellent ability to depict high grade coronary artery stenoses[1] and its capability to quantify coronary calcification[2] and monitor the development of calcific deposits[3]. This editorial will focus on the current evidence indicating that electron beam computed tomography has a role in the diagnosis and treatment of patients with coronary artery disease.

Electron beam computed tomography as a substitute for cardiac catheterization?

Could electron beam computed tomography serve as a substitute for invasive coronary angiography to identify patients whose symptoms are caused by high grade coronary artery stenoses? Is the test good enough to refer patients, on the basis of electron beam computed tomography images only, to interventional catheter-based therapy? There is no doubt that symptomatic and asymptomatic patients with evidence of large areas of ischaemia need depiction of their coronary anatomy[4–6] to determine the need for and technical feasibility of revascularization. The decision whether and how to revascularize is ultimately based on the patient’s symptoms, the number of diseased vessels, details of the coronary anatomy such as the presence of calcification or diffuse disease and involvement of the periphery of the coronary arteries in the disease process, and left ventricular function.

Does electron beam computed tomography provide a ‘one stop shop’ for all these necessary details? There are reports about the ability of electron beam computed tomography to diagnose myocardial malperfusion[7] or stress-induced wall motion abnormalities[8], but the technique is currently not used in daily clinical work for assessment of myocardial ischaemia. Although it is possible to identify high grade stenoses with a sensitivity of 92% in those who have good image quality, precluding an assessment of stenoses[1] and the evaluation process may be prohibitively time-consuming[9]. Moreover, severe calcification interferes with the visualization of coronary artery stenoses and the anatomy of side branches and peripheral vessels — knowledge of which is crucial for the cardiac surgeon — cannot be determined[1]. Finally, although qualitative and quantitative assessment of regional and global left ventricular function[10] is accurate, this technique has not been used clinically to identify patients with low left ventricular ejection fraction who are currently believed to derive the greatest prognostic benefit from surgical revascularization. Therefore, no item of the triad perfusion, anatomy and function, can currently be assessed by electron beam computed tomography with the degree of reliability which is needed to make such important treatment decisions. In particular, the information on coronary anatomy provided by electron beam computed tomography is so limited that additional invasive angiography is still warranted before therapeutic decisions can be made.

Electron beam computed tomography as a replacement for other non-invasive techniques to detect significant coronary disease?

Can the information about coronary calcification and coronary anatomy provided by electron beam computed tomography be used as a replacement for the exercise electrocardiogram or other imaging techniques, such as the stress echocardiogram or the perfusion scintigram[11] in patients with symptoms suggestive of coronary artery disease? Indeed, both the severity of coronary artery disease, as assessed by coronary angiography[12,13] and the amount of coronary plaque[14,15] are highly correlated with the electron beam computed tomography calcium score. Electron beam computed tomography is inexpensive (400–500 $ in the U.S.A. and 450 DM in Germany), and requires only 15 min examination time without any patient preparation. The radiation exposure is...
low and there is no need for the application of contrast material. Moreover, the test can be performed in patients with resting ECG abnormalities or digitalis medications, as well as in those unable to exercise.

Rumberger et al.[16] employed a theoretical model to assess the costs and effectiveness of this approach, as compared to the more traditional non-invasive testing methods such as treadmill exercise, stress echocardiography and stress thallium-201. The testing model was adapted from the original publication by Patterson et al.[17]. This model assumes a de novo presentation of patients with a clinical history of obstructive coronary artery disease. The three established tests plus four electron beam computed tomography diagnostic algorithms based on four different cut-off values of calcium score were applied in this model in addition to a strategy aiming for angiography as the first line technique. Positive tests were confirmed by coronary angiography to guide further treatment. The parameters for sensitivity (68% for treadmill exercise testing[18], 90% for thallium-201[19], 84% for stress echocardiography[20]) and specificity (77% for treadmill exercise testing[18], 77% for thallium-201[19], 87% for stress echocardiography[20]) used in this model were derived from review data in the literature. As sensitivity decreases but specificity increases with increasing calcium scores, different parameters for sensitivity (range 95%–71%) and specificity (46%–90%) for the four calcium scores were derived from large electron beam computed tomography studies[11,13,21,22]. In the group of patients with low to moderate disease prevalence (<70%), the model identified electron beam computed tomography as the test which minimized direct costs (calcium scores of 168, 80, and 37, respectively) and maximized cost-effectiveness (same scores), whereas direct angiography proved most cost-effective in patients with a higher prevalence. Therefore, electron beam computed tomography is an interesting alternative to the established stress tests for detecting significant coronary artery disease. However, the technique has some disadvantages: the major shortcoming of the electron beam computed tomography approach is the low availability of the device in most European countries. Secondly, electron beam computed tomography lacks the power of localizing ischaemia to specific anatomical sites, an important consideration in applying stress echo or single photon computed tomography scintigraphic imaging. Thirdly, in contrast to the echocardiographic and scintigraphic literature, there is a paucity of data relating electron beam computed tomography calcium scores to patient prognosis[23] and outcome. Thus, further direct evidence of successful and cost-effective clinical application is clearly needed before electron beam computed tomography calcium scores can be recommended as a substitute for the currently used techniques to identify patients with obstructive coronary disease.

**Electron beam computed tomography for risk stratification in asymptomatic subjects?**

What is the current role of electron beam computed tomography in identifying asymptomatic patients at high risk for coronary events? Identification of these patients has a high health priority because evidence of subclinical coronary disease might result in preventing premature death and myocardial infarction by directing ‘primary’ prevention more aggressively to these patients. Current risk stratification based on models such as the Framingham Risk Model[24] has only limited sensitivity and specificity for identifying those who will ultimately suffer from catastrophic coronary events. Low sensitivity is indicated by the fact that more than 50% of deaths from coronary artery disease and first myocardial infarcts occur in patients thought to be at low risk for such events by conventional risk assessment[25]. Many patients totally unaware of their life threatening illness die suddenly from acute coronary thrombosis due to the rupture of a non-obstructing plaque containing a large lipid core[26,27]. In fact, in the majority of patients the initial manifestation of coronary artery disease is not angina pectoris but unheralded death or myocardial infarction[28]. On the other hand, specificity is so low that even if we treat all patients at high risk by conventional risk factor assessment, at least 60% of them would not have a coronary event in the next ten years without such costly intervention. The reason for the disappointingly low predictive value of established risk factors (cholesterol, nicotine, diabetes, hypertension)[29] for coronary events in individual asymptomatic patients is that the high number of events results from multiplying a low absolute event rate by a large number of people at risk. Although symptomatic smokers with serum cholesterol and systolic blood pressure levels in the highest quintiles have coronary heart disease death rates that are approximately 20 times greater than non-smoking men with systolic blood pressure and cholesterol levels in the lowest quintile, the coronary death rate in this ‘high risk’ group is only 58 per 10 000 person years or 0.58% per year[29].

When considering the mechanism of many sudden coronary events (rupture of a vulnerable non-obstructing plaque with subsequent thrombus
formation), it is not surprising that commonly used stress tests (which aim at detecting severe coronary obstruction) also have very low power to predict myocardial infarction or coronary death in asymptomatic patients\(^{30,31}\). In fact, the power of these tests may even be lower than that of appropriate risk models. Thus, our current tools are suboptimal to direct primary prevention to high risk patients and to maximize effects at an acceptable cost to society.

Can we do better than just look at risk factors or use stress tests to identify patients at exceptionally high risk of subsequent coronary events? Screening for coronary calcium by using electron beam computed tomography is an attractive possibility, to improve our current risk stratification process. If patients without calcium were at low risk and those with increasing amounts of calcium were at increasing risk, this stratification process might result in the desired effect, of allocating primary prevention investment to the patients at highest risk. In an initial non-randomized study, calcium scores by electron beam computed tomography >100 and >160 had odds ratios for coronary events of 20:1 and 35:1\(^{32}\), which were larger than the ones achieved by combining risk factors. This confirmed previous findings by Detrano and co-workers on the value of calcium screening by fluoroscopy\(^{33,34}\). Risk ratios for a coronary event (CAD death, non-fatal MI, coronary revascularization, angina) over a follow-up of 1 year in their study population was 2.6 (\(P<0.001\)). More recently, however, the same authors\(^{35}\) found that adding calcium screening by electron beam computed tomography to the Framingham risk profile\(^{36}\) did not improve the prediction of hard coronary events, such as death or myocardial infarction, in this same high risk population in California. Indeed, in their fluoroscopy study\(^{33}\), the risk ratio for coronary death was only 1:0, which is consistent with their current electron beam computed tomography data\(^{35}\). The recent electron beam computed tomography study\(^{35}\), however, suffers from a few problems which need to be addressed: firstly, patients were aware of their calcium status and this knowledge may have influenced subsequent treatment. Secondly, the group with early events (within the first 30 months of observation) which comprised >10% of the initial fluoroscopy study group were excluded from the electron beam computed tomography study. Thirdly, patients in these studies\(^{33,35}\) had a mean age of 66 years and were thought to have an 8-year coronary risk ≥10% on the basis of the Framingham risk equation. Thus the results do not necessarily pertain to younger patients and those at lower risk. Despite these study limitations, it is possible that just looking at calcium scores by electron beam computed tomography may be too narrow an approach to solve the complex problem of early identification of individuals at the highest risk for coronary events.

**Monitoring progression and regression of coronary calcification**

If the calcium score per se does not add to risk stratification in older adults thought to be at high risk based on conventional risk factors, can one expect to identify those at highest risk by detecting accelerated progression of coronary calcification by serial electron beam computed tomography examinations? Although the reproducibility of the most commonly used electron beam computed tomography protocols is not high enough to detect small differences in calcium scores\(^{36,37}\), a new volumetric scoring method, which is able to reduce the interstudy percent score change from 15% to 9%\(^{38}\), may be accurate enough to achieve this goal. Using this new scoring method, Callister and co-workers reported that successful treatment of hypercholesterolaemia by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors over 12–15 months resulted in a decrease of the calcium volume score, whereas patients without such treatment showed a net increase in calcium score\(^{35}\). If these differences in calcium score over time result in a difference in event rates it is conceivable that serial measurements of calcium scores by electron beam computed tomography, using the new scoring method, will provide a powerful and much needed predictive tool.

It may appear surprising that arterial calcification is not necessarily a relentlessly progressive process\(^{39}\). Indeed, in vivo regression of calcification in atherosclerotic lesions has not been reported previously. However, arterial calcification is an actively regulated process\(^{40}\). Just as eliminating osteoprotegerin, a secreted protein which inhibits osteoclast formation, will result in massive arterial calcification in a mouse model\(^{41}\), it is conceivable that activation of osteoclast activity within atherosclerotic lesions might result in a net loss of calcific deposits. Thus, serial evaluation of arterial calcification by electron beam computed tomography may provide important new information about the factors influencing the development of such lesions.

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Is electron beam computed tomography on its way into mainstream cardiology? Even if the detection
and quantification of coronary calcification proves helpful in decision making in clinical cardiology and will aid in the management of patients with chronic stable angina,[4] electron beam computed tomography is unlikely to become the method of choice for this purpose. The latest generation CT scanners has only a scan time of 500 ms. These scanners will become much more widely available than electron beam computed tomography since they can also be used for applications outside the cardiovascular system. Initial reports indicate that determination of coronary calcium using these scanners may be as equally effective in determining coronary calcium as electron beam computed tomography in patients with suspected coronary artery disease.[42] The variability between CT and electron beam computed tomography measurements is below the range of repeated electron beam computed tomography studies.[42]. Further progress can be expected with the implementation of prospective ECG-gating and the application of spiral.

In which persons should electron beam computed tomography scanning be considered? At the time of writing, there is no definite and proven indication for use of this technique for clinical decision making in patients.[43]. Further large studies are currently underway[44] to look prospectively at the value of electron beam computed tomography in asymptomatic persons in whom a decision regarding the need for medical risk intervention is uncertain. In such patients, scanning may establish the presence and the extent of calcified plaque in the coronary arteries and help the clinician channel expensive interventions, towards those patients who will benefit most.

U. SECHTEM
Robert Bosch Krankenhaus,
Stuttgart, Germany

References


