Coronary calcification and coronary artery disease activity: a dilemma unresolved?

The early, non-invasive detection of coronary artery disease is a major challenge confronting contemporary cardiology. In particular, the early identification of vulnerable plaques that may lead to acute coronary syndromes (ACS) poses a major dilemma. In recent years, electron beam computed tomography (EBCT) has been suggested to represent a useful tool for the detection and quantification of coronary artery calcification, an established marker of coronary atherosclerosis. In this issue of the journal (see pages 273–80), Anand *et al*.[1] review the role of coronary calcium imaging with EBCT in the detection of early atherosclerosis in asymptomatic individuals. Their message is optimistic but a number of unresolved issues exist that may, at present, limit the widespread application of this technique in the general population.

Calcium, coronary artery disease and prognosis

Clinical and experimental studies have shown a direct correlation among the extent of coronary calcification, atherosclerotic burden and risk of future cardiovascular events. Although calcium deposits are found mainly in advanced atheromatous plaques, recent studies have shown coronary calcification in up to 95% of patients with ACS[2] and in young patients with a first, unheralded myocardial infarction (MI).[3] In these studies,[3] however, the culprit vessel was not found to be calcified in all cases and the mean calcium score of culprit arteries was only marginally higher than that of other arteries. Moreover, studies have shown a similar degree of calcification in stable atheromatous plaques compared to 'vulnerable' plaques.[4]

These observations are intriguing given the consistent finding in different studies that coronary calcification, as detected by EBCT or by other means, is a predictor of cardiovascular events. Indeed, Keelan *et al*.[5] reported that in symptomatic patients undergoing angiography, extent of coronary calcification on EBCT correlated with angiographic extent of coronary artery disease and was highly predictive of future cardiac events. Although findings in the study of Keelan *et al*.[5] are of interest, this study is not without limitations. A relatively small group of patients were recruited who underwent EBCT at the time of diagnostic coronary arteriography. Furthermore, the assessment of patient outcome was an opportunistic end point as the original aim of the study was to assess the correlation between EBCT calcium scores and extent of angiographic coronary artery disease. The Pohle study,[3] which was carried out in young patients with a first MI, also has limitations as it involved a small number of subjects and controls were selected retrospectively.

More recently, the St Francis Heart Study, a prospective, randomised study involving over 5,800 asymptomatic subjects without signs or a history of coronary disease, was presented (non peer-reviewed report).[6] This study was carried out to assess whether EBCT scanning provides additional diagnostic information compared to the Framingham-derived prognostic criteria. In the St Francis Heart Study, 122 subjects developed at least one of the following events over a mean of 4.5 years of follow-up: coronary death, non-fatal MI, myocardial revascularisation, peripheral vascular surgery or stroke. High EBCT-derived calcium scores predicted the occurrence of cardiovascular events with 'unprecedented accuracy'. The trial confirmed results of previous studies regarding the high sensitivity but low specificity for coronary disease when low EBCT scores are found. The positive predictive value for high (> 600) EBCT calcium scores was rather disappointing at 14%. Although the St Francis Heart Study was a large, well-designed trial, the selected composite end point may represent a limitation of the study. Surgical and/or percutaneous intervention could have been influenced by EBCT results.

Calcium and plaque vulnerability

It is established that coronary atheromatous plaques responsible for ACS are not necessarily severe. Rapid coronary artery disease progression is rather unpredictable and has been shown to be determined by a number of complex mechanisms including, among others, inflammation and thrombogenesis. The mechanisms responsible for both plaque instability and rapid disease progression are not completely understood at present. Understanding these processes is crucial for the identification of diagnostic strategies and the selection of clinically relevant markers of risk. Imaging techniques, catheter devices and biochemical tests are currently being assessed in the search for markers of plaque instability and risk of rapid coronary stenosis progression, particularly in asymptomatic individuals. Preliminary results with EBCT are promising and these have been discussed by Anand *et al*.[1]

Why are high EBCT calcium scores good predictors of risk? Is it just because they reflect the presence of extensive coronary artery disease or is it because calcification, at least in its earliest stages, is the expression of both atherogenesis and inflammatory activity? The role of calcification in atherogenesis and atheromatous plaque disruption, if any, is not well understood. It has been suggested that calcified stenoses and hypocellular fibrotic plaques are less prone to disruption[7] and this contrasts with the finding that high calcium scores are associated with increased risk of cardiovascular events.

The role of calcium in arterial remodelling is also controversial. Burke *et al*.[8] reported that calcification occurs primarily in areas of apoptosis or lipid cores, initially as microscopic deposits. Plates of calcium later develop in the fibrotic plaque and calcium granules can be detected in lipid cores highly infiltrated by macrophages. The latter finding is interesting and may provide a link between calcification, inflammation and plaque vulnerability. Remodelling in the Burke study[8] was associated with the presence of the two forms of calcium within the plaque, casting doubts as to the true role of inflammation in this setting.

Coronary calcification, as detected by EBCT, can be reversed by pharmacological interventions known to improve patient survival and to reduce plaque instability, i.e. treatment with HMG-CoA reductase inhibitors (statins).[9] This finding if confirmed, will be of paramount importance regarding the usefulness of EBCT for the assessment of disease progression and the effects of different therapeutic interventions on plaque instability.

Due to the fact that plaque vulnerability may have different manifestations in different individuals, it is likely that a combination of techniques, as opposed to a single unique tool, will be required to accurately identify individuals at risk. We concur with Anand *et al*. that EBCT calcium scores may represent a useful marker of coronary disease extent in asymptomatic individuals. Further evidence, including health economic analysis, is required before EBCT can be proposed as a tool to screen the UK population. We believe that, at present, and until more compelling evidence is available, EBCT should be used only in subjects in whom appropriate characterisation with conventional markers is inconclusive.

References

1. Anand DV, Lahiri A, Lipkin D. Electron beam computed tomography coronary calcium imaging for the early detection of coronary artery disease in asymptomatic individuals. *Br J Cardiol* 2003;**10**:273-80.
2. Schmermund A, Baumgart D, Gorge G *et al*. Coronary artery calcium in acute coronary syndromes: a comparative study of electron-beam computed tomography, coronary angiography, and intracoronary ultrasound in survivors of acute myocardial infarction and unstable angina. *Circulation* 1997;**96**:1461-9.
3. Pohle K, Ropers D, Maffert R *et al*. Coronary calcifications in young patients with first, unheralded myocardial infarction: a risk factor matched analysis by electron beam tomography. *Heart* 2003;**89**:625-8.
4. Burke AP, Weber DK, Kolodgie FD *et al*. Pathophysiology of calcium deposition in coronary arteries. *Herz* 2001;**26**:239-44.
5. Keelan PC, Bielak LF, Ashai K *et al*. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation* 2001;**104**:412-17.
6. St Francis Heart Study: Coronary calcium scores enhance Framingham-based risk stratification. Practice News. (www.acc.org)
7. Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ. Structure-dependent dynamic mechanical behaviour of fibrous caps from human atherosclerotic plaques. *Circulation* 1991;**83**:1764-70.
8. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodelling in coronary atherosclerosis. *Circulation* 2002;**105**:297-303.
9. Callister TQ, Raggi P, Cooil B *et al*. Effect of HMG-CoA reductase inhibitor on coronary artery disease as assessed by electron-beam computed tomography. *N Engl J Med* 1998;**339**:1972-8.

Juan-Pablo Kaski
Senior House Officer (Paediatrics)
Whittington Hospital, Highgate Hill,
London, N19 5NF.

Juan Carlos Kaski
Director of Coronary Artery Disease Research Unit,
and Head of Cardiological Sciences
St George's Hospital Medical School,
Cranmer Terrace, London, SW17 ORE.

Correspondence to: Professor JC Kaski
(email: jkaski@sghms.ac.uk)

Br J Cardiol 2003;**10**:251–2