Incidence and clinical relevance of coronary calcification detected by electron beam computed tomography in heart transplant recipients

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Background  Patients treated by cardiac transplantation who survive beyond one year are at significant risk from fatal coronary artery disease. The development of coronary artery calcification in these patients is discussed and methods available to detect it are reviewed.

Objectives  To assess the clinical importance of coronary artery calcium in heart transplant recipients.

Methods  In a cohort of 102 cardiac transplant recipients, electron beam computed tomography was used to measure calcium in the coronary arterial wall 63 days to 9.1 years (median 4.6 years) after transplantation. The results were compared with angiographic findings and with conventional coronary disease risk factors. The patients were followed for a mean of 2.12 years (1.2–4.02 years) to assess the relationship between these findings and future cardiac events.

Results  Forty-one (40.2%) had a stenosis of >24% in one or more major coronary artery at angiography. Forty-six (45%) had a coronary calcium score >0. The absence of calcium had a negative predictive value with respect to angiographic disease in any vessels of 87.5%. Logistic regression revealed that dyslipidaemia, systemic hypertension and organ ischaemic time were significant predictors of calcification. At follow-up, both an abnormal coronary angiogram and coronary calcium were found to be the only significant predictors of late events. Multivariate analysis suggested that the detection of coronary calcium did not offer any additional predictive information over that provided by the angiogram itself.

Conclusion  Electron beam computed tomography is well suited to the assessment of calcium in the coronary arteries of heart transplant recipients, although the mechanisms of this calcification remain poorly understood. Calcium is detected more frequently than would be suggested by studies using intravascular ultrasound. It is associated with the presence of angiographic disease, and with some conventional risk factors for coronary disease. At follow-up the presence of coronary calcium was associated with an adverse clinical outcome, as it is in conventional ischaemic heart disease.

Key Words:  coronary calcification, cardiac transplantation, transplant coronary atherosclerosis, electron beam computed tomography.

Introduction

Coronary artery disease has become the leading cause of morbidity and mortality in heart transplant patients and accounts for 36% of mortality in individuals surviving 1 year beyond transplantation[1]. Management of accelerated coronary atheroma that occurs in transplant recipients thus becomes a problem, especially since post-transplant mortality from infection and rejection is now very low. At 5 years, 40 to 50% of transplant recipients have angiographic evidence of disease[2], which predicts a fivefold higher risk of cardiac events.

The development of conventional atherosclerosis is thought to be secondary to an immune/inflammatory response initiated by oxidized low density lipoprotein. It is a focal intimal disease[3]. Transplant coronary atheroma is also thought to be a result of injury, but the histological changes are diffuse. The aetiology of transplant coronary atheroma is obscure, but is probably multifactorial and includes not only the injury sustained during organ procurement, preservation and

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reperfusion, but also damage from viral infection, drugs and immunosuppression regimens. The injury exhibits macrophages, smooth muscle cells and lymphocytes and all layers of the vessel wall are affected\[4–5\]. The injury produces intimal thickness circumferentially and results in the lumen remaining centrally located. This intimal thickening has been measured by intravascular ultrasound in the mid to proximal left anterior descending artery. It appears in the majority of patients 1 or more years after transplantation with the most rapid phase of progression in the first 2 years\[8–10\]. While diffuse lesions are more common in the distal vasculature, focal non-circumferential involvement is more common proximally and some of these lesions may, in fact, represent donor atheroma\[11\]. After 5 years, the atheroma becomes more focal and shares more the characteristics of non-transplant coronary disease. When this occurs, the media changes are much more variable. There is usually thickening, although thinning can occur, and this may be focal or uniform. Inflammatory cells and foam cells may be present. The adventitia is almost always abnormal, with extensive adventitial fibrosis and fibrous tissue infiltration of subepicardial tissues. The latter fibrosis may limit the ability of the vessel to dilate and remodel, which in conventional atheroma helps to reduce luminal obstruction.

In transplants, the detection of coronary disease is difficult. Symptoms of myocardial ischaemia are usually absent because of interruption of the ventricular sympathetic afferent nerves normally responsible for the transmission of cardiac pain. Re-innervation is described, but is uncommon. In addition, the diffuse nature of the disease makes it difficult to detect by conventional non-invasive techniques, which are aimed at assessing focal obstruction to epicardial coronary blood flow. These methods have a low sensitivity for the diffuse vasculopathy of transplanted hearts\[11\]. Of the techniques currently in use, dobutamine stress echocardiography appears to be more sensitive\[13,14\]. Although there are limitations with angiography, most transplant programmes perform annual angiographic studies to monitor development and progression of atheroma.

Techniques that interrogate vessel wall anatomy are the most sensitive, and early atheromatous changes are most easily measured using intravascular ultrasound. Furthermore, intravascular ultrasound findings appear to relate to late cardiac events. In one study, patients with severe intimal hyperplasia had a fourfold higher cardiac event rate than those without\[15\].

Calcification which occurs in conventional coronary atheroma, has been recognised for many years. It was considered to be a rather late event, but recently it has become apparent that calcification starts early in the development of atheromatous plaques. The process remains poorly understood, but appears to share several features with normal bone formation, such as cellular proliferation and matrix deposition. Type 1 collagen is associated with calcification, both in bone and atheroma, as are phosphatases and calcium binding phospholipids; the latter tend to occur in matrix vesicles and serve as nucleators of crystal formation. Vascular smooth muscle cells are also present in plaque, but they differ from those in the normal vessel media in that they contain little contractile protein. They do, however, have large numbers of synthetic organelles. Other changes are a high concentration of messenger RNA for osteopontin, a protein involved in the regulation of bone mineralization\[16\]. Immunohistochemical studies have shown osteopontin to be specifically associated with calcifying coronary atheroma\[17\].

Electron beam computed tomography has been shown to be useful in the semi-quantitative evaluation of calcification of the coronary arterial wall. Although there are some recognised limitations in this type of calcium measurement that are under investigation\[18,19\] both calcium score and area of calcific deposits assessed by electron beam computed tomography have been shown to correlate well with histomorphometric calcium area\[20\]. There have now been several studies of coronary calcification, as detected by electron beam computed tomography in non-transplant patients. Calcification is more prevalent in older populations, with a later onset in women. It is also more frequently found in those with risk factors for coronary disease. Calcification also has some relationship with angiographically defined disease and appears to be correlated with risk of future cardiac events\[21\].

Little has been written regarding calcification in heart transplant patients. Intravascular ultrasound has shown that the prevalence of calcification is low in the first 5 years after transplantation, but significantly more frequent in patients evaluated later\[8,9,22\]. Initially it was thought that calcification was a marker for the age of the allograft, and was not associated with an adverse prognosis\[10\]. However, there is now evidence that calcification may predict cardiac events. Although intravascular ultrasound appears to be a safe technique in transplant recipients\[23\], it is not suitable for measuring distal coronary vasculature (less than about 2 mm diameter) or vessels with marked tortuosity, and may therefore be expected to miss some focal areas of calcification. In a study attempting to document the morphology of all three main coronary arteries, only 68% of circumflex and 60% of right coronary arteries proved accessible, even with state-of-the-art intravascular ultrasound probes\[11\]. Furthermore, it may be difficult to distinguish between dense fibrous plaque and calcification.

Electron beam computed tomography therefore has considerable potential in the assessment of calcification, particularly since it is possible to assess the entire vascular tree in a non-invasive fashion. As far as we are aware, we are the only group to have used electron beam computed tomography to examine calcification in the transplanted coronary artery, and although these investigations have been performed in only a small group of patients, they do provide some early insight into the relationship between calcification, angiographic disease, risk factors and later coronary events.
Methods

The electron beam computed tomography scan protocol and calcification scoring have been described previously[24]. Briefly, the scans were performed with patients supine on the scanner couch. The scanner was set to acquire 3 mm thick transaxial tomograms with 100 ms exposure time. Each scan was triggered by the ECG so that each was acquired at the same phase of the cardiac cycle. During a single breath hold, 20 contiguous tomograms were acquired. During a second breath hold, a further 20 tomograms were obtained, thus imaging the entire coronary vasculature. The amount of calcification was scored in a semi-quantitative fashion. Regions of interest in the coronary arteries with two or more adjacent voxels with a density of more than or equal to 130 Hounsfield units (HU) were scored. The area of each region (mm²) was multiplied by a number related to the maximal density of that region of interest as follows: 1 if maximal density was 130 to 199 HU, 2 if 200 to 299 HU, 3 if 300 to 399 HU, 4 if 400 HU or more.

Electron beam computed tomography was performed on 102 cardiac transplant recipients. The mean age was 58, and 88 were male. The scans were performed 63 days to 9·1 years (median 4·6 years) after transplantation and were compared with coronary angiograms that were performed within a median of 39 days of the electron beam computed tomography scan (75th centile 83 days)[24]. We also assessed the relationship of calcification to known risk factors[25] and studied the relationship between these variables and future cardiac events[26].

Heart transplant patients were followed for a mean of 2·12 years (1·2–4·02 years). The investigations assessed were angiography, electron beam computed tomography, ECG (abnormal if >1 mm ST depression 130 ms after the J point), and radionuclide ventriculography (abnormal if ejection fraction of <50% at rest or after stress). The angiographic assessment reported not only the presence of haemodynamically significant stenoses (>50%) but also relatively mild luminal obstruction (>25%). In the follow-up study of cardiac events[26], heterotopic heart transplants (five) and heart–lung transplants (two) were excluded; four were lost to follow-up. Cardiac events were defined as myocardial infarction, clinical heart failure, cardiac death or myocardial revascularization and all were analysed as independent predictors.

Results

Forty-one (40·2%) had one or more major coronary artery with a stenosis of >24% at angiography. Forty-six (45%) had coronary calcium (defined as a calcification score >0 measured by electron beam computed tomography).

In these 102 patients, we found that calcification was more frequently present in the right coronary artery than the left anterior descending and circumflex coronary arteries, even though there was no excessive angiographic disease in the right coronary artery. The positive and negative predictive values of calcification in angiographic disease are shown in Fig. 1. As can be seen, the absence of calcification had a high negative predictive value with respect to angiographic disease in any vessel (up to 94·6%) and compares well with other methods for non-invasive assessment of transplant coronary disease. Although the number of patients with calcification was higher than might have been expected from intravascular ultrasound studies, the calcification scores were low compared to the scores commonly found in patients with conventional atheroma. It was also of interest that 12 with angiographically trivial disease showed evidence of calcification by electron beam computed tomography.

In this same cohort of patients, we assessed the relationship between calcification and risk factors for conventional coronary disease[25]. The factors analysed are shown in Table 1. In this study, calcification was
considered present if the calcification score >0, and angiographic disease was considered present if one or more major coronary arteries had a stenosis of ≥25%. Dyslipidaemia was also measured and was defined as a high total cholesterol and/or high fasting triglyceride and/or a high Lp(a). Logistic regression revealed the dyslipidaemia, systemic hypertension and organ ischaemic time were significant predictors of calcification (Table 2).

In our follow-up study[26], both an abnormal coronary angiogram and coronary calcification were found to be the only significant predictors of late events, after a follow-up of 2.12 years (mean). However, multivariate analysis suggested that the detection of calcification did not offer any additional predictive information over that provided by the angiogram itself. Kaplan–Meier plots of the proportion of patients presenting free of cardiac events, are seen in Figs 2 and 3. The nature of the events on which this analysis was based, and the timing of events relative to the transplant date and electron beam computed tomography scan date, are given in Table 3.

Table 1 Factors assessed as potentially associated with transplant coronary calcification (reprinted with permission[25])

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition of abnormality used as dichotomous variable</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>BP &gt;150/90 and or already on antihypertensive therapy</td>
</tr>
<tr>
<td>Fasting total cholesterol</td>
<td>&gt;6·0 mmol . l⁻¹ (240 mg . dl⁻¹)</td>
</tr>
<tr>
<td>Fasting HDL</td>
<td></td>
</tr>
<tr>
<td>Fasting LDL</td>
<td></td>
</tr>
<tr>
<td>Fasting triglycerides</td>
<td>&gt;3·0 mmol . l⁻¹ (265 mg . dl⁻¹)</td>
</tr>
<tr>
<td>Fasting Lp(a)</td>
<td>&gt;30 mg . dl⁻¹</td>
</tr>
</tbody>
</table>

Immunosuppression at time of CT scan

Number of rejection episodes

Donor’s sex

Donor organ ischaemic time

Table 2 Determinants of coronary calcification by logistic regression analysis (reprinted with permission[25])

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95% confidence limits</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipoproteinaemia</td>
<td>23·13</td>
<td>4·3–125·6</td>
<td>0·001</td>
</tr>
<tr>
<td>Ischaemic time (min)</td>
<td>1·01</td>
<td>1·00–1·02</td>
<td>0·03</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>3·44</td>
<td>0·96–12·4</td>
<td>0·05</td>
</tr>
</tbody>
</table>

Figure 2 Kaplan–Meier plot of proportion of patients surviving free of cardiac events. Comparison with (----) and without (—–) coronary calcification. (Reprinted with permission[26].)
It is possible that the timing of electron beam computed tomography scans relative to transplant date could have a bearing on the negative predictive accuracy of electron beam computed tomography for late events. In our study, the median time between transplant and electron beam computed tomography scan was 4.6 years. In patients whose time was less than the median, the total mean calcium score in those who sustained cardiac events was 0.9 compared with 0 for those remaining event free (Mann–Whitney test \( P = 0.46 \)). However, in those whose scans were performed later than 4.6 years after transplantation, the total mean calcium score in those who sustained cardiac events was 2.68 compared to 0 for those remaining event free, a significant difference (Mann–Whitney test \( P = 0.013 \)). Although the number of events was too small to draw firm conclusions, it is possible that the usefulness of electron beam computed tomography in predicting future events depends on how long after transplantation the scan is performed.

**Discussion**

Electron beam computed tomography shows that coronary calcium is present more frequently in the coronary arteries of transplanted hearts than was suspected from intravascular ultrasound studies, which have suggested that calcification is infrequent and occurs late \([9,22]\). St Goar found no evidence of calcification by intravascular ultrasound in those patients who had angiographically normal coronary arteries. The latter patients were studied 1 or more years after transplantation \([6]\).

Our study of risk factors for calcification in transplant recipients provided results in keeping with Anderson’s findings, that pre-transplant hypercholesterolaemia was independently related to the degree of intimal thickening \([9]\).

Although calcification is of considerable importance, it simply represents the surrogate end-point for the prediction of late cardiac events. Angiographic abnormalities have been shown to be strong predictors of such events \([1,2]\) and recent data suggests that calcification may be an independent predictor of late cardiac events, especially in non-transplant patients \([21]\). In our follow-up study \([23]\), the presence of calcification in transplanted coronary arteries was associated with an adverse outcome, as it is in native atheroma. It may simply act as a marker for the amount of disease, rather than be intrinsically linked to plaque rupture and/or vessel occlusion.

The limitations of our studies include the short follow-up period, and the small number of assessed patients.

In conclusion, electron beam computed tomography studies have shown that coronary calcification occurs earlier than suspected in cardiac transplant recipients. Although the biochemical and molecular mechanisms that regulate the development of calcification remain obscure, its presence appears to relate to late cardiac events. Thus electron beam computed tomography may prove a useful non-invasive tool in the assessment of transplant vasculopathy.

**References**


