Electron-Beam Computed Tomography in the Assessment of Coronary Artery Disease After Heart Transplantation

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Background—Our aim was to compare the electron-beam CT (EBCT) features of coronary arteries in heart transplant recipients with those of biplane coronary angiography and intracoronary ultrasound (ICUS).

Methods and Results—We examined 112 heart transplant recipients (25 female; age, 17 to 69 years; median, 52 years) 1 to 153 months (median, 46 months) after surgery by EBCT to detect coronary artery calcifications. Calcifications were quantified by the Agatston scoring system. EBCT scores were compared with coronary angiography in all patients and ICUS of the left anterior descending coronary artery (LAD) in 100 patients. Coronary artery calcifications were found in 84 patients (75%). Angiographically, 16 patients displayed >50% coronary artery stenoses, all of whom had some degree of coronary artery calcification and only 1 of whom had a score of <55 (P=0.0001). With this threshold, EBCT had a sensitivity of 94%, a specificity of 79%, a positive predictive value of 43%, and a negative predictive value of 99% for detecting stenosis. ICUS confirmed the presence of calcified plaques in all patients with an LAD score ≥9. EBCT total calcium score was associated with the degree of intimal proliferation in that patients without ICUS features of allograft vasculopathy had a median score of 0 (25th percentile, 0; 75th percentile, 0), whereas patients with Stanford class IV vasculopathy had a median score of 41 (9 to 98, P<0.0001).

Conclusions—EBCT is a promising noninvasive test for the detection of coronary heart disease in cardiac transplant recipients. (Circulation. 2000;101:2078-2082.)

Key Words: transplantation ■ coronary disease ■ tomography ■ calcium

Cardiac transplantation has evolved as an established treatment of advanced heart failure. Today, 80% of heart transplant recipients survive the first year, and almost 50% survive for ≥10 years at many centers. The most important limitation to even longer survival is the occurrence of coronary artery disease within the graft, which accounts for >20% of the later mortality. Intimal proliferation in graft coronary arteries has already been noted in the early heart transplantation experience in all patients surviving for ≥1 month and was found to be inaccessible to clinical diagnosis. The histological hallmark of allograft vasculopathy, intimal proliferation, remains undetected even by cardiac catheterization in a sizable number of patients, whereas intracoronary ultrasound (ICUS) reflects these alterations in greater detail. Because the transplanted heart stays denervated and myocardial ischemia is thus not heralded by its typical symptoms, yearly cardiac catheterizations are routinely performed at many centers, which is associated with significant discomfort, risk, and costs. Traditional noninvasive testing methods for coronary artery disease, which include electrocardiography, stress echocardiography, and stress scintigraphy, have failed in the detection of coronary allograft disease. Coronary artery calcium quantification by electron-beam CT (EBCT) has demonstrated great potential in the prediction of atherosclerotic coronary heart disease of the general population. In contrast to the notion that coronary artery calcification is an atypical or late feature of allograft vasculopathy, quantification of coronary artery calcification by EBCT has recently been shown to correlate closely with the occurrence of coronary artery stenoses in heart transplant recipients as well. In this report, we compare the EBCT features of coronary heart disease in heart transplant recipients with those of coronary angiography and ICUS.

Methods

In a prospective, blinded trial, 112 heart transplant recipients (25 female; age, 17 to 69 years) were included 1 to 153 months (median, 46 months; 2 within 6 weeks after surgery) after orthotopic heart transplantation. Donor age was 9 to 67 years (median, 34 years). Patients were examined by EBCT with an Evolution XP scanner (Siemens), which used the imaging protocol described by Agatston. Briefly, this protocol uses 20 to 40 contiguous transverse images of the entire heart, with a slice thickness of 3 mm and ECG triggering at 80% of the R-R interval during inspiration. Depending on heart size and rate, the entire scan required 25 to 45 seconds. To quantify coronary artery calcium load, calculations were defined as...
areas with density of >130 Hounsfield units (HU) and a lesion area of >1 mm². Lesions were manually included in separate regions of interest (ROIs). For each ROI, plaque area and density were automatically determined by use of standard software of the scanner console. With the Agatston scoring method, each ROI was assigned a calcification score, which was defined as the product of plaque area and a plaque density factor. Density factor was 1 for a peak plaque density of 130 to 199, 2 for 200 to 299, 3 for 300 to 399, and 4 for >399 HU. The sum of all coronary artery lesion scores was defined as the total calcium score.

All patients underwent standard biplane coronary angiography on the same day as the EBCT examination. Coronary angiograms were evaluated for the presence of segmental stenosis. Stenoses were visually classified as <25%, 25% to 50%, 51% to 75%, or >75%. In 101 patients, ICUS recordings of the left anterior descending coronary artery (LAD) were acquired in the same procedure with a 30-MHz phased-array ultrasound catheter (Five-64, Endosonics), which included a continuous manual pullback maneuver. ICUS recordings were classified according to the Stanford classification system. With this system, allograft vasculopathy was classified as minimal (grade I) if coronary intimal proliferation was <0.3 mm thick in less than half of the vessel circumference, as mild (II) if ≤0.3 mm thick in more than half of the circumference, as moderate (III) if 0.3 to 0.5 mm or >0.5 mm thick but in less than half the circumference, and as severe (IV, accelerated disease) if the intimal layer was >1 mm thick or >0.5 mm thick in more than half of the vessel circumference. The most severe lesion was used to classify each patient. Separately, the presence of coronary artery calcification was noted on the ICUS recordings.

The association of EBCT calcium scores with coronary artery stenosis and the degree of intimal proliferation, according to the Stanford classification, were tested by factorial ANOVA of the log-transformed score data. Pairwise comparisons used the Scheffé method. Associations of the log-transformed EBCT total calcium score with patient age, time since surgery, and donor age were tested by multiple regression analysis. The relative contributions of EBCT scores and clinical variables for predicting coronary artery stenosis and the degree of intimal proliferation were assessed by logistic regression analysis. The null hypothesis was rejected at P<0.05. Receiver operating characteristics (ROCs) of EBCT for detecting coronary artery stenosis and for predicting the degree of intimal proliferation were determined with the LABROC1 procedure (Macintosh version, Charles E. Metz, University of Chicago, Chicago, Ill, 1991).

Results

EBCT detected coronary artery calcifications in 84 patients (75%). The total calcium score of male patients was higher (median, 19; 25th percentile, 2; 75th percentile, 77) than that of female patients (median, 2; 25th percentile, 0; 75th percentile, 44; ANOVA, P=0.01). Total calcium score was not associated with donor sex (P=0.08) or patient age (multiple regression analysis, P=0.51). Calcium load increased with both time since transplantation (multiple regression, P=0.0008) and donor age (P=0.0002), but a correlation coefficient, r², of 0.17 indicated that most of the score variability was not explained by these 2 parameters.

Coronary angiography revealed >50% luminal obstruction in 16 patients. In 90 patients, no stenosis was found; 1 patient had <25% stenosis, 5 had 25% to 50% stenosis, 10 displayed 51% to 75% stenosis, and 6 had >75% stenosis. In patients with >75% stenosis, a significantly longer time since transplantation (108±43 months) had elapsed than in all others (17 to 49±30 months; ANOVA, P<0.0001). Donor age was higher in patients with >50% stenosis (41±13 years) than in patients with ≤50% stenosis (33±13 years, P=0.04).

Patient age (ANOVA, P=0.59), patient sex (χ² test, P=0.27), and donor sex (χ² test, P=0.57) were not associated with the degree of stenosis.

High-grade (>50%) coronary artery stenosis was closely associated with high total calcium scores (ANOVA, P<0.0001, Figure 1). All patients with >50% stenosis had some degree of coronary artery calcification. Using a total calcium score threshold of 55, EBCT had a sensitivity of 94% and a specificity of 79% for detecting >50% stenoses. With this threshold, the negative predictive value was 99%, the positive predictive value 43%, and the overall diagnostic accuracy 81%. To exclude the possibility that the association of EBCT total calcium score with coronary artery stenosis was only secondary to its correlation with donor age, patient sex, and time since transplantation, logistic regression that included these parameters was performed. The EBCT score was the only significant predictor of >50% stenosis (odds ratio, OR, for increasing the score by e¹, 1.9±0.2 [SEM], P=0.006) compared with donor age (in years: OR, 1.06±0.04, P=0.1), patient sex (for men: OR, 1.1±0.6, P=0.8), or time since transplantation (in months: OR, 1.03±0.01, P=0.06). The area under the fitted ROC curve for predicting >50% stenosis was Az=0.89±0.04 (Figure 2).

For the differentiation of >75% stenosis from normal coronary arteries, this measure of diagnostic power was higher (Az=0.94±0.05). Because sensitivity and specificity for predicting stenosis are inversely related, an “optimal” threshold was calculated from the critical test values of the fitted ROC curve as the score value associated with the greatest sum of sensitivity and specificity. The optimal threshold was 55 for the prediction of both >50% and >75% stenoses.

The ICUS confirmed coronary intimal thickening in 94 of 101 patients (93%). Stanford class I disease was found in 10 patients, class II in 14, class III in 8, and class IV in 62.

Women displayed a significantly lower degree of intimal proliferation than men (χ² test, P=0.004), whereas donor sex did not correlate with allograft vasculopathy (P=0.4). In class IV, 11 of the 62 patients were female, and in the group without intimal proliferation, 5 of 7 patients were female. The extent of allograft vasculopathy was also predicted by donor age (ANOVA, P=0.001). Mean donor age was 21±3 years.
for patients without allograft vasculopathy and 36 ± 2 years for patients with class IV disease. On pairwise comparison, patients with class II and class IV disease had a higher donor age than patients without allograft vasculopathy (P = 0.001 and P = 0.004) or with minimal disease (P = 0.002 and P = 0.006, respectively). Patient age and time since transplantation were not associated with the degree of intimal proliferation (ANOVA, P = 0.34 and P = 0.6, respectively). All patients with angiographic stenosis were in Stanford class IV. The EBCT total calcium scores closely correlated with the degree of intimal proliferation (ANOVA, P < 0.0001). Specifically, patients with class IV allograft vasculopathy had a higher score (median, 41; 25th percentile, 9; 75th percentile, 98) than patients without (median, 0, 0, and 0, P < 0.0001) or with any other degree of intimal proliferation (P = 0.0002 to P = 0.03, Figure 3). Again, the EBCT score (OR, 1.91 ± 0.15; P < 0.0001) was a more powerful predictor of accelerated allograft vasculopathy than donor age (in years: OR, 1.01 ± 0.02; P = 0.6) or patient sex (for men: OR, 1.2 ± 0.29; P = 0.5) on logistic regression.

The area under the ROC curve for predicting accelerated allograft vasculopathy by EBCT calcium scoring was Az = 0.93 ± 0.05 (Figure 4). The optimal score threshold was 3, with a sensitivity of 82% and a specificity of 97%. Limiting this analysis to calcifications of the LAD only did not improve diagnostic power. In this case, ROC data were degenerate, which implied an exact fit. The binormal ROC curve was horizontal at a constant true positive fraction of 0.58. For the differentiation of both normal coronary arteries and mild allograft vasculopathy from accelerated disease, Az was 0.82 ± 0.04 (Figure 4). The optimal score threshold for this case was 13, with a sensitivity of 71% and a specificity of 81%.

For correlation of coronary artery calcification on ICUS with EBCT calcium screening, 12 studies were excluded because of incomplete data. In the remaining 89 patients, a highly significant correlation of both methods was found (χ² test, P < 0.0001). No calcified plaques were found in the LAD by either method in 37 patients, whereas the presence of calcified plaque was confirmed by both methods in another 38 patients (concordant test results in 75 of 89, 84%). In 7 patients, calcifications of the LAD were present on EBCT only, with LAD scores from 1 to 9. In another 7 patients, only ICUS detected calcifications; none of these patients had any degree of coronary artery stenosis on angiography, and 4 had calcified plaques in other coronary artery branches, with a total score of 1 to 45.

**Discussion**

Coronary artery calcium quantification was a sensitive method for detecting coronary artery stenosis and predicted the degree of intimal proliferation in cardiac transplant recipients. Our data confirmed the role of EBCT calcium screening as a method for coronary disease assessment and extended its role in conventional atherosclerotic heart disease to heart transplant recipients. The diagnostic power of EBCT calcium scoring, as measured by ROC analysis, was as good in this investigation of heart transplant recipients as that of

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**Figure 2.** ROCs of EBCT coronary calcium screening for prediction of angiographically documented >50% luminal obstruction in 112 heart transplant recipients. Use of a total calcium score of 55 as a threshold for predicting stenosis results in good sensitivity and specificity (arrow). TPF indicates true-positive fraction (sensitivity); FPF, false-positive fraction (1 − specificity).

**Figure 3.** Severity of coronary artery calcification in 101 heart transplant recipients with various degrees of intimal proliferation as determined by ICUS. Degree of intimal proliferation is graded according to Stanford classification; severity of calcification is expressed by EBCT (ebt) total calcium score. ANOVA P < 0.0001.

**Figure 4.** ROCs of EBCT coronary calcium screening for prediction of accelerated allograft vasculopathy on ICUS in 101 heart transplant recipients. × indicates ROCs for differentiating Stanford class 4 from classes 0 to 3; ○, ROCs for differentiating class 4 from normal intimal thickness. TPF indicates true-positive fraction (sensitivity); FPF, false-positive fraction (1 − specificity).
calcium scoring in the nontransplant population.\textsuperscript{9} Interestingly, the optimal score thresholds for predicting high-grade coronary artery stenosis were also very similar to those in a symptomatic nontransplant population.\textsuperscript{9}

The excellent sensitivity of EBCT calcium scoring in heart transplant recipients is in contrast to the earlier notion that plaque calcification is rarely encountered in allograft coronary disease.\textsuperscript{10,11} Possible explanations for this discrepancy include advanced donor age in our patients, later imaging, and limited sensitivity of earlier ICUS protocols for the detection of coronary calcification. Donor age has increased over the years as the demand for cardiac grafts substantially exceeded the number of available organs, and the acceptance of older donors has not compromised clinical success.\textsuperscript{12} With older donors, the prevalence of coronary atherosclerosis within the graft naturally increases, but preexistent coronary atherosclerosis may also precipitate allograft vasculopathy.\textsuperscript{13} In 1 investigation, early coronary atherosclerotic disease was found by ICUS in 56\% of heart transplant recipients.\textsuperscript{14} Other data indicate that preexistent coronary atherosclerosis on ICUS progresses independently from de novo allograft vasculopathy within the first year.\textsuperscript{15,16} Because these 2 entities cannot be differentiated morphologically, only serial studies that begin in the peroperative period will enable us to appreciate the importance of each process separately. EBCT screening may help to identify the recipients of grafts with preexistent coronary atherosclerosis early in the process, so that aggressive medical treatment can be directed at these high-risk patients. For preexistent coronary disease, the established role of EBCT as a potent tool for coronary risk assessment applies.

Late imaging also explains a higher incidence of coronary artery calcification. Earlier ICUS studies, with a lower incidence of coronary allograft calcification, reported a mean interval between transplantation and imaging as 2.4±0.1 years,\textsuperscript{11} 2.9±2 years,\textsuperscript{10} and 3.3±0.2 years,\textsuperscript{6} whereas this interval was 4.2±2.8 years in this investigation. The progression of allograft vasculopathy with time has been established before\textsuperscript{6} and is confirmed by the present data.

Limited sensitivity of earlier ICUS protocols for the detection of coronary calcifications is another reason for a higher incidence of coronary artery calcification in our investigation. Some of the earlier investigations used ICUS of only a few coronary artery segments and thus were unable to detect calcified lesions at the remaining sites.\textsuperscript{6,11}

Our results indicate a close correlation of EBCT calcium scores with the ICUS degree of intimal proliferation. Although correlation of the 2 methods on a segmental basis yielded a similar incidence of coronary artery calcifications, test results were still discordant in 16\% of the patients. Explanations for this discrepancy include either underestimation or overestimation of coronary calcium load by either ICUS or EBCT.

Underestimation of coronary calcification by ICUS may occur because not all vessel segments are depicted, calcified plaque area is underestimated, and microcalcifications remain undetected. Underestimation of coronary artery calcification by EBCT may occur because calcifications with a size of <1 mm\textsuperscript{2} are not included in the Agatston score by definition, because such small lesions cannot be reliably distinguished from image noise. Hyperattenuating foci with a size of <2 mm\textsuperscript{2} have been found to be poorly reproducible by EBCT.\textsuperscript{17} The use of a 130-HU threshold to define calcifications is also a practical necessity and trades some of the sensitivity of the method for a reasonable specificity. Another reason for the limited sensitivity of EBCT for the detection of very small calcium deposits is the volume-averaging effect that is inherent in all tomographic methods. EBCT may still detect microcalcifications if the average voxel density exceeds the predefined density threshold for calcium. However, histopathological correlation of EBCT calcium screening indicates that below a calcified plaque area of 1 mm\textsuperscript{2}, calcifications may not be detected.\textsuperscript{18} Another source of calcium load underestimation is the possible occurrence of gaps between 2 EBCT images due to cardiac and respiratory motion. The latter effect may be diminished by the use of overlapping rather than contiguous slices. Recent innovations in scanner technology and scoring algorithms may improve both sensitivity and reproducibility of EBCT scoring in this regard, but it remains uncertain whether the detection of smaller lesions would improve the clinical utility of the test.

Overestimation of coronary artery calcifications by EBCT may also occur as an effect of image noise.

Overall, we believe that most of the discrepancy between ICUS and EBCT estimates of calcium load is caused by underestimation of calcified lesions by ICUS and image noise in EBCT.

EBCT calcium scoring is unique in that it is the only noninvasive method to quantify coronary artery calcification,\textsuperscript{19} and histopathological correlation has established an excellent accuracy of calcium quantification by EBCT.\textsuperscript{20} Direct correlation of ICUS with EBCT calcium quantification in nontransplant patients on a segmental basis has indicated that EBCT may be more sensitive to detect minute calcifications than ICUS, despite its lower spatial resolution.\textsuperscript{21} Apparently, discrepancies between ICUS and EBCT occur at the lower end of the calcified volume spectrum and do not compromise either the detection of significant luminal obstruction or the differentiation of normal coronary arteries from accelerated transplant vasculopathy. The fact that the association of the segmental LAD calcium scores with intimal proliferation is weaker than that of the total calcium score supports the concept that the prognostic impact of coronary artery calcifications is not strictly site-specific.\textsuperscript{21}

Despite the unique role of EBCT for the quantification of total coronary calcium load, ICUS remains the standard of reference for assessing allograft vasculopathy, because ICUS alone depicts intimal proliferation regardless of its calcium content. For practical purposes, the association of EBCT total calcium scores with angiography and ICUS seems to be sufficiently close to allow its use as a surrogate marker for coronary artery disease after heart transplantation.

The use of EBCT in heart transplant recipients has significant cost-containment potential, provided that it is used as a screening method for treatable coronary disease. With >3000 cardiac transplantations worldwide per year\textsuperscript{1} and routine coronary angiograms on a yearly basis at many centers, there
is a substantial savings potential. One possible application would be the selection of candidates for coronary angiography with a high probability of >50% stenosis, particularly because the benefit of performing yearly routine coronary angiography in unselected heart transplant recipients remains doubtful. In this context, it is important to note that EBCT total calcium scores closely correlate with subsequent coronary events both in the asymptomatic general population and in heart transplant recipients. Although >50% stenosis of graft coronary arteries can be treated by angioplasty, bypass surgery, or retransplantation with limited success, the progression of intimal proliferation can be decreased by HMG-CoA reductase inhibitors. The effect of lipid-lowering drug therapy has recently been shown to correlate with conventional coronary disease, and our data give us reason to expect a similar correlation for heart transplant recipients.

In conclusion, EBCT calcium scoring is a highly sensitive method for detecting coronary artery stenosis and predicts the degree of intimal proliferation in heart transplant recipients. As an inexpensive, noninvasive test, it may serve to detect the presence of preexistent coronary heart disease of the graft early after transplantation, to select high-risk patients for invasive testing, and possibly even to follow the course of coronary allograft disease in therapeutic trials.

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