

Incidence and Severity of Transplant Coronary Artery Disease Early and up to 15 Years After Transplantation As Detected by Intravascular Ultrasound

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Objectives. The purpose of this study was to quantify the severity of transplant coronary artery disease and to assess lesion characteristics early and up to 15 years after heart transplantation by using intracoronary ultrasound.

Background. Intravascular ultrasound has the ability to measure the components of the arterial wall and has been shown to be a sensitive method for detection of transplant coronary artery disease.

Methods. A total of 304 intracoronary ultrasound studies were performed in 174 heart transplant recipients at baseline and up to 15 (mean 3.3 ± 0.2) years after transplantation. Mean intimal thickness and an intimal index were calculated, and lesion characteristics (eccentricity, calcification) were assessed for all coronary sites imaged (mean 3.0 ± 0.1 sites/study). The Stanford classification was used to grade lesion severity.

Results. Compared with findings in patients studied at baseline (<2 months after transplantation, n = 50), mean intimal thick-

ness (0.09 ± 0.02 vs. 0.16 ± 0.02 mm, $p < 0.01$), intimal index (0.07 ± 0.01 vs. 0.14 ± 0.02 , $p < 0.01$) and mean severity class (1.5 ± 0.2 vs. 2.3 ± 0.2 , $p < 0.01$) were significantly higher at year 1 (n = 52) after transplantation. Thereafter, all three variables further increased over time and reached highest values between years 5 and 15. Calcification of lesions was detected in 2% to 12% of studies up to 5 years after transplantation, with a significant increase to 24% at years 6 to 10 ($p < 0.05$).

Conclusions. Severity of transplant coronary artery disease appeared to progress with time after transplantation in this cross-sectional study. This characteristic was most prominent during the 1st 2 years after transplantation, whereas calcification of plaques occurred to a significant extent only later in the process. These data may serve as a reference for comparison of intravascular ultrasound findings in other studies of patients with transplant coronary artery disease.

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Transplant coronary artery disease has emerged as the major cause of morbidity and mortality in long-term heart transplant survivors (1-4). The prevalence of angiographically detectable transplant coronary artery disease at 1, 3 and 5 years after

transplantation in cyclosporine-treated patients was 14%, 37% and 50%, respectively, in the Stanford series (5). However, because of the unique morphology of transplant coronary artery disease (6), angiography underestimates disease severity, as demonstrated by pathologic-angiographic correlation studies (7). Intracoronary ultrasound is a new imaging modality that has the ability to image the blood vessels in cross section, delineate vessel wall thickness and morphology and quantitate lumen dimensions (8-11). The diagnostic value, reproducibility and safety of this method in transplant recipients have been established by our group (12-14) and by others (15,16). Although preliminary reports (17,18) of progression of transplant coronary artery disease detected with this method have appeared, quantitative measurements of transplant coronary artery disease at various time intervals after transplantation in a large cohort have not been reported to date. The purposes of this study were to quantify the severity of transplant coronary artery disease and to assess lesion characteristics to provide a reference for the intracoronary ultrasound appearance of transplant coronary artery disease early and during long-term follow-up after heart transplantation.

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Methods

Study patients. The study group consisted of 174 consecutive heart transplant recipients (147 men, 27 women with a mean age \pm SE at transplantation of 45.2 ± 0.7 years) who were evaluated with intracoronary ultrasound during routine baseline (early postoperative) or annual coronary angiography. Eighty-two of these patients were studied once, 55 twice, 36 three times and 1 four times at 1- or 2-year intervals. Thus, a total of 304 intracoronary ultrasound studies were available for analysis, ranging from 2 weeks to 15 years (mean 3.3 ± 0.2) after transplantation. For comparison, patients were categorized into groups on the basis of the time interval between transplantation and the intracoronary ultrasound study. Separate groups were formed for those who underwent studies performed during the 1st 8 weeks and at 1, 2, 3, 4 and 5 years after transplantation. Because of the smaller number of subjects who underwent intracoronary ultrasound studies long after transplantation, those who underwent studies performed between years 6 to 10 and years 11 to 15 after transplantation were combined into two additional groups.

All patients gave written informed consent to the protocol, which was approved by the Committee for the Protection of Human Subjects in Research at Stanford University Medical Center.

Ultrasound imaging procedure. Intracoronary imaging was performed with a 30-MHz ultrasound transducer and rotating mirror enclosed within an acoustic housing at the tip of a 5F or 4.3F 135-cm long catheter (CVIS Inc.). At a focal depth between 1.5 and 4.5 mm, axial resolution of the image is 150 μ m and lateral resolution is 200 μ m. The radius of penetration is approximately 5 mm (19). Images were acquired at 30 frames/s and recorded on 0.5-in. (1.27-cm) SVHS videotape for subsequent off-line analysis.

After completion of coronary angiography, sublingual nitroglycerin, 0.4 mg, was given before the intracoronary imaging system was passed into the left anterior descending artery over a 0.014-in. (0.036 cm) guide wire. An 8F high flow coronary guiding catheter with an internal diameter of 0.082 in. (0.208 cm) was used for all studies. The ultrasound catheter was advanced to the midportion of the left anterior descending coronary artery, avoiding vessel segments <2 mm. Up to four distinct locations, separated by ≥ 1 cm, were selected for ultrasound measurements. Ultrasound gain settings were adjusted for optimal visualization of the vessel-lumen interface. Measurement sites were selected where the lumen was circular, and areas of vessel bifurcations and side branches were avoided.

Ultrasound analysis. Ultrasound images were examined on-line and later digitized onto a $512 \times 512 \times 8$ -bit matrix in 34 frame sequences by an image processing computer (Dextra Medical Inc.) dedicated to echocardiographic analysis. The frame at end-diastole with the largest vessel diameter from the digitized cardiac cycle was selected for analysis. The lumen-vessel wall interface was traced by planimetry and, if measurable intimal thickness was present, the external border of the

intimal layer (intima-media interface) was also measured by planimetry. This procedure allowed calculation of mean intimal thickness and an intimal index defined as the ratio of the difference of total area minus intimal area to total area. The measurements from all sites (mean, 3.0 ± 0.1 sites/study) were averaged for each study. The Stanford classification (12), based on intimal thickness and vessel circumference involved, was used to grade lesion severity as follows: class 0 = no measurable intimal layer by ultrasound; class 1 (minimal) = an intimal layer <0.3 -mm thick involving $<180^\circ$ of the vessel circumference; class 2 (mild) = an intimal layer <0.3 mm thick involving $>180^\circ$ of the vessel circumference; class 3 (moderate) = an intimal layer 0.3- to 0.5-mm thick or an intimal layer >0.5 -mm thick involving $<180^\circ$ of the vessel circumference; and class 4 (severe) = >0.5 -mm intimal thickening involving $<180^\circ$ of the vessel circumference or an intimal layer >1.0 mm at any point of the vessel circumference. Patients were classified according to the most severe lesion. Intimal thickening >0.3 mm (class 3 or 4) was considered significant on the basis of reported values of intimal thickness in a normal population (20). Eccentric lesions were defined as involving $<180^\circ$ of the vessel circumference. Real time images were also reviewed for calcification, which was identified by the presence of acoustic shadowing.

Statistical analysis. Measurements made during succeeding years on the cohort are averaged for each variable and expressed as mean value ± 1 SEM or percent of patients. The differences between means for succeeding years were computed and the nominal two-sided *p* value for each comparison was calculated. These *p* values are presented only as an aid to the reader. They are conservative because they do not take pairing of measurements into account in this cohort study. The proportions were handled in a similar fashion. Two sample *t* tests were used for the means and fourfold chi-square tests for the proportions. The tables and graphs indicate *p* values < 0.05 and < 0.01 .

Results

Clinical characteristics of the patient groups are listed in Table 1. Patients studied at or >6 years after transplantation were significantly younger at transplantation than patients studied at baseline or 1 to 5 years ($p < 0.01$). Otherwise, there were no significant differences with respect to gender, after transplantation diagnosis before transplantation and number of sites studied. Intimal thickness, intimal index and mean severity class for the different time intervals are depicted in Table 2 and Figure 1. All three variables were significantly higher at year 1 after transplantation than at baseline (intimal thickness 0.16 ± 0.02 mm vs. 0.09 ± 0.02 mm, $p < 0.01$; intimal index 0.14 ± 0.02 vs. 0.07 ± 0.01 , $p < 0.01$; mean severity class 2.3 ± 0.2 vs. 1.5 ± 0.2 , $p < 0.01$); intimal thickness was also significantly higher at year 2 than at year 1 (0.23 ± 0.03 mm vs. 0.16 ± 0.02 mm, $p < 0.05$). Thereafter, intimal thickness and intimal index continued to increase to a maximum of 0.33 ± 0.04 mm at years 5 to 10 and 0.27 ± 0.05 at years 11 to 15, respectively, but differences between successive time intervals

Table 1. Clinical Characteristics of the Study Patients

Years After Transplantation	Pts (no.)	Age at Transplantation (yr)	Female	Pretransplant Diagnosis			Sites Studied (no.)
				CMP	CAD	Other	
Baseline (<2 mo)	50	49.3 ± 1.8	6 (12%)	20 (40%)	30 (60%)	0 (0%)	3.3 ± 0.1
1	52	48.5 ± 1.4	12 (23%)	22 (42%)	28 (54%)	2 (4%)	3.0 ± 0.1
2	47	45.3 ± 1.6	7 (15%)	27 (57%)	20 (43%)	0 (0%)	3.0 ± 0.1
3	33	47.6 ± 1.7	6 (18%)	17 (52%)	15 (45%)	1 (3%)	2.9 ± 0.2
4	34	46.3 ± 1.8	7 (21%)	16 (47%)	18 (53%)	0 (0%)	3.2 ± 0.2
5	35	43.9 ± 1.9	7 (20%)	15 (43%)	19 (54%)	1 (3%)	2.8 ± 0.2
6 to 10	42	37.7 ± 1.8*	7 (17%)	16 (38%)	26 (62%)	0 (0%)	3.1 ± 0.2
11 to 15	11	32.8 ± 2.8*	1 (9%)	3 (27%)	7 (64%)	1 (9%)	2.6 ± 0.3

*p < 0.01 versus values in groups studied at baseline and up to year 5 after transplantation. Data are expressed as mean value ± SEM or number (%) of subjects. CAD = coronary artery disease; CMP = cardiomyopathy; Pts = patients.

were not significant. Mean severity class was highest in studies performed at year 5 (3.2 ± 0.2). At baseline, only 11 (22%) of 50 patients had no evidence of intimal thickening, and intimal thickness was classified as mild (class 1 or 2) in another 26 patients (52%) in this group. The remaining 26% of patients with significant lesions in the cardiac graft coronary arteries were assumed to have preexisting intimal disease (12). In contrast, at 5 years after transplantation, some degree of intimal thickening was present in all studies and the percent of studies with significant disease (class 3 or 4) increased from 26% at baseline to 83% at year 5 (Fig. 2). Figure 3 shows the prevalence of lesion characteristics in the different groups. Eccentric lesions were present in 18% of baseline studies in contrast to their presence in 27% to 51% of later studies (p < 0.01) (Fig. 3A). Calcification of lesions was detected in 2%–12% of studies up to year 5 after transplantation and increased significantly to 24% at years 6 to 10 (p < 0.05) and to 46% at years 11 to 15 (Fig. 3B). Except for calcification and intimal index, transplant coronary artery disease tended to be less severe in patients studied at years 11 to 15 after transplantation (intimal thickness 0.30 ± 0.06 mm, intimal index 0.27 ± 0.05, mean severity class 2.8 ± 0.3 [class 0, 0%; class 3 to 4, 54%] and 27% eccentric lesions) than in patients studied at years

5–10 after transplantation. Intracoronary ultrasound findings varied considerably from site to site in each group (Table 3).

Discussion

This study provides, for the first time, a reference for the appearance of transplant coronary artery disease early and during long-term follow-up after heart transplantation in a cross-sectional study. The severity of transplant coronary artery disease appeared to progress with time, especially during the 1st 2 years after transplantation, confirming our previous results (21) in a small patient group studied serially with intracoronary ultrasound.

Transplant coronary artery disease is currently the major factor limiting long-term survival after heart transplantation (22,23), and the pathogenesis of this process remains poorly understood. Histologically, the disease is characterized by a predominantly diffuse and concentric intimal proliferation in large and medium-sized segments of the epicardial coronary arteries (24). Also, during the early phases of transplant coronary artery disease, intimal hyperplasia is characterized by vessel wall expansion with minimal lumen narrowing (25). These factors may explain why coronary angiography is usually

Table 2. Intravascular Ultrasound Variables

Years After Transplantation	Pts (no.)	Intimal Thickness (mm)	Intimal Index	Stanford Class	Ecc	Calc
Baseline (<2 mo)	50	0.09 ± 0.02*	0.07 ± 0.01*	1.5 ± 0.02*	18%	8%
1	52	0.16 ± 0.02†	0.14 ± 0.02	2.3 ± 0.2	44%	2%
2	47	0.23 ± 0.03	0.17 ± 0.02	2.5 ± 0.2	43%	9%
3	33	0.26 ± 0.04	0.20 ± 0.03	2.7 ± 0.2	39%	6%
4	34	0.27 ± 0.03	0.21 ± 0.03	2.5 ± 0.2†	35%	12%
5	35	0.33 ± 0.04	0.24 ± 0.03	3.2 ± 0.2	51%	6%†
6 to 10	42	0.33 ± 0.04	0.25 ± 0.03	3.0 ± 0.2	38%	24%
11 to 15	11	0.30 ± 0.06	0.27 ± 0.05	2.8 ± 0.3	27%	46%

*p < 0.01, †p < 0.05 versus value in succeeding year. Data are expressed as mean value ± SEM or percent of studies. Calc = studies showing calcification; Ecc = studies showing eccentric lesions; Pts = patients; Stanford Class = Stanford classification of lesion severity.

Figure 1. Bar graphs showing the correlation of mean intimal thickness (A), mean intimal index (B) and mean Stanford class of lesion severity (C) with time after transplantation. Data are expressed as mean value \pm SEM. BL = baseline (<2 months after transplantation).

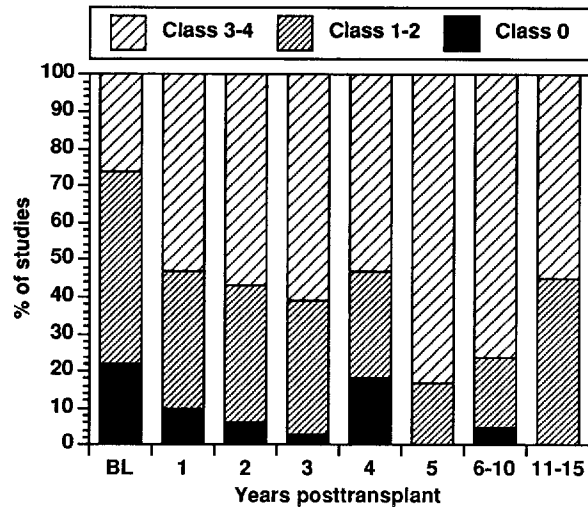
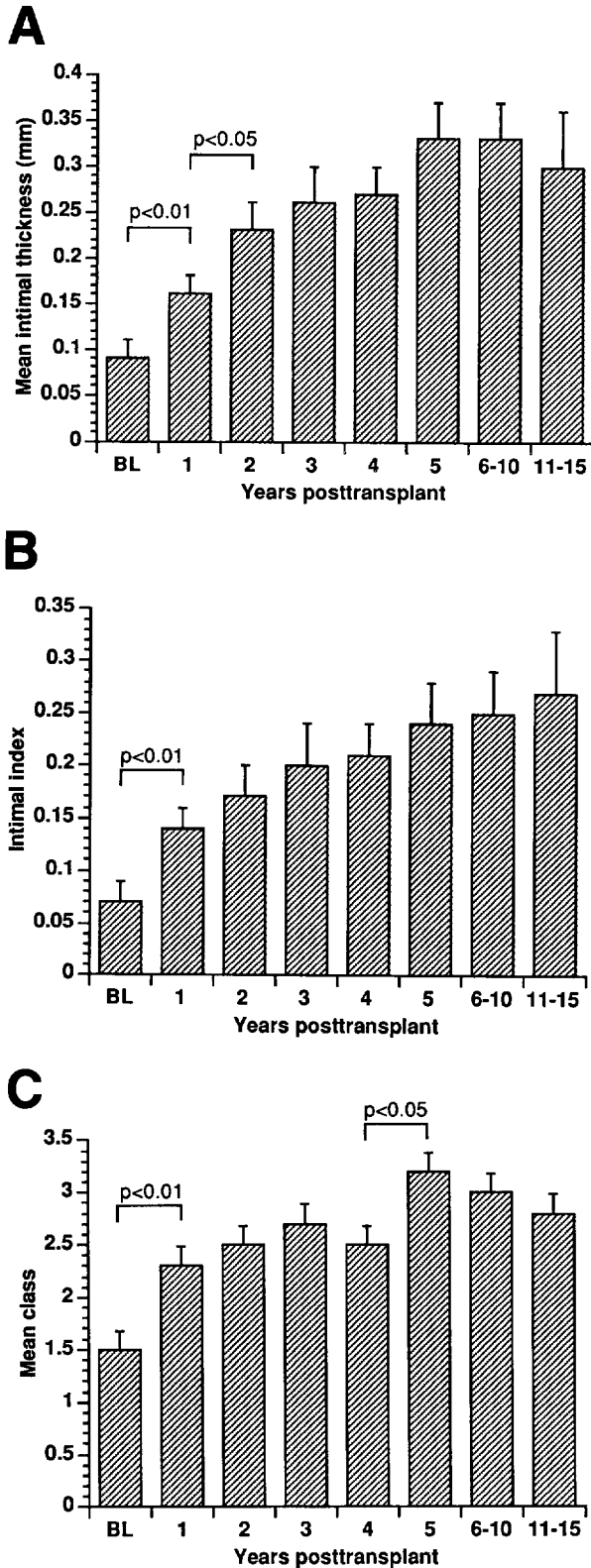


Figure 2. Bar graph showing the distribution of transplant coronary artery disease severity classes 0 to 4 (Stanford classification) in studies performed at different time intervals after transplantation. See text for definition of classes. BL = baseline (<2 months after transplantation).

unable to detect the disease until focal stenoses or distal pruning of the vessel has developed. The need for improved methods for early detection of transplant coronary artery disease has prompted the use of intracoronary ultrasound in these patients. This technique, in contrast to coronary angiography, allows identification and measurement of the components of the vessel wall, in addition to measurement of lumen dimensions. Intracoronary ultrasound has repeatedly been shown to be more sensitive than angiography for detecting intimal thickening in heart transplant recipients (12,15,16) and is the method of choice to study the early changes of transplant coronary artery disease. The choice of 0.3 mm on the intracoronary ultrasound image as the upper limit of normal in the present study was derived from prior work by this laboratory (19) and from pathologic observations (20) in 216 unselected men and women between the ages of 21 and 40 years. The range of intimal thickness in the left anterior descending coronary artery was 0.066 to 0.301 mm in that population. Only 22% of our patients studied during the 1st 2 months after transplantation had no evidence of intimal thickening and 26% already had class 3 and 4 changes.

The present data confirm the results of earlier, smaller preliminary studies suggesting that prevalence and severity of transplant coronary artery disease increase with time after transplantation (17,26,27). In the present study, the most striking progression of disease occurred during the 1st 2 years after transplantation. This finding is in accordance with a previous report from this institution in comparing individual coronary sites in a small group of patients studied serially with intracoronary ultrasound (21). After 2 years, progression of disease continued from year to year but average intimal thickness remained <0.3 mm and severity class remained 0 to 2 up to 4 years after transplantation. The highest values of intimal thickness were measured in patients 5 to 10 years after

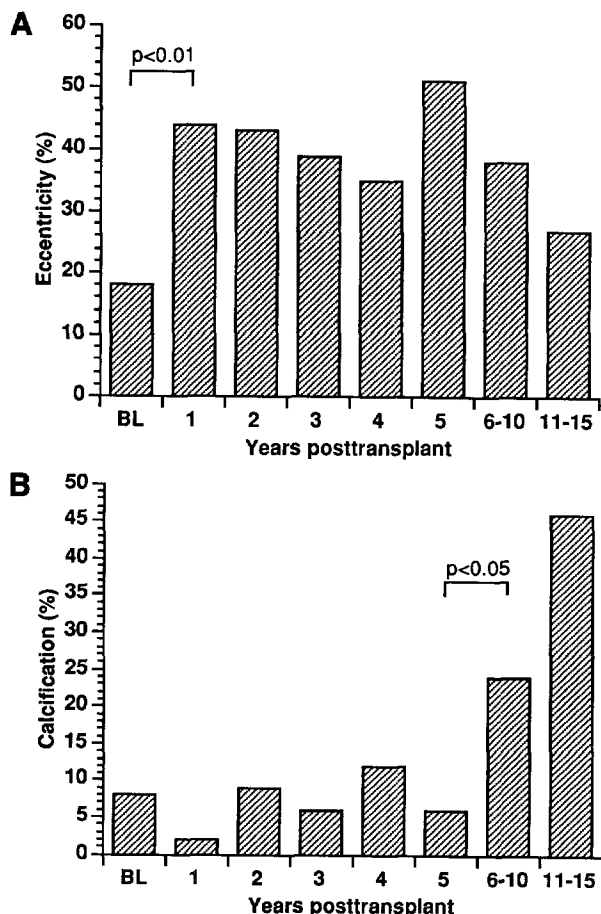


Figure 3. Bar graph showing the correlation of presence of eccentric lesions (A) and calcified lesions (B) with time after transplantation. Data are expressed as mean value \pm SEM. BL = baseline (<2 months after transplantation).

transplantation. A tendency to less severe transplant coronary artery disease was noted in the subjects studied later after transplantation. This latter group probably represented a selection of long-term survivors excluding those patients who died earlier from transplant coronary artery disease. However, an influence of different immunosuppressive regimens used over time cannot be excluded because 7 of the 11 patients studied 11 to 15 years after transplantation underwent transplantation in the years before cyclosporine was in general use. Patients studied 6 to 15 years after transplantation were significantly younger than those studied earlier. Whether this difference simply reflects increasing upper age criteria for recipients over time or points to a better survival in younger patients cannot be determined from our data. The only other study providing quantitative intracoronary ultrasound data in transplant patients was performed by Anderson et al. (27), who reported progression of intimal thickening in a small number of patients 1 to 8 years after transplantation.

Although transplant coronary artery disease is considered to typically have a diffuse distribution (24), the process is not uniform, as highlighted by our findings of considerable varia-

tion of intimal thickness at different sites in the same vessel and the incidence of eccentric lesions present in 35% to 51% of studies performed 1 to 10 years after transplantation. Given this nonuniformity, it is clear that several vessel segments should be studied in the same patient to obtain a sufficient sample to assess disease severity. The prevalence of calcified lesions was low in the present study during the 1st 5 years after transplantation, a finding that has been observed by other groups (16,27). However, calcification was significantly more frequently visible in patients evaluated later. It can be hypothesized that calcification is a marker of the age of the allograft but is not associated with an adverse prognosis.

Study limitations. Several limitations of this study have to be taken into account when interpreting the results. First, this was a cross-sectional rather than a longitudinal study. The data are therefore not valid to assess progression rates of transplant coronary artery disease in individual patients. Because intracoronary ultrasound was introduced into clinical use only in the late 1980s, results of longitudinal studies in long-term survivors will not be available for several years. Second, our results represent the incidence and severity of transplant coronary artery disease in selected survivors, but not in the general heart transplant population. Patients who died before ultrasound follow-up studies of graft atherosclerosis are not represented in this study. It is likely that these patients had the most severe forms of transplant coronary artery disease and that the results obtained here are therefore biased to more favorable patterns. As mentioned earlier, this bias is likely to explain our finding of less severe transplant coronary artery disease in patients studied 11 to 15 years after transplantation. Third, only the proximal two thirds of the left anterior descending vessel were examined in this study; therefore, the reported measurements reflect the disease process in only a limited number of coronary sites in each patient. Fourth, the study was not performed in blinded manner; the investigators had access to clinical information, especially to interval after transplantation. However, each intracoronary ultrasound study was analyzed separately without knowledge of findings from previous studies; therefore, measurement bias is unlikely. Fifth, we did not compare intracoronary ultrasound findings with coronary angiographic findings. This comparison was not the purpose of the present study and the time course of angiographic findings after transplantation has been described previously (3-5). Finally, we did not correlate clinical and laboratory variables with intracoronary ultrasound findings as this is a large topic by itself.

Conclusions. Severity of transplant coronary artery disease appeared to progress with time after transplantation, especially during the 1st 2 years after transplantation, whereas calcification of plaques occurred to a significant extent only later. These observations parallel those of pathologic studies in the time course of the disease. We believe that the intracoronary ultrasound measurements reported here provide reference for future studies. Quantitative measurements of transplant coronary artery disease obtained with intravascular ultrasound may

Table 3. Comparison of Intravascular Ultrasound Findings at Different Sites in the Left Anterior Descending Coronary Artery

Years After Transplantation	Average at All Sites	Site 1	Site 2	Site 3	Site 4
Intimal Thickness (mm)					
Baseline (<2 mo)	0.09 ± 0.02	0.09 ± 0.02	0.09 ± 0.02	0.08 ± 0.02	0.07 ± 0.02
1	0.16 ± 0.02	0.16 ± 0.03	0.18 ± 0.02	0.15 ± 0.02	0.10 ± 0.02
2	0.23 ± 0.03	0.21 ± 0.03	0.29 ± 0.04	0.23 ± 0.04	0.13 ± 0.03
3	0.26 ± 0.04	0.24 ± 0.04	0.32 ± 0.05	0.33 ± 0.07	0.21 ± 0.06
4	0.27 ± 0.03	0.27 ± 0.04	0.25 ± 0.04	0.32 ± 0.06	0.21 ± 0.04
5	0.33 ± 0.04	0.31 ± 0.05	0.37 ± 0.05	0.31 ± 0.06	0.28 ± 0.06
6 to 10	0.33 ± 0.04	0.28 ± 0.04	0.31 ± 0.04	0.39 ± 0.05	0.30 ± 0.06
11 to 15	0.30 ± 0.06	0.31 ± 0.07	0.31 ± 0.10	0.27 ± 0.06	0.22 ± 0.14
Intimal Index					
Baseline (<2 mo)	0.07 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.07 ± 0.02	0.06 ± 0.02
1	0.14 ± 0.02	0.13 ± 0.02	0.15 ± 0.02	0.13 ± 0.02	0.10 ± 0.02
2	0.17 ± 0.02	0.15 ± 0.02	0.22 ± 0.03	0.18 ± 0.03	0.10 ± 0.03
3	0.20 ± 0.03	0.19 ± 0.03	0.24 ± 0.03	0.25 ± 0.04	0.17 ± 0.05
4	0.21 ± 0.03	0.21 ± 0.03	0.19 ± 0.03	0.24 ± 0.03	0.18 ± 0.03
5	0.24 ± 0.03	0.23 ± 0.03	0.27 ± 0.03	0.23 ± 0.03	0.21 ± 0.03
6 to 10	0.25 ± 0.03	0.21 ± 0.03	0.24 ± 0.03	0.29 ± 0.03	0.23 ± 0.04
11 to 15	0.27 ± 0.05	0.28 ± 0.06	0.25 ± 0.07	0.24 ± 0.05	0.20 ± 0.12
Stanford Classification of Lesion Severity					
Baseline (<2 mo)	1.5 ± 0.02	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
1	2.3 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.5 ± 0.3
2	2.5 ± 0.2	2.0 ± 0.2	2.4 ± 0.2	2.2 ± 0.2	1.7 ± 0.3
3	2.7 ± 0.2	2.3 ± 0.2	2.6 ± 0.2	2.7 ± 0.3	2.0 ± 0.3
4	2.5 ± 0.2	2.2 ± 0.3	2.0 ± 0.3	2.3 ± 0.3	2.0 ± 0.3
5	3.2 ± 0.2	2.7 ± 0.2	2.5 ± 0.3	2.4 ± 0.3	2.4 ± 0.3
6 to 10	3.0 ± 0.2	2.7 ± 0.2	2.6 ± 0.2	2.8 ± 0.3	2.4 ± 0.4
11 to 15	2.8 ± 0.3	2.6 ± 0.6	2.3 ± 0.4	2.7 ± 0.3	2.3 ± 0.9
Eccentric Lesions					
Baseline (<2 mo)	18%	4%	10%	16%	12%
1	44%	30%	25%	30%	17%
2	43%	18%	31%	30%	28%
3	39%	28%	25%	9%	12%
4	35%	27%	21%	19%	14%
5	51%	22%	32%	27%	32%
6 to 10	38%	27%	19%	9%	14%
11 to 15	27%	11%	0%	22%	0%
Calcified Lesions					
Baseline (<2 mo)	8%	2%	4%	2%	0%
1	2%	2%	2%	3%	0%
2	9%	5%	8%	5%	8%
3	6%	0%	7%	0%	0%
4	12%	3%	4%	4%	5%
5	6%	4%	0%	4%	0%
6 to 10	24%	12%	8%	18%	5%
11 to 15	46%	22%	25%	33%	33%

Data are expressed as mean value ± SEM or percent of lesions. **Boldface** values indicate highest and lowest measurements at different sites in the respective time interval.

be useful to assess the impact of prevention and intervention strategies, especially early after transplantation.

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