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Influence of Pre-Existing Donor Atherosclerosis on the Development of Cardiac Allograft Vasculopathy and Outcomes in Heart Transplant Recipients

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OBJECTIVES This study sought to evaluate the influence of donor lesions on the development of cardiac allograft vasculopathy and outcomes in heart transplant recipients.

BACKGROUND After orthotopic heart transplantation (OHT), coronary artery narrowing occurs as a combination of pre-existing donor lesions and new lesions that develop as a result of cardiac allograft vasculopathy.

METHODS Intravascular ultrasound (IVUS) studies were performed in 301 recipients at 1.3 ± 0.6 months and again at 12.2 ± 0.8 months after OHT. Additional IVUS studies were performed in 90 patients at two and three years of follow-up. Sites at baseline with maximum intimal thickness ≥0.5 mm were defined as pre-existing donor lesions. The angiographic diagnosis of transplant coronary artery disease (TCAD) was defined as a new ≥50% diameter narrowing of a major epicardial vessel.

RESULTS Donor lesions were present in 30% of the hearts. By IVUS, sites with donor lesions did not have a greater increase in intimal area compared with sites without donor lesions. Angiographically, the incidence of TCAD up to three years after transplantation was higher in recipients with donor lesions than in recipients without donor lesions (25% vs. 4%, $p < 0.001$). However, the three-year mortality rate was similar between recipients with or without donor lesions (4.5% vs. 5.2%, $p = 1.0$).

CONCLUSIONS Pre-existing donor lesions do not act as a nidus for accelerating the progression of intimal hyperplasia. However, patients with donor lesions have a higher incidence of angiographic TCAD. Donor lesions do not affect the long-term survival of patients with OHT up to three years. (J Am Coll Cardiol 2006;47:2470–6) © 2006 by the American College of Cardiology Foundation

Transplant coronary artery disease (TCAD) is the primary limitation to long-term survival of heart transplant recipients (1–4). After orthotopic heart transplantation (OHT), coronary artery narrowing is caused by a combination of pre-existing donor atherosclerosis and new lesions that develop as a result of cardiac allograft vasculopathy. Angiographic evidence of TCAD is present in 42% of heart transplant recipients at five years (5). After five years, TCAD and late graft failure (likely caused by allograft vasculopathy) together account for 30% of all OHT deaths (6). The prevalence of atherosclerosis in the donor pool is high (7,8). When sites with a maximum intimal thickness ≥0.5 mm are defined as atherosclerotic, the presence of donor atherosclerosis varies from 17% in individuals <20 years old, to 28% in subjects <30 years old, and by age 40, >70% of individuals show ≥1 coronary artery site with donor atherosclerosis (7). With increasing demand for cardiac transplantation and a decreasing donor pool, more hearts with pre-existing donor atherosclerosis are being transplanted; thus the long-term impact of pre-existing donor atherosclerosis becomes an important concern. Previous studies show a relationship of older donor age to the development of TCAD and poor survival after cardiac transplantation (2,9–12). It is unclear whether pre-existing donor atherosclerosis predisposes the recipients to developing accelerated TCAD. It is also uncertain whether the presence of pre-existing donor atherosclerosis affects the survival of heart transplant recipients. The objective of this study was to evaluate the influence of pre-existing donor atherosclerosis on the development of cardiac allograft vasculopathy and clinical outcomes in cardiac transplant recipients.

METHODS

Patient population. The current study is a retrospective analysis of the intravascular ultrasound (IVUS) core laboratory images combined from several clinical trials. Only patients who survived the first year after heart transplantation and had baseline and one-year IVUS studies were included in the present study. The population consisted of 301 patients who underwent de novo heart transplantation between 1992 and 1997. All recipients received triple immunosuppression, consisting of cyclosporine, prednisone, and azathioprine or mycophenolate mofetil during the first

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Abbreviations and Acronyms

EEM = external elastic membrane
IVUS = intravascular ultrasound
MIT = maximum intimal thickness
OHT = orthotropic heart transplantation
TCAD = transplant coronary artery disease

year after transplantation. One hundred ninety of these patients were in a trial that randomized them to either azathioprine or mycophenolate mofetil. The trials were approved by the institutional review board of each participating center, and informed consent was obtained from all patients.

Angiography. Coronary angiograms were performed within 6 to 8 weeks after transplantation and subsequently at annual intervals. Multiple angiographic views of the right and left coronary arteries were obtained. Of the 301 patients, 100% of one-year survivors, 94% (273 of 291) of two-year survivors, and 90% (256 of 286) of three-year survivors underwent serial angiography studies. The angiographic reports were performed by quantitative coronary angiography at an independent core laboratory. Cine film recording used a six- to eight-inch image intensifier mode. The recordings of contrast-filled catheters provided scaling factors for measuring luminal diameters via computerized vessel edge detection software. The angiographic diagnosis of TCAD was based on observing a new lesion ≥50% diameter narrowing of a major epicardial vessel.

IVUS imaging procedure. The IVUS examinations were performed in all patients within six to eight weeks and at one year after transplantation. Of the 301 recipients, 90 patients had additional IVUS studies at two and three years of follow-up. After full anticoagulation with heparin 100 units/kg, a guide catheter was advanced over a guidewire into the selected coronary artery. Patients received 0.4 mg sublingual nitroglycerin and/or 200 μg intracoronary nitroglycerin before advancing the IVUS catheter. A 30-MHz ultrasound transducer (4.3-F, CVIS, Sunnyvale, California; 3.5-F, Hewlett-Packard, Palo Alto, California) was inserted into a distal position of the selected vessel where the luminal diameter exceeded 2 mm. A manual slow (>30 s) pullback was performed from the distal position to the proximal site of the coronary artery. The dates of inclusion into the study preceded the use of automated pullback devices. The catheter location was recorded with cine angiography. Continuous IVUS images were recorded on S-VHS videotape with voice annotation.

IVUS imaging analysis. The IVUS tapes were sent to a core laboratory that was blinded to patient treatment. The IVUS images were digitized by the echoPlaque program (echoPlaque version 2.5, INDEC Systems, Santa Clara, California). Landmarks for IVUS such as side branches, calcification, pericardium, and cardiac veins were used in matching the sites. Two to four matched sites from each artery were chosen using side-by-side comparison of the baseline and follow-up images. These sites included the left main and the proximal, middle, and distal sites of each coronary artery. Frames during the diastolic phase of the cardiac cycle were selected for measurement. The frame with the most severe intimal thickening from each site was identified in the first-year IVUS study after OHT. These selected frames were matched with sites from the baseline IVUS study. For the IVUS studies obtained at three-year follow-up, the frame with the most severe intimal thickening from each site was identified in the third-year IVUS study, and then these selected frames were matched with sites from baseline and the first- and second-year IVUS studies. Only sites that had clear matching identifiers were chosen for analysis. Luminal and vessel contours were drawn with the planimetry software on each cross-sectional view by manually tracing the border between the intima and the lumen, and the boundary between the media and adventitia at the external elastic membrane (EEM). In each site, maximum intimal thickness (MIT), intimal area, external elastic membrane area (EEM area), and lumen area were measured. The cross-sectional area stenosis was defined as (intimal area/EEM area) × 100%.

The following definitions for lesion characteristics were used: donor lesions were defined as sites with MIT ≥0.5 mm at baseline study. At one year after transplantation, donor lesions with an increase ≥0.5 mm in MIT were defined as progression of donor lesions, and donor lesions with a decrease ≥0.5 mm in MIT were defined as regression of donor lesions. New lesions were defined as lesions with an increase in MIT ≥0.5 mm at one year that had a previous baseline MIT <0.5 mm.

Clinical events. Patients were classified as having end point events if they had any of the following within 36 months after transplantation. The primary end point was death from any cause. The secondary end point was the presence of TCAD confirmed by angiography.

Statistical analysis. Descriptive statistics were presented as the mean value ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Comparisons between baseline and follow-up were determined by paired *t* test. For comparisons between recipients of hearts with or without pre-existing donor lesions, the clinical characteristics were analyzed with use of the Independent *t* test for continuous variables and Fisher exact or chi-square tests for categorical data. Differences between sites with progression of donor lesions or with new lesions were tested by the Independent *t* test. Comparisons between three groups (sites with or without donor lesions) were performed using one-way analysis of variance followed by multiple comparisons with Bonferroni correction if this was significant. Survival analysis was performed by applying the Kaplan-Meier method. Differences in survival of freedom from TCAD between recipients with or without pre-existing donor lesions were assessed using the log-rank test. A two-sided p value < 0.05 was considered statistically significant.

Table 1. Clinical Characteristics of Recipients

Characteristics	Recipients With DL (n = 89)	Recipients Without DL (n = 212)	p
Baseline demographics			
Donor age (yrs)	39.5 ± 10.1	25.4 ± 11.2	<0.001
Recipient age (yrs)	53.3 ± 7.6	52.2 ± 9.7	0.3
Recipient female gender	15 (16.9)	53 (25.0)	0.1
HLA mismatch	4.64 ± 1.32	4.53 ± 1.37	0.5
Pretransplantation CAD	47 (52.8)	111 (52.4)	1.0
Recipient with CMV mismatch (D+/R−)	15 (16.9)	23 (10.8)	0.3
Cold ischemic time (h)	2.8 ± 0.9	3.0 ± 0.9	0.2
Risk factors			
Cholesterol, mean value during the first yr (mg/dl)	208.9 ± 39.3	206.9 ± 39.7	0.7
Diabetes	33 (37.1)	91 (42.9)	0.3
Hypertension	81 (91.0)	204 (96.2)	0.1
The use of medications			
Statins	55 (61.8)	116 (54.7)	0.3
Calcium blockers	61 (68.5)	161 (75.9)	0.2
Azathioprine at yr 1	60 (67.4)	132 (62.3)	0.4
Rejection 3A or higher grade at yr 1	44 (49.4)	107 (50.5)	0.9

Values are n (%) or mean ± SD.
CAD = coronary artery disease; CMV = cytomegalovirus; D+ = donor positive; DL = donor lesions; R− = recipient negative; HLA = human leukocyte antigen.

RESULTS

Patient enrollment. A total of 301 de novo cardiac transplant recipients (248 men, 53 women; mean age 52.5 ± 9.2 years) with three-year follow-up were analyzed. The IVUS imaging was performed in all recipients at 1.3 ± 0.6 months and again at 12.2 ± 0.8 months after OHT. The 1,103 sites from 333 coronary arteries (mean 3.3 sites per artery) were matched by IVUS imaging between the two studies approximately one year apart. Of the 333 coronary arteries, there were 254 left anterior descending arteries, 55 left circumflex arteries, and 24 right coronary arteries. The mean donor age was 29.6 ± 12.7 years (range 11 to 67 years). In addition, 304 sites from 90 arteries were matched from baseline to the third year after transplantation.

Prevalence and progression of donor lesions. Donor lesions were shown at 196 sites from 96 arteries in 89 (30%) of the 301 hearts. At one-year follow-up, of the 196 sites with donor lesions, 16 (8%) showed progression of intimal hyperplasia on the donor lesion, 5 (3%) sites showed regression of donor lesions, and 175 (89%) sites had an absolute change <0.5 mm in maximum intimal thickness. The mean age of the 89 donor hearts with donor lesions was 39.5 ± 10.1 years, as compared with a mean age of 25.4 ± 11.2 years in 212 hearts without donor lesions ($p < 0.001$). The other clinical characteristics were similar between recipients of hearts with or without pre-existing donor lesions (Table 1).

One-year IVUS data in 301 patients. To further categorize the effect of pre-existing donor atherosclerosis in the heart transplant patients, the 1,103 sites were divided into three groups: 1) 196 (18%) sites with donor lesions; 2) 179 (16%) sites without donor lesions but from arteries with a donor lesion; and 3) 728 (66%) sites without donor lesions from arteries without donor lesions (Table 2). Because all three major epicardial arteries were not imaged with IVUS, we cannot be certain whether the sites from arteries without donor lesions also came from hearts without donor lesions in any other arteries. The average increase in maximum intimal thickness and cross-sectional area stenosis from baseline to 12 months was smaller in donor lesions than in

Table 2. IVUS Parameters at the First Year After Transplantation

Parameters	Arteries With DL: Sites With DL (Group 1) (n = 196)	Arteries With DL: Sites Without DL (Group 2) (n = 179)	Arteries Without DL: Sites Without DL (Group 3) (n = 728)
Δ MIT (mm)	0.06 ± 0.30	0.14 ± 0.22*	0.11 ± 0.21‡
Δ IA (mm^2)	0.54 ± 2.08	0.90 ± 1.60	0.75 ± 1.46
Δ LA (mm^2)	−0.89 ± 2.97	−0.65 ± 2.42	−0.74 ± 2.82
Δ EEM area (mm^2)	−0.35 ± 2.67	0.25 ± 2.32	0.01 ± 2.85
IA/EEM area (%)			
Baseline	31.33 ± 12.88	12.57 ± 5.43†	9.61 ± 3.97§‖
Yr 1	33.82 ± 13.69	17.96 ± 10.51†	14.02 ± 9.00§‖
Yr 1 to baseline	2.49 ± 10.47	5.39 ± 8.82*	4.41 ± 8.07‡

p value, using one-way analysis of variance followed by multiple comparisons with Bonferroni correction. *$p < 0.01$, †$p < 0.001$, compared group 2 with 1. ‡$p < 0.05$, §$p < 0.001$, compared group 3 with 1. ‖$p < 0.001$, compared group 3 with 2.
DL = donor lesions; EEM = external elastic membrane; IA = intimal area; IA/EEM area = cross-sectional area stenosis; IVUS = intravascular ultrasound; LA = lumen area; MIT = maximum intimal thickness.

Table 3. IVUS Parameters in Sites With Progression of Donor Lesions and Sites With New Lesions at the First Year After Transplantation

Parameters	Progression of DL (n = 16)	New Lesions (n = 51)	p
Δ MIT (mm)	0.71 ± 0.18*	0.73 ± 0.23*	0.7
Δ IA (mm^2)	4.15 ± 2.83*	4.47 ± 2.07*	0.6
Δ LA (mm^2)	−4.05 ± 2.30*	−3.54 ± 2.75*	0.5
Δ EEM area (mm^2)	0.10 ± 2.02	0.93 ± 2.62†	0.3
Δ (IA/EEM area) (%)	19.05 ± 9.29*	25.29 ± 10.87*	0.04

*$p < 0.001$; †$p < 0.05$, baseline compared with the first year after transplantation. Abbreviations as in Table 2.

the two groups without donor lesions ($p < 0.05$). However, the cumulative cross-sectional area stenosis was larger in donor lesions than in the two groups without donor lesions at the first year after transplantation ($p < 0.001$).

At the first year, a total of 51 sites from 38 arteries developed new lesions in 36 (12%) of the 301 hearts. Of the 51 sites, 12 sites came from 9 (9%) of the 96 arteries with donor lesions and 39 sites came from 29 (12%) of the 237 arteries without baseline lesions ($p = 0.5$). Of the 96 arteries with donor lesions, 14 (15%) arteries had donor lesion progression and 82 (85%) did not show progression. New lesions were present in 2 (14%) of the 14 arteries that showed progression, and in 7 (9%) of the 82 arteries without donor lesion progression ($p = 0.6$). As shown in Table 3, for the same degree of increase in intimal area, the EEM of the vessel enlarged in new lesions, whereas sites with progression of donor lesions had no significant change in EEM area.

Three-year IVUS data in 90 patients. Of the 304 sites matched from baseline to three-year follow-up: 1) 45 (15%) sites had donor lesions; 2) 38 (13%) sites did not have donor lesions but came from arteries with a donor lesion present; and 3) 221 (72%) sites did not have donor lesions and came from arteries without donor lesions (Table 4). No significant differences were found in the average change in maximum intimal thickness, intimal area, or cross-sectional area stenosis among the three groups during the three-year follow-up. Similar to the IVUS findings at the first year, the cumulative cross-sectional area stenosis was larger in donor lesions than in the two groups without donor lesions from baseline to three-year follow-up, $p < 0.01$ (Fig. 1). The incidence of angiographic TCAD was higher in recipients with donor lesions (25%) than in recipients without donor lesions (4%) at a mean 33.5 ± 6.7 months of follow-up, $p < 0.001$ (Fig. 2). However, a similar rate of progression of cross-sectional area stenosis by IVUS was found between donor lesions and the two groups without donor lesions (Fig. 3). Angiographically significant coronary narrowing (>50% diameter stenosis) will be reached sooner in patients with donor lesions because they start at a higher percent stenosis.

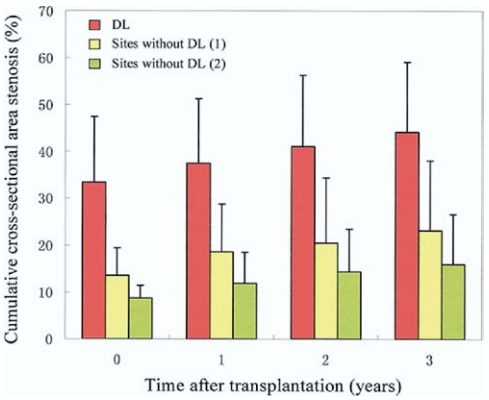

Figure 1. Bar graphs show that the cumulative cross-sectional area of stenosis was larger in donor lesions than in the two groups without donor lesions up to three years after transplantation (all $p < 0.001$). In sites without donor lesions, the cumulative cross-sectional area of stenosis was larger in arteries with donor lesions than in arteries without donor lesions up to three years after transplantation (all $p < 0.01$). The p value used one-way analysis of variance, followed by multiple comparisons with Bonferroni correction. DL = donor lesions; Without DL (1) = sites without donor lesions but from arteries with donor lesions; Without DL (2) = sites without donor lesions from arteries without donor lesions.

Survival. By three years after transplantation, 4 (4.5%) of the 89 recipients with donor lesions died (1 cardiovascular event, 1 pulmonary embolism, and 2 unknown cause). In the 212

Table 4. IVUS Parameters During the 3-Year Follow-Up

Parameters	Arteries With DL: Sites With DL (Group 1) (n = 45)	Arteries With DL: Sites Without DL (Group 2) (n = 38)	Arteries Without DL: Sites Without DL (Group 3) (n = 221)
Change in MIT (mm)			
Yr 1 to baseline	0.14 ± 0.24	0.15 ± 0.21	0.08 ± 0.18
Yr 2 to yr 1	−0.02 ± 0.37	−0.0003 ± 0.17	0.04 ± 0.14
Yr 3 to yr 2	0.07 ± 0.24	0.07 ± 0.19	0.06 ± 0.18
Change in IA (mm^2)			
Yr 1 to baseline	1.01 ± 2.14	0.93 ± 1.56	0.56 ± 1.37
Yr 2 to yr 1	−0.02 ± 1.99	0.20 ± 1.47	0.31 ± 0.92
Yr 3 to yr 2	0.59 ± 1.31	0.57 ± 1.33	0.33 ± 1.04
Change in (IA/EEM area) (%)			
Yr 1 to baseline	4.09 ± 10.14	4.97 ± 9.41	3.24 ± 5.96
Yr 2 to yr 1	3.58 ± 11.16	1.95 ± 9.35	2.49 ± 6.23
Yr 3 to yr 2	3.05 ± 6.62	2.67 ± 8.74	1.59 ± 5.57

$p > 0.05$ for overall comparison by one-way analysis of variance. Abbreviations as in Table 2.

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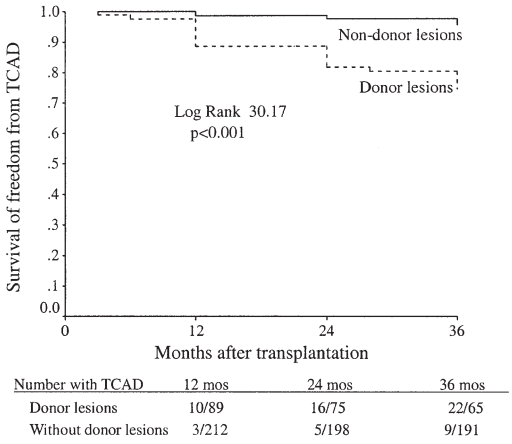

Number with TCAD	12 mos	24 mos	36 mos
Donor lesions	10/89	16/75	22/65
Without donor lesions	3/212	5/198	9/191

Figure 2. Kaplan-Meier estimate of freedom from angiographic transplant coronary artery disease (TCAD) by three years after transplantation. Recipients with donor lesions: n = 89; recipients without donor lesions: n = 212.

recipients without donor lesions, 11 (5.2%) patients died (4 cardiovascular events, 2 rejections, 1 infection, 1 pulmonary embolism, 1 cancer, and 2 of unknown cause). The three-year mortality rate was similar between recipients with and without donor lesions (p = 1.0). During the three-year follow-up, repeat transplantation was performed in only one patient, who did not have baseline donor lesions but in whom severe TCAD developed at the first year after transplantation.

DISCUSSION

The IVUS data in this study showed that 30% of recipients had donor lesions defined as a maximum intimal thickness ≥0.5 mm at baseline IVUS examination. At the first year after transplantation, 8% of the sites with donor lesions showed progression of donor lesions, 3% showed regression of donor lesions, and 89% had an absolute change <0.5 mm in maximum intimal thickness. Most importantly, the current study found by IVUS imaging that the presence of pre-existing donor atherosclerosis does not accelerate the development of cardiac allograft vasculopathy either at the site of pre-existing donor lesions or elsewhere within the same artery, however, patients with pre-existing donor atherosclerosis have a higher degree of angiographic coronary artery narrowing during the three-year follow-up. This seems to be paradoxical, but it can be explained by the differences in the observational techniques of IVUS versus angiography.

Intravascular ultrasound is more sensitive than coronary angiography in detecting donor atherosclerosis (13). In addition, the use of serial IVUS detects not only early development of cardiac allograft vasculopathy but also the rate of progression of this disease (14,15). It is important to distinguish the definition of cardiac allograft vasculopathy by IVUS versus angiography because these two examinations show different phenomena in the development of cardiac allograft vasculopathy. By IVUS, the development of cardiac allograft vasculopathy is defined as an increase in maximal intimal thickness of at least 0.5 mm from baseline. In contrast, the angiographic evidence of TCAD is defined by luminal narrowing, which can be caused by a combination of pre-existing donor atherosclerosis and new lesions that develop after transplantation. The observation from IVUS that donor lesions do not have a greater rate of intimal progression after transplantation can be reconciled with angiographic reports that hearts with donor lesions develop more TCAD is shown in Figure 3. The threshold of a 50% diameter stenosis will be reached sooner in arteries with donor lesions, despite the observations by IVUS that the rate of progression of cumulative cross-sectional area stenosis is similar. Consistent with previous studies (9,16), the current study found that patients with pre-existing donor atherosclerosis have more severe coronary artery narrowing up to three years after transplantation not because they progress more rapidly but because they start at a greater percentage of stenosis.

In the serial examinations by IVUS, the first year data showed that the average increase in maximum intimal thickness was lower in sites with donor lesions than in sites without donor lesions; in contrast, the three-year data showed that no significant difference was noted for the change in intimal thickening between sites with or without donor lesions. Other studies have also shown a similar or slower progression of intimal hyperplasia in sites with donor lesions compared with sites without donor lesions (14,16–19). These results suggest that pre-existing donor atherosclerosis does not provide a nidus for accelerating intimal growth compared with sites without donor lesions. Therefore, the presence of pre-existing donor atherosclerosis is not a trigger for the subsequent development of cardiac allograft vasculopathy (16). In addition, there was no association between the progression of pre-existing donor atherosclerosis and the development of new lesions within the same artery in the present study (17). After transplantation, all of the coronary arteries of the donor heart are

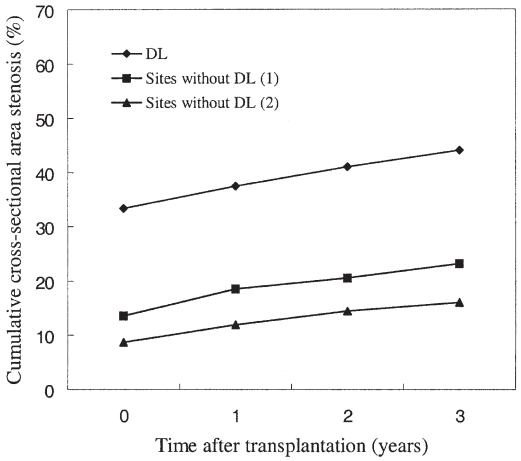

Figure 3. The cumulative cross-sectional area of stenosis at sites with and without donor lesions by three years after transplantation. DL = donor lesions; Sites Without DL (1) = sites without donor lesions but from arteries with donor lesions; Sites Without DL (2) = sites without donor lesions from arteries without donor lesions.

exposed to the same immune and nonimmune environment, which might lead to a similar rate of progression of intimal hyperplasia at sites with or without pre-existing donor atherosclerosis.

Little is known about the influence of donor lesions on vascular remodeling. This study found that sites with donor lesions did not show compensatory vessel enlargement as further intimal thickening developed. This observation suggests that the presence of pre-existing donor lesions may impede compensatory expansive remodeling as intimal thickening progresses (18,20). Expansive remodeling may be a compensatory mechanism in the early development of native and transplant atherosclerotic lesions, which prevents luminal loss (21,22). The ability to undergo compensatory vessel enlargement in the presence of plaque formation is dependent on intact endothelial function (23). In sites with donor lesions, more endothelial cell dysfunction and adventitial fibrosis may inhibit vessel enlargement as intimal thickening progresses after transplantation. One study has reported that early constriction of vessels caused an overall decrease in EEM area and was associated with a greater lumen loss during follow-up (24). Consequently, in patients with donor lesions, angiographic TCAD more frequently develops (defined as ≥50% diameter stenosis) because of a lack of expansive remodeling and pre-existing luminal stenosis.

The mechanism of the development of cardiac allograft vasculopathy is not fully understood but is likely a consequence of both long-acting immunologic rejection and nonimmunologic factors, such as hyperlipidemia, hypertension, and hyperglycemia (3,4). Previous studies have shown that statin treatment is associated with lower risks of death, serious rejection, and the development of cardiac allograft vasculopathy (25–27). Mycophenolate mofetil was more efficacious than azathioprine in reducing progression of cardiac allograft vasculopathy and improving survival among heart transplant recipients (28,29). In the present study there was no difference in the use of statin and azathioprine, total cholesterol levels, the incidence of diabetes and hypertension, cytomegalovirus infection, and acute allograft rejection between patients with and without donor lesions.

The influence of pre-existing donor lesions on clinical outcomes is unclear. The mean age of donors in this study was 29.6 years. As expected, the mean age in hearts with donor lesions (39.5 years) was 14 years older than transplant hearts without donor lesions (25.4 years). One study evaluated 479 adult heart transplant recipients and found that the correlation between older donor age (>40 years) and poor survival was confined within the first post-transplantation month (10). Consistent with previous reports (9,30), the present study also found that in recipients who survived beyond the first post-transplantation year, pre-existing donor lesions did not affect the survival of heart transplants up to three years after OHT. Similarly, recent studies describe that the presence of donor lesions by IVUS was not predictive of adverse outcomes (31), whereas rapid progression of intimal thickening in the first year after transplantation (an increase of ≥0.5 mm in MIT from baseline to one-year measurement, including progression of donor lesions and new lesions) predicts all-cause mortality, nonfatal myocardial infarction, and the subsequent development of angiographically severe coronary artery disease (31,32).

Intravascular ultrasound has been recognized as the most sensitive diagnostic tool for early detection of cardiac allograft vasculopathy, but remains an invasive procedure, thus limiting its widespread use (33). A recent study argued that multislice computed tomography may be more sensitive than conventional coronary angiography for detecting thickened segments in heart transplant patients (34). However, future research is needed to determine whether IVUS examinations can be replaced by multislice computed tomography in heart transplant patients.

Study limitations. This study did not analyze the influence of pre-existing donor lesions on the first-year mortality in heart transplant recipients because only patients who survived beyond the first post-transplantation year were included in the present study. The small number of mortality end points is inherent to serial IVUS studies. The IVUS imaging was performed in only one coronary artery per patient in 276 (92%) of the 301 cardiac transplant recipients. This may affect the reported incidence of pre-existing donor lesions and development of cardiac allograft vasculopathy. All IVUS images were performed with manual pullback of the IVUS catheter because motorized pullback devices were not available during the period of this study. This could lead to difficulty in matching sites from the baseline and follow-up studies. Volumetric analysis of plaque burden by automated pullback of the IVUS catheter may avoid the problems associated with matching individual sites, however, variability in the pullback length between consistent angiographic markers such as bifurcations can produce errors in volumetric analyses.

Conclusions. Assessing the influence of pre-existing donor atherosclerosis on the development of cardiac allograft vasculopathy is complex, and the pathophysiological mechanisms are not fully understood. This three-year serial IVUS study shows that pre-existing donor atherosclerosis does not act as a nidus for accelerating the progression of intimal hyperplasia. The presence of a donor lesion as a marker of a heart that existed in an atherosclerotic environment also does not predispose to the development of new lesions elsewhere in the same artery after transplantation. Donor lesions may impede compensatory expansive remodeling as intimal thickening progresses. The use of older hearts with pre-existing donor atherosclerosis is associated with an increase in the angiographic incidence of TCAD up to three years after transplantation not because the rate of progression of cardiac allograft vasculopathy is greater, but because the donor lesion starts from a position that is more narrowed at the time of transplantation. In recipients who survived beyond the first post-transplantation year, pre-existing donor atherosclerosis did not affect the long-term

survival of heart transplantation up to three years after transplantation. This study suggests that the selective use of donor hearts with mild coronary artery disease is an acceptable option for cardiac transplantation.

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