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Donor-Transmitted Atherosclerosis Associated With Worsening Cardiac Allograft Vasculopathy After Heart Transplantation: Serial Volumetric Intravascular Ultrasound Analysis

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Background. The influence of preexisting donor-transmitted atherosclerosis (DA) on cardiac allograft vasculopathy (CAV) development remains unclear. **Methods.** We performed 3-dimensional intravascular ultrasound (3D-IVUS) analysis in 42 heart transplantation (HTx) recipients at 2.1 ± 0.9 months (baseline) and 12.2 ± 0.4 months post-HTx, as well as consecutive 3D-IVUS analyses up to 3 years post-HTx in 35 of the 42 recipients. Donor-transmitted atherosclerosis was defined as a maximal intimal thickness of 0.5 mm or greater at baseline. Changes in volumetric IVUS parameters were compared in recipients with (DA group) and without DA (DA-free group) at baseline, 1 year, and 3 years post-HTx. **Results.** Donor-transmitted atherosclerosis was observed in 57.1% of 42 recipients. The DA group exhibited a significantly greater increase in plaque volume at 1 year post-HTx ($P < 0.001$), leading to increased percent plaque volume (plaque volume/vessel volume, [%]) ($P < 0.001$) and decreased luminal volume ($P = 0.021$). Donor-transmitted atherosclerosis was independently associated with a greater increase in percent plaque volume during the first post-HTx year ($P = 0.011$). From 1 to 3 years post-HTx, the DA group underwent continuous reduction in luminal volume ($P = 0.022$). These changes resulted in a higher incidence of angiographic CAV at 3 years post-HTx in the DA group (58.8% vs 5.6%, $P = 0.002$). **Conclusions.** This volumetric IVUS study suggests that DA correlates with the worsening change in CAV several years post-HTx. Donor-transmitted atherosclerosis recipients may require more aggressive treatment to prevent subsequent CAV progression.

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Heart transplantation (HTx) is a lifesaving option for patients with end-stage heart failure. Despite many advances in immunosuppression management, cardiac allograft vasculopathy (CAV) is still a major cause of morbidity and mortality in HTx recipients.[1,2] It is estimated that 30% of HTx recipients develop CAV within 5 years after HTx, and that CAV is responsible for 10% to 15% of cardiac deaths after the first post-HTx year.[1] Due to the substantial demand for HTx and international organ shortage, hearts with higher donor age are being transplanted,[1,3,4] which may lead to a higher prevalence of preexisting donor transmitted atherosclerosis (DA) in transplanted hearts.[5] These observations warrant further investigation of the influence of DA on CAV progression.

Although several studies using intravascular ultrasound (IVUS) have evaluated CAV in recipients with DA,[6-12] the impact of DA on CAV progression is still controversial. The majority of previous studies using 2-dimensional (2D) IVUS analysis showed that CAV progression was independent of the presence or absence of DA,[6-11] whereas one 3D IVUS study linked DA and CAV progression at the end of the first post-HTx year.[12] These inconsistent results might be due to differences in IVUS methodology,[13,14] indicating the need for further 3D-IVUS study. Further, recent changes in immunosuppression protocols, such as the use of tacrolimus (Tac) instead of cyclosporine (CsA) and mycophenolate mofetil (MMF) instead of azathioprine, have been suggested to affect the incidence and progression of CAV.[15-17] Most previous studies evaluating the impact of DA on CAV development were performed in recipients who were treated with CsA,[6-12] and the impact of DA on CAV progression in recipients treated with the newer immunosuppressants has not been fully elucidated.

In addition, 1 previous serial IVUS study demonstrated that the rate of increasing intimal thickness in CAV was different between during and after the first post-HTx year.[18] These differences in findings during and after the first post-HTx year suggest that DA also might exert different effects on the course of CAV progression during these early and late periods. However, very few studies have evaluated the influence of DA several years after HTx,[11] and, to our knowledge, no serial 3D-IVUS study has yet been conducted.

Here, to clarify the influence of DA on CAV progression, we aimed to evaluate changes in CAV during and after the first post-HTx year in recipients with and without DA using serial 3D-IVUS.

MATERIALS AND METHODS

Patient Selection and Study Protocol

We retrospectively reviewed the medical records of 54 recipients who underwent HTx at the National Cerebral and Cardiovascular Center (NCVC) in Japan from May 1999 to March 2013 (Figure 1). Our previous paper detailed the management of HTx recipients in our institution.[19]

Briefly, all de novo HTx recipients in our institution received triple immunosuppressive therapy consisting of calcineurin inhibitors, namely, CsA or Tac, MMF, and corticosteroids.[20] From May 1999 to June 2006, de novo HTx recipients were initially treated with CsA. Tacrolimus was used as an alternative to CsA as the primary immunosuppressant beginning in 2005. From October 2006, all first-time recipients received Tac instead of CsA. Since 2007, we have considered converting from MMF to everolimus (EVL) during the maintenance period for the following recipients: (1) those with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2), (2) those with an increase in maximal intimal thickness (MIT) on routine IVUS examination or major DA on baseline IVUS, and (3) those with MMF-related leukopenia. When EVL was continued for at least 6 months, it was defined as EVL use in this study. Because the majority of our recipients required left ventricular assist device support as a bridge to transplantation, their surgical site wound after transplantation was generally complicated. Therefore, we have not applied EVL just after transplantation in our institution because of reports that it is associated with a higher incidence of incisional complications than MMF.[21]

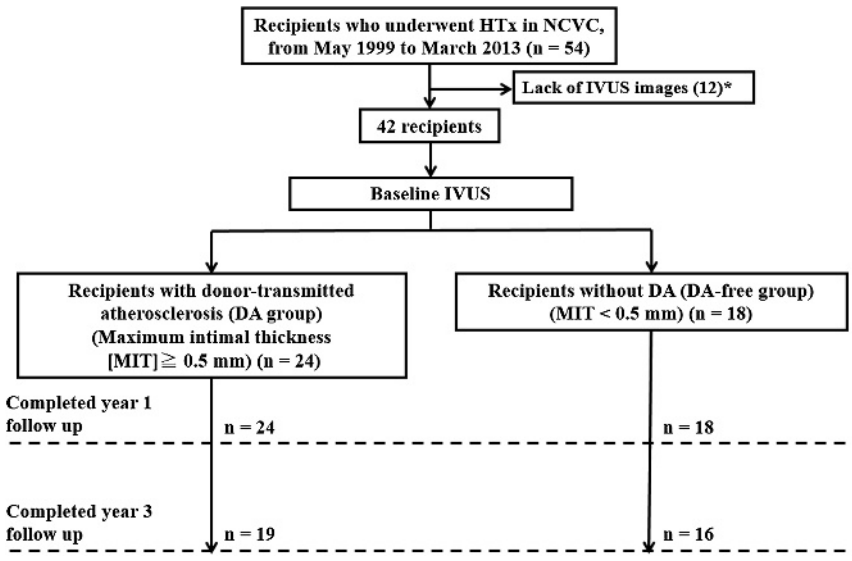

FIGURE 1. Study flowchart *Twelve recipients were excluded because of lack of IVUS images at baseline or 1 year post-HTx, due to death within 1 year (n = 1), revascularization at baseline (n = 1), and other reasons (eg, unsatisfactory quality of IVUS images or no IVUS examination due to clinical reasons) (n = 10).

Coronary angiography (CAG) and IVUS examinations were performed 5 to 12 weeks after HTx (baseline) and repeated to evaluate CAV annually. All CAG and IVUS data were newly reviewed and analyzed by 1 investigator (T.W.) from March 2013 to March 2014. Angiographic severity of CAV was classified according to the International Society of Heart and Lung Transplantation (ISHLT) guidelines,[22] and defined as ISHLT CAV 0 (not significant), CAV 1 (mild), CAV 2 (moderate), CAV 3 (severe). Angiographic severity of CAV was evaluated from 3 coronary arteries, and the progression of severity was assessed in all 3. We evaluated the serial IVUS data of the left anterior descending (LAD) artery from baseline to 3 years post-HTx using 3D-IVUS analysis as well as conventional cross-sectional IVUS analysis.

Of 54 recipients, 12 recipients were excluded because of lack of IVUS images at baseline or 1 year post-HTx, namely, due to death within 1 year (n = 1), revascularization at baseline (n = 1) and other reasons (eg, unsatisfactory quality of IVUS images) (n = 10). The case of death within 1 year post-HTx was caused by infection, not coronary artery disease. One recipient who underwent revascularization at baseline had severe coronary artery stenosis due to preexisting major DA. The remaining 42 recipients who had both baseline and 1-year posttransplant IVUS data were included in this study. Of these, 35 recipients who had complete serial IVUS data up to 3 years post-HTx underwent additional IVUS analyses. The study sample was stratified into 2 groups according to the presence (DA group) or absence (DA-free group) of DA at baseline IVUS. Donor-transmitted atherosclerosis was defined as present when any cross-sectional baseline IVUS image showed a MIT of $\geq$ 0.5 mm.[10-12] We compared the change in IVUS data from baseline to 1 year post-HTx, and from 1 to 3 years post-HTx between 2 groups. Baseline clinical characteristics were collected at the time of the baseline IVUS examinations. The details of immunosuppression use and other medications, such as statin therapy, were also collected at 1 and 3 years post-HTx. The study protocol was approved by the ethics committee of the NCVC of Japan. Informed consent had been obtained from all subjects (IRB number M25-019 at NCVC).

Follow-Up Criteria for Endomyocardial Biopsy

Routine endomyocardial biopsies were performed weekly for 3 weeks after HTx, every 2 weeks from 3 weeks to 2 months, at 3 months, every 1.5 months from 3 months to 6 months, every 3 months from 6 months to 12 months, and then at 6-month intervals until the end of the fifth year, after which we performed endomyocardial biopsy annually. International Society of Heart and Lung Transplantation grade 2R[23] or greater acute cellular rejection in the routine endomyocardial biopsy was treated with augmented immunosuppression and intravenous steroids.[20]

Catheterization and Intravascular Ultrasound Procedures

From May 1999 to December 2003, a 30-MHz short monorail imaging catheter (Ultra Cross; Boston Scientific, Natick, MA) and imaging console with a motorized pullback system (SONOS100; Hewlett-Packard, Andover, MA) were used. Subsequently, we used a 40-MHz mechanical ultrasound catheter (IntraFocus, Terumo, Tokyo, Japan) from January 2004 to January 2008, and a ViewIT (Terumo) with a mechanical pullback system (TU-C200; Terumo) from February 2008 to March 2013. The ultrasound transducer was advanced into the distal portion of the target artery. Automated IVUS pullback was performed at a constant speed of 0.5 or 1.0 mm/s. Intravascular ultrasound images were stored on S-VHS tape for offline 3D-IVUS analysis. Cross-sectional images of the LAD spaced precisely 1 mm apart were selected for cross-sectional analysis. The maximum length analyzed was 50 mm of the LAD, from the distal position to the ostium. Each area on cross-sectional IVUS was manually traced. Maximal intimal thickness was measured at the site with the greatest intimal thickness in the analyzed length. Three-dimensional IVUS analyses were all performed using volumetric analysis software (Nicoras T2000 Ver 2.1, Terumo) and are summarized in Figure 2. Plaque area was defined as the difference between the area occupied by the lumen and external elastic membrane borders. Volumetric analyses were conducted as the summation of each area (vessel [external elastic membrane], plaque, and lumen) and were calculated by automatic border detection on the basis of the manually traced cross-sectional area of every 1 mm of analyzed length. Each volume in the serial IVUS data was analyzed at the same length in the paired studies. If lengths were different among paired IVUS datasets, the longest common length from the paired data was selected. Each volume was standardized to account for differences in analyzed length between different subjects, which was calculated as volume index:

$$\text{Volume index}\left(\text{mm}^3/\text{mm}\right) = \left[\frac{\text{Volumetric value}}{\text{Analyze length}}\right] \quad (1)$$

Percent plaque volume index was used to evaluate components of both vessel remodeling and intimal change indicating CAV progression:

$$\text{Percent plaque volume index}\,(\%) = \left[\frac{\text{Plaque volume}}{\text{Vessel volume}}\right] \times 100 \quad (2)$$

Change in MIT and volumetric IVUS data were calculated as:

$$\text{Change in IV US data} = (\text{IVUS data at follow up}) - (\text{IVUS data at baseline}) \quad (3)$$

We compared changes in coronary vessel, plaque, lumen volumes, and percent plaque volume between the DA and DA-free groups.

"Rapidly progressive vasculopathy" was defined as a change in MIT of 0.5 mm or greater at the end of the first post-HTx year, which is known as a predictor for poor clinical outcomes at 5 years post-HTx.[24] "Paradoxical vessel remodeling" from baseline to the first post-HTx year, which was defined as (Δvessel volume/Δplaque volume) less than 0, has also been reported to be a primary determinant of long-term mortality.[25]

Statins and Other Medications

Treatment with statins and other medications did not change over the 14-year time frame in this study (May 1999

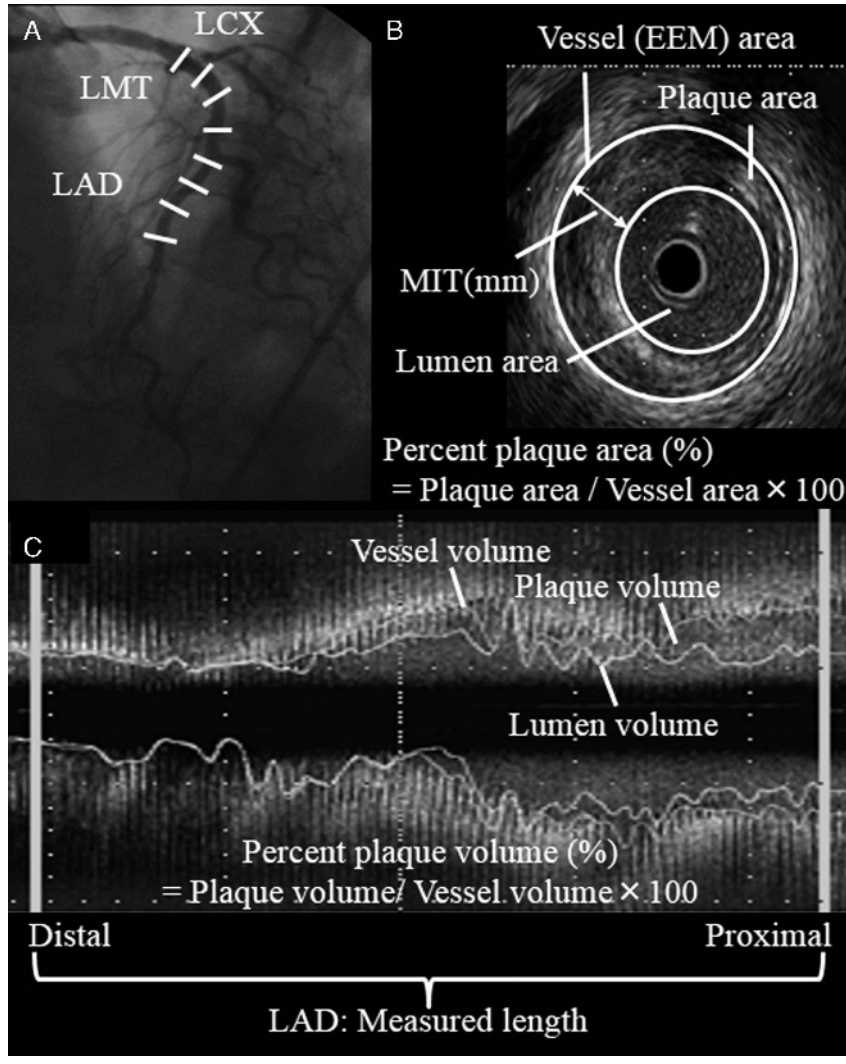

FIGURE 2. Definition of volumetric indices in IVUS analyses. A, Angiography. B, Two-dimensional IVUS analyses. C, Three-dimensional IVUS analyses. EEM, external elastic membrane; LCX, left circumflex artery; LMT, left main trunk.

to March 2013). Treatment with statins and other conventional medications (ie, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and antiplatelet drugs) were generally initiated within 2 months after HTx and subsequently maintained for all recipients, unless they experienced adverse effects. If adverse effects were observed before HTx, these medications were not started, or other medications were selected. Pravastatin was generally used,[26] but if the lipid profile worsened or if an increase in intimal thickness on IVUS was identified on routine IVUS examination, the statin dosage was increased or a more powerful agent, such as atorvastatin, rosuvastatin, or pitavastatin, was substituted. When doses of at least 20 mg/d for pravastatin or atorvastatin, 5 mg/d for rosuvastatin, and 4 mg/d for pitavastatin were instituted, the patient was considered to be on a "high-dose" statin. "Aggressive statin therapy" was defined as the use of a more powerful statin or a higher dose of pravastatin. The majority of patients received aspirin and amlodipine.

Statistical Analysis

The data are expressed as mean ± standard deviation for normally distributed continuous variables, median with interquartile range for nonnormally distributed continuous variables, and number (percentages) for categorical variables. The χ^2 test was used to test for differences in categorical variables between groups, and continuous data were compared using unpaired *t* tests, or Wilcoxon rank sum test when the variable was not normally distributed. The Wilcoxon signed-rank test was used to compare baseline to 1 year, and 1 year to 3 years post-HTx volumetric IVUS data in each group. Serial changes in volumetric IVUS data from baseline to 1 year post-HTx, and from 1 to 3 years post-HTx, were compared between DA and DA-free groups using the Wilcoxon rank sum test. Multivariable linear regression analyses models were used to analyze the association between DA and change in volumetric IVUS data (Models 1, 2 and 3 in Table 4). Because the change in percent plaque and plaque volume at the first post-HTx year did not show a normal distribution, we assessed the logarithmic transformation (log) of the change in these IVUS data as follows: Log (1 – minimum actual value of the change in IVUS data). Changes in MIT were treated as categorical variables by defining the median value as the cut-off point in change in MIT during the first post-HTx year. The cut-off point of a 0.1-mm increase in MIT was chosen. A *P* value

less than 0.05 was considered significant. All analyses were performed using commercial software (STATA version 13, Stata Corporation, College Station, TX).

RESULTS

Baseline Clinical Demographics

Donor-transmitted atherosclerosis was observed in 24 (57.1%) study subjects (Table 1). Donor age in the DA group was significantly older ($P = 0.010$). No subject had experienced apparent acute cellular rejection (ISHLT grade ≥ 2R) by the time of the baseline IVUS (mean 2.1 ± 0.9 months post-HTx). One recipient in the DA group and 2 in the DA-free group exhibited acute cellular rejection during the first year post-HTx.

One recipient in the DA-free group had already converted from MMF to EVL due to impaired renal function by the time of the baseline IVUS (Table 2). Five recipients in the DA group were switched from MMF to EVL by the first post-HTx year, 2 of them due to having a preexisting major DA on baseline IVUS.

IVUS Data and Coronary Angiographic Severity of CAV

The DA group showed a significant increase in plaque volume ($P < 0.001$) at 1 year post-HTx compared with baseline, indicating a significant increase in percent plaque volume ($P < 0.001$) and significant decrease in luminal volume ($P = 0.021$) (Table 3). In the DA-free group, significant shrinkage of vessel volume was observed ($P = 0.028$), resulting in smaller luminal volumes ($P = 0.020$) accompanied by increased percent plaque volume ($P = 0.035$). There were no significant differences in the incidence of "Rapidly progressive vasculopathy" or "Paradoxical vessel remodeling" between the 2 groups.

No recipients had more severe angiographic CAV than ISHLT grade 2 at baseline and 1 year post-HTx. Twelve recipients in the DA group had CAV 1 at the baseline CAG. The frequency of angiographic new or progressive CAV in any coronary artery was likely to be higher in the DA group than in the DA-free group, albeit that this difference did not reach significance ($P = 0.069$).

The presence of DA was independently associated with an increase in percent plaque volume at 1 year post-HTx in multivariable regression models (Table 4). Donor-transmitted atherosclerosis was also significantly associated with an increase in plaque volume (**Table S1, SDC**, http://links.lww.com/TP/B306).

Intravascular ultrasound data and coronary angiographic severity of CAV at 1 and 3 years post-HTx are shown in

TABLE 1.

Baseline characteristics

Variable	DA group, n = 24	DA-free group, n = 18	*P*
Donor age, y[a]	44.3 ± 10.6	34.2 ± 13.6	0.010
Male donor, n (%)[b]	14 (58.3)	10 (55.6)	0.857
Recipient age, y[a]	35.9 ± 12.8	36.1 ± 10.1	0.958
Male recipient, n (%)[b]	20 (83.3)	13 (72.2)	0.385
LVAD before HTx, n (%)[b]	22 (91.7)	17 (94.4)	0.729
CMV mismatch (D+/R-), n (%)[b]	6 (25.0)	2 (11.1)	0.257
Cold ischemic time, min[c]	212.0 (176.5-226.5)	205.5 (179.0-215.0)	0.315
Primary indication			
nonischemic cardiomyopathy, n (%)[b]	23 (95.8)	17 (94.4)	0.834
BMI, kg/m^2 [a]	19.5 ± 3.3	18.9 ± 2.6	0.554
Pre-HTx history			
Hypertension, n (%)[b]	3 (12.5)	5 (27.8)	0.212
Hyperlipidemia, n (%)[b]	4 (16.7)	5 (27.8)	0.385
Diabetes, n (%)[b]	5 (20.8)	3 (16.7)	0.734
Prior smoking history, n (%)[b]	9 (37.5)	6 (33.3)	0.780
PRA class I ≥10, n (%)[b]	3 (12.5)	2 (11.1)	0.891
PRA class II ≥10, n (%)[b]	0 (0)	0 (0)	1.000
Medications at baseline			
Calcium channel blocker, n (%)[b]	18 (75.0)	14 (77.8)	0.834
ACE-I/ARB, n (%)[b]	21 (87.5)	13 (72.2)	0.212
Antiplatelet drugs, n (%)[b]	24 (100.0)	16 (88.9)	0.094
Laboratory data at baseline			
Triglycerides, mg/dL[c]	102.5 (82.5-144.0)	133.0 (117.0-159.0)	0.071
Total cholesterol, mg/dL[a]	180.5 ± 35.0	199.1 ± 34.0	0.093
LDL cholesterol, mg/dL[c]	96.8 (85.5-114.2)	102.2 (95.0-114.8)	0.303
HDL cholesterol, mg/dL[c]	56.0 (45.0-65.5)	60.0 (51.0-73.0)	0.186
HbA1c, %[c]	4.8 (4.5-5.0)	4.6 (4.4-4.9)	0.272
Acute cellular rejection ≥ grade 2R up to 1 year post-HTx, n (%)[b]	1 (4.2)	2 (11.1)	0.387

[a] Data are expressed as mean ± SD.
[b] Numbers of subjects (%) for categorical values.
[c] Median (IQR) for continuous values.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CMV, cytomegalovirus; D+/R–, donor CMV-positive/recipient CMV-negative; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LVAD, left ventricular assist device; PRA, panel-reactive antibody.

TABLE 2.

Immunosuppression and statin therapy at baseline and 1 y post-HTx

	DA group, n = 24	DA-free group, n = 18	*P*
CsA			
Baseline	7 (29.2)	6 (25.0)	0.773
1 y post-HTx	7 (29.2)	5 (27.8)	0.921
Tac			
Baseline	17 (70.8)	12 (66.7)	0.773
1 y post-HTx	17 (70.8)	13 (72.2)	0.921
MMF			
Baseline	24 (100.0)	17 (94.4)	0.243
1 y post-HTx	19 (79.2)	17 (94.4)	0.161
EVL			
Baseline	0 (0.0)	1 (5.6)	0.243
1 y post-HTx	5 (20.8)	1 (5.6)	0.161
Statin at baseline, n (%)	24 (100.0)	18 (100.0)	1.000
Strong statin[a], n (%)	9 (37.5)	6 (33.3)	0.780
High-dose statin[b], n (%)	9 (37.5)	5 (27.8)	0.580
Aggressive statin therapy [c], n (%)	17 (70.8)	11 (61.1)	0.508
Statin at 1 y post-HTx, n (%)	23 (95.8)	18 (100.0)	0.381
Strong statin[a], n (%)	14 (58.3)	6 (33.3)	0.108
High-dose statin[b], n (%)	8 (33.3)	8 (44.4)	0.463
Aggressive statin therapy[c], n (%)	19 (79.2)	12 (66.7)	0.463

Data are expressed as number of subjects (%).
[a] Strong statins include atorvastatin, rosuvastatin, and pitavastatin.
[b] High-dose statins include doses of at least 20 mg/d for pravastatin or atorvastatin, 5 mg/d for rosuvastatin, and 4 mg/d for pitavastatin.
[c] Aggressive statin therapy was defined as[1]: strong statin use, or[2] high-dose pravastatin use.

Table 5. In the DA group, a significant reduction in vessel volume was observed ($P = 0.033$), leading to reduced luminal volume 3 years post-HTx ($P = 0.022$). In the DA-free group, there were no significant differences in any IVUS data between 1 and 3 years post-HTx.

Regarding the angiographic severity of CAV, CAV 2 or more was not observed at 3 years post-HTx. The incidence of angiographic CAV at any coronary artery was higher in the DA group than in the DA-free group at 1 and 3 years post-HTx ($P = 0.007$ and $P = 0.027$). There was no significant difference in the incidence of angiographic new or progressive CAV between the 2 groups.

The DA group was more likely to be converted to EVL from MMF by 3 years post-HTx (9 recipients [47.4%] in the DA group vs. 3 [18.8%] in the DA-free group) (**Table S2, SDC,** http://links.lww.com/TP/B306), although the difference was not significant ($P = 0.076$). Five recipients (3 in the DA group and 2 in the DA-free group) were switched from MMF to EVL due to CAV progression from 1 to 3 years post-HTx. The use of statin therapies was comparable between the 2 groups.

Clinical Prognosis

No study subjects died at a mean follow-up period of 6.2 ± 4.3 years post-HTx. Two DA recipients underwent revascularization, 1 underwent percutaneous coronary intervention at 6.5 years post HTx and the other underwent coronary artery bypass grafting at 4.1 years post HTx due to severe coronary artery narrowing.

DISCUSSION

In this evaluation of the impact of DA on early and mid-term CAV progression using serial 3D-IVUS analysis, we found that the presence of DA was associated with a greater increase in percent plaque volume and in plaque volume at the end of the first post-HTx year. Luminal volume in the DA group appeared to continue decreasing after the first post-HTx year, mainly due to shrinkage of vessel volume. Our results show that recipients with DA had more severe disease from baseline IVUS, and may have had subsequent worsening of morphological changes on IVUS several years after HTx. This may have resulted in a higher incidence of angiographic CAV at 3 years post-HTx in the DA patients. These findings suggest that recipients with DA at baseline IVUS may require early aggressive treatment to prevent the subsequent CAV progression.

This study mainly focused on the change in percent plaque volume as the parameter for evaluating CAV progression. Because the development of CAV is suggested to be affected by vessel remodeling in relation to intimal change as well as intimal thickness,[14,27,28] change in MIT alone may not be fully sensitive in the detection of CAV progression. Given that volumetric IVUS findings reflects both change in intima and vessel remodeling in the entire coronary artery, it may be a more sensitive parameter for evaluating CAV development.[14]

In their multicenter study using 2D-IVUS analysis, Wong et al[9] revealed that the presence of DA (defined as MIT $\geq$ 0.15 mm) did not affect any coronary artery morphological change on IVUS compared with recipients without DA. Li et al[11] serial 2D-IVUS analysis showed that sites with donor lesions (defined as MIT $\geq$ 0.5 mm) did not have a greater increase in intimal area compared with sites without donor lesions during 3 years post-HTx, whereas Yamasaki et al[12] serial 3D-IVUS analysis at the first post-HTx year revealed that the presence of DA (defined as MIT $\geq$ 0.5 mm) was an independent predictor for an increase in plaque volume. Our serial volumetric IVUS study confirmed Yamasaki et al results, and added that the presence of DA may affect subsequent worsening of morphological changes on IVUS after the first post-HTx year.

New immunosuppression regimens have been suggested to affect morphological changes in CAV as well as clinical course.[1] Because the majority (71.4%) of our recipients received Tac, our results may reflect these changes. The cumulative incidence of acute cellular rejection in our study was lower than that in previous studies, at 7.1% in the first post-HTx year in the present study versus 50.2% in Li's study[11] and 34.2% in Yamasaki's study.[12] Because acute cellular rejection is known to correlate with CAV progression,[4,29] it may have masked the impact of DA in the previous studies. Our results suggest a marked impact of DA on CAV progression in recipients with lower rates of acute cellular rejection due to improved immunosuppressive regimens.

More recent studies have also suggested that EVL-based immunosuppression suppresses the development of CAV.[17,19,30] Our present results show that DA was independently associated with worsening of morphological change on IVUS in the first post-HTx year regardless of EVL initiation during this year. Because our recipients seldom received EVL during the first post-HTx year (14.3% of all subjects and 20.8% in the DA group), this observation may be of limited significance. A recent multicenter study

TABLE 3.

IVUS measurements and coronary angiography at baseline and 1 y post-HTx

	DA group, n = 24	DA-free group, n = 18	*P*
Vessel volume, mm^3/mm[a]			
Baseline	13.5 (11.7-14.5)	11.5 (9.3-14.2)	0.053
1 y post-HTx	13.5 (11.0-15.3)	9.7 (8.3-12.7)	0.007
P (baseline vs 1 y)	0.123	0.028	
Plaque volume, mm^3/mm [a]			
Baseline	2.0 (1.0-2.7)	0.6 (0.5-0.7)	<0.001
1 y post-HTx	2.4 (1.3-3.7)	0.6 (0.5-0.7)	<0.001
P (baseline vs 1 y)	<0.001	0.267	
% plaque volume, % [a]			
Baseline	12.0 (7.6-21.7)	4.9 (3.7-6.8)	<0.001
1 y post-HTx	19.8 (10.2-24.1)	6.1 (4.7-7.5)	<0.001
P (baseline vs 1 y)	<0.001	0.035	
Lumen volume, mm^3/mm [a]			
Baseline	10.9 (9.8-13.2)	10.7 (8.8-13.4)	0.594
1 y post-HTx	10.8 (8.6-12.4)	9.2 (8.0-11.5)	0.223
P (baseline vs 1 y)	0.021	0.020	
Incidence of rapidly progressive vasculopathy, n (%)[b]	4 (16.7)	2 (11.1)	0.611
Incidence of greater increase in MIT (≥0.1 mm) at 1 y, n (%)[b]	16 (66.7)	6 (33.3)	0.032
Incidence of paradoxical vessel remodeling, n (%)[b]	14 (58.3)	6 (44.4)	0.372
Coronary angiographic severity of CAV			
CAV 1 at baseline, n (%)[b]	12 (50.0)	1 (5.6)	0.002
Angiographic new and progressive CAV during 1 y post-HTx, n (%)[b]	4 (16.7)	0 (0.0)	0.069
CAV 1 at 1 y post-HTx, n (%)[b]	13 (50.0)	1 (5.6)	0.001
Percent change in IVUS measurement			
Vessel volume, % [c]	–4.2 (–10.8 to 2.5)	–9.8 (–19.2 to 0.4)	0.322
Plaque volume, % [c]	23.3 (6.1-72.5)	6.6 (–11.1 to 26.4)	0.093
% plaque volume, % [d]	4.0 (1.5-6.8)	0.8 (–0.2 to 2.0)	0.010
Lumen volume, % [c]	–9.0 (–19.4 to 0.4)	–13.3 (–20.2 to –1.7)	0.799
Baseline length, mm [a]	50 (36.8-50.0)	47.6 (38.7-50.0)	0.657

Data are expressed as [a] median (IQR) for continuous values and [b] numbers of subjects (%) for categorical values. Rapidly progressive vasculopathy was defined as an increase in MIT >0.5 mm at the first year post-HTx. Paradoxical vessel remodeling was defined as (Δvessel volume/Δplaque volume) < 0. [c] Percent changes for each volumetric IVUS data measure were calculated as: [(volumetric index at 1 year post-HTx-volumetric index at baseline)/(volumetric index at baseline)] × 100%. [d] Change in percent plaque volume was calculated as: percent plaque volume at 1 year post-HTx -percent plaque volume at baseline.

suggested that EVL, but not MMF, suppressed an increase in intimal thickness in the first post-HTx year.[17] Our results suggest that recipients who have DA on the baseline IVUS may require a more aggressive strategy to prevent subsequent CAV progression during the first post-HTx year.[30] Our previous study revealed that conversion to EVL from MMF in the maintenance of heart transplant recipients reduced worsening of morphological changes on

TABLE 4.

Multivariable linear regression analysis for change in percent plaque volume at 1 y post-HTx

	Model 1			Model 2			Model 3		
Variable	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***
DA	0.52	0.14-0.90	0.009	0.52	0.16-0.88	0.005	0.53	0.13-0.94	0.011
Smoking history	0.52	0.08-0.97	0.023	0.52	0.16-0.88	0.013	—	—	—
Donor age	0.02	–0.001 to 0.03	0.073	—	—	Not selected	—	—	—
Male donor	0.38	–0.03 to 0.78	0.071	—	—	Not selected	—	—	—
Aggressive statin therapy at 1 y	0.11	–0.40 to 0.62	0.658	—	—	—	–0.06	–0.51-0.38	0.776
CsA use at baseline	0.11	–0.35 to 0.56	0.630	—	—	—	–0.01	–0.44-0.43	0.969
Switch to EVL during first post-HTx year	–0.14	–0.74 to 0.46	0.647	—	—	—	–0.35	–0.94-0.23	0.230
Recipient age	—	—	—	–0.01	–0.03-0.004	0.128	—	—	—
Male recipient	—	—	—	–0.65	–1.12 to –0.17	0.009	—	—	—

Table shows aggressive statin therapy at 1 y post-HTx, CsA use at baseline, switch to EVL during 1 y post-HTx, recipient age, sex, and associated variables with $P < 0.1$ in model 1 in all clinical characteristics of Table 1 or 2.

Model 1: adjusted for recipient age and recipient sex.

Model 2: multivariate stepwise linear regression, including recipient age, sex, and associated variables with $P < 0.1$ in model 1 (ie, DA, smoking history before HTx and donor age, sex). Recipient age and sex were always included in this model.

Model 3: multivariable regression analysis including DA, aggressive statin therapy at 1 y post-HTx, CsA use at baseline, switch to EVL during 1 y post-HTx.

CI, confidence interval.

TABLE 5.

IVUS measurements and coronary angiography at 1 and 3 y post-HTx

	DA group, n = 19	DA-free group, n = 16	*P*
Vessel volume, mm^3/mm [a]			
1 y post-HTx	13.2 (10.7-15.3)	10.2 (8.7-12.8)	0.043
3 y post-HTx	12.0 (9.9-14.3)	10.7 (8.6-12.3)	0.197
P (1 y vs 3 y)	0.033	0.215	
Plaque volume, mm^3/mm [a]			
1 y post-HTx	1.7 (1.3-3.3)	0.6 (0.6-0.8)	<0.001
3 y post-HTx	2.0 (1.3-3.4)	0.8 (0.4-1.3)	0.004
P (1 y vs 3 y)	0.277	0.121	
% Plaque volume, % [a]			
1 y post-HTx	12.2 (9.5-23.9)	6.1 (4.8-7.4)	<0.001
3 y post-HTx	18.8 (9.0-24.8)	8.1 (4.2-11.9)	0.007
P (1 y vs 3 y)	0.904	0.070	
Lumen volume, mm^3/mm [a]			
1 y post-HTx	11.1 (8.8-12.5)	9.4 (8.3-11.8)	0.289
3 y post-HTx	9.4 (7.9-12.0)	8.5 (7.8-11.4)	0.716
P (1 y vs 3 y)	0.022	0.179	
Incidence of paradoxical vessel remodeling, n (%)[b]	5 (26.3)	7 (43.8)	0.279
Coronary angiographic severity of CAV			
CAV 1 at 1 y post-HTX, n (%)[b]	9 (47.4)	1 (12.5)	0.007
Angiographic new and progressive CAV from 1 to 3 y post-HTx, n (%)[b]	2 (10.5)	1 (5.9)	0.615
CAV at 3 y post-HTx, n (%)[b]	9 (47.4)	2 (12.5)	0.027
Percent change in IVUS measurement			
Vessel volume, % [c]	–7.8 (–17.5 to 8.8)	–2.6 (–8.6 to 2.8)	0.175
Plaque volume, % [c]	–14.8 (–44.8 to 9.4)	19.7 (–33.0 to 70.7)	0.128
% plaque volume, % [d]	–0.3 (–3.7 to 4.8)	1.9 (–1.1 to 4.6)	0.289
Lumen volume, % [c]	–8.4 (–21.5 to 2.3)	–6.1 (–11.9 to 1.6)	0.466

Data are expressed as [a] median (IQR) and [b] numbers of subjects (%) for categorical values. Paradoxical vessel remodeling was defined as (Δvessel volume/Δplaque volume) < 0. [c] Percent changes for each volumetric IVUS data measure were calculated as: [(volumetric index at 3 years post-HTx–volumetric index at 1 year post-HTx)/(volumetric index at 1 year post-HTx)] × 100%. [d] Change in percent plaque volume was calculated as: percent plaque volume at 3 years post–HTx-percent plaque volume at 1 year post-HTx.

IVUS compared with continuing MMF.[19] In our present study, the DA group tended to be converted to EVL from MMF during 3 years post-HTx compared with the DA-free group; nevertheless, the DA group experienced an ongoing reduction in luminal volume after 1 year post-HTx. On the other hand, the observational design of our study might prevent exact understanding of the correlation between EVL initiation and CAV progression after 1 year post-HTx.

The difference in CAV progression between the DA and DA-free groups may be explained by differences in the degree of preexisting endothelial dysfunction in the donor heart. Similar to native coronary artery disease, the development of CAV also begins as a response to endothelial cell injury, resulting in endothelial dysfunction.[27,28] Advanced age is reported to be associated with the impairment of vascular endothelial function in native coronary arteries.[31] Our results also showed that the incidence of DA increases with increasing donor age. This suggests that the presence of DA is a marker of preexisting endothelial cell dysfunction of the transplanted coronary artery.

Assessing the morphological changes in CAV is complex.[32-35] Coronary endothelial dysfunction is thought to lead to both a plaque increase and worsening of vessel remodeling.[28] In their 2D-IVUS analysis, Kobashigawa et al[32] showed that the amount of plaque increase was more than the amount of luminal decrease, suggesting inadequate compensatory dilation during the first post-HTx year. Similarly, in our study, the DA group exhibited significant plaque progression during the first post-HTx year accompanied by inadequate compensatory vessel dilation, which resulted in significant luminal narrowing, and which in turn progressed after the first post-HTx year due to vessel constriction without an increase in plaque. These results support the concept that presence or absence of a plaque increase affects vessel remodeling in the coronary artery, and that this may lead to the difference in morphological changes in IVUS for CAV progression during and after the first post-HTx year.

In their serial 2D-IVUS study, Tsutsui et al[33] reported that early lumen loss on CAV was caused by intimal thickening, while late lumen loss was caused by vessel constriction. Our results showed that the mechanism for lumen loss in the DA group was consistent with that in Tsutsui et al's study. In contrast, morphological changes in CAV in the DA-free group differed from those in the DA group, with early vessel volume shrinkage only. These findings suggest that the presence or absence of DA may affect coronary morphological changes in CAV during the first several years after HTx.

Our study showed that recipients with DA had a higher incidence of angiographic CAV at 3 years post-HTx as compared to those without DA, which may suggest a poor long-term clinical outcome after HTx.[1] In addition, 3 of our recipients with DA, including 1 who was excluded from this study due to revascularization at baseline IVUS, underwent coronary revascularization. On the other hand, the incidence of rapid progressive vasculopathy[24] and paradoxical

vessel remodeling,[25] which are known to be predictive of a poor clinical outcome in HTx recipients, were comparable between the 2 groups. Further long-term observation is needed to clarify the effect of DA on clinical outcomes.

Limitation

Several limitations of our study warrant mention. The study was conducted under a single-center design with a small study sample. Of 42 recipients with paired IVUS data at baseline and the first post-HTx year, 7 recipients had not yet reached 3 years post-HTx when the present retrospective observational study was performed. As recipients in the present study were screened over a 14-year time frame, the inevitable changes in treatment over the 14 years may suggest that the recipients were not well-matched. For example, 7 recipients who underwent HTx before 2004 could not receive EVL during 3 years post-HTx regardless of whether they would have met the criteria for EVL initiation, because we could not use EVL until 2007. A methodological limitation of our IVUS analysis was that we used 2 different IVUS systems during the study period. Although all data collected on both systems were analyzed on 1 analyzer, this device change may have affected our results. Since analyzed length differed across subjects, we used the volumetric index (mm^3/mm) to adjust for these differences, but this length difference might also have affected our results. Although percent plaque volume may be more sensitive and accurate for evaluating the development of CAV, it has not been confirmed whether this parameter is more closely associated with prognosis.

CONCLUSIONS

This volumetric IVUS study suggests that the presence of DA may predict worsening of morphological change on IVUS several years post-HTx. The international organ shortage makes inevitable the acceptance of older donors, and the associated DA. Recipients with DA at baseline IVUS may require early aggressive treatment to prevent subsequent CAV progression.

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