ORIGINAL RESEARCH

# Ischemic Cardiomyopathy is Associated With Coronary Plaque Progression and Higher Event Rate in Patients After Cardiac Transplantation

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***Background*—**Cardiac allograft vasculopathy is the leading cause of graft failure and death in heart transplant (HTx) recipients; however, the association between the etiology of heart failure (ischemic cardiomyopathy [ICM] or non-ICM) that led to HTx and progression of cardiac allograft vasculopathy, and adverse events after HTx has not been explored.

***Methods and Results*—**We retrospectively included 165 HTx patients, who were followed-up with at least 2 virtual histology–intravascular ultrasound examinations after HTx, and grouped them as ICM (n=46) or non-ICM (n=119). Coronary artery plaque volume was analyzed using virtual histology–intravascular ultrasound, and cardiovascular event data—a composite of myocardial infarction, hospitalization for heart failure and arrhythmia, revascularization, retransplantation, and death including cardiovascular death—were collected from the medical records of all study subjects. ICM patients had significantly higher plaque volume at both first ($P$=0.040) and follow-up ($P$=0.015) intravascular ultrasound examinations. After multivariate adjustment for traditional coronary risk factors, ICM was significantly associated with plaque progression (odds ratio 3.10; CI 1.17 to 9.36; $P$=0.023). Ten-year cardiovascular event-free survival was 50% in ICM patients compared with 84% in non-ICM patients (log-rank test $P$=0.003). In multivariate Cox proportional hazard analysis, ICM was significantly associated with a higher event rate after HTx (hazard ratio 2.02; 95% CI 1.01 to 4.00; $P$=0.048).

***Conclusion*—**Our study demonstrates that ischemic etiology of cardiomyopathy prior to HTx may be independently associated with plaque progression and higher event rate after HTx. **(*J Am Heart Assoc*. 2014;3:e001091 doi: 10.1161/JAHA.114.001091)**

**Key Words:** cardiac allograft vasculopathy • ischemic cardiomyopathy • nonischemic cardiomyopathy • plaque progression • virtual histology–intravascular ultrasound

Heart transplantation (HTx) is the definitive treatment for end-stage heart failure due to ischemic cardiomyopathy (ICM) and non-ICM. According to the 28th Adult Heart Transplant Report, non-ICM (53%) is the leading cause of HTx, followed by ICM (38%).[1] Cardiac allograft vasculopathy (CAV) is a unique form of rapidly progressing coronary artery disease (CAD) that develops in HTx recipients. It is characterized by intimal proliferation in the early stages and luminal narrowing in the later stages, ultimately resulting in myocardial ischemia and infarction.[2] CAV is one of the main causes contributing to graft loss and mortality in the early years after HTx. Mortality due to CAV is around 10% between years 1 and 3, and the contribution increases in subsequent years.[3]

Pathogenesis of CAV is complex and heterogeneous. Both immunological and nonimmunological factors play significant roles in endothelial injury and consequent development of CAD. Morphology of coronary artery involvement in CAV is different from that in typical atherosclerosis; however, previous ex vivo histopathological studies and recent intravascular ultrasound (IVUS) studies have described a dichotomous pattern of coronary atherosclerosis in HTx recipients, suggesting that immunological reaction is not the only etiology for CAV. Typical atherosclerosis could be one possible etiology.[4] Both traditional and nontraditional risk factors for CAD contribute to the pathogenesis of CAV.[5] Consequently, in patients with history of ICM, there is a risk of

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potential interaction between the donor-related heart and preexisting coronary risk factors.

In the current study, we hypothesized that ischemic etiology of cardiomyopathy leading to HTx is a risk factor for plaque progression and higher event rate in HTx patients.

## Methods

### Study Patients

Since 2004, IVUS of the left anterior descending coronary artery has been performed for surveillance of CAV in HTx recipients in conjunction with routine annual coronary angiography in the HTx program at the Mayo Clinic in Rochester, Minnesota. Between 2006 and 2011, 214 of 251 HTx recipients (year of HTx 1992–2010), who underwent routine annual coronary angiography, underwent virtual histology–IVUS (VH-IVUS) examinations. Patients were included if they had undergone at least 2 VH-IVUS examinations ≥12 months apart to assess for changes in plaque volume index and other plaque characteristics. Exclusion criteria included patients without follow-up VH-IVUS, those without serial virtual histology data, and those with poor VH-IVUS film qualities (Figure 1). Finally, 165 patients who met the inclusion criteria were enrolled in the study. For patients with >2 VH-IVUS evaluations during the study period, the initial and the last (follow-up) VH-IVUS data were used for analysis. All laboratory tests were performed at the time of initial and follow-up VH-IVUS examinations as part of routine clinical examinations. The study protocol was approved by the Mayo Clinic institutional review board, and written informed consent was obtained from all the study participants.

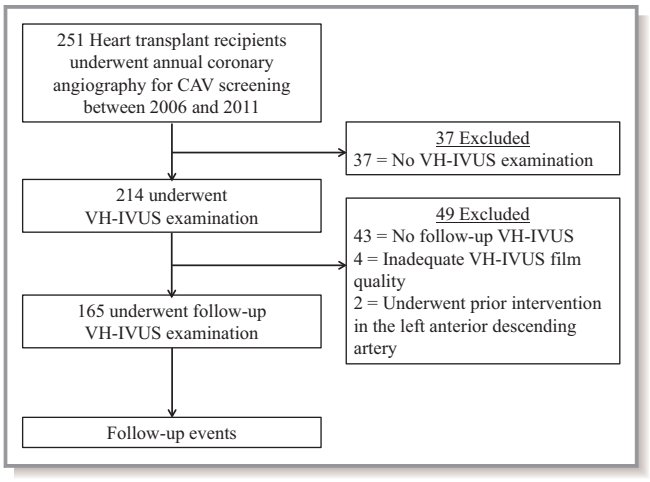


**Figure 1.** Study design. CAV indicates cardiac allograft vasculopathy; VH-IVUS, virtual histology–intravascular ultrasound.

### Definitions of ICM and Non-ICM

All the study patients were grouped as ICM (n=46) or non-ICM (n=119), depending on the etiology for heart failure leading to HTx. ICM was defined as patients with a history of myocardial infarction or revascularization (coronary artery bypass grafting or percutaneous coronary intervention), with >75% stenosis of left main or proximal left anterior descending artery, or with >75% stenosis of ≥2 epicardial vessels.[6] Non-ICM was defined as patients who underwent HTx for end-stage heart failure related to dilated cardiomyopathy, restrictive cardiomyopathy, congenital heart diseases, radiation-induced cardiomyopathy, valvular heart diseases, and eosinophilic cardiomyopathy.

### Immunosuppression Therapy and Rejection Score

Maintenance immunosuppression was a triple therapy regimen with calcineurin inhibitors, proliferation signal inhibitors[7,8] and azathioprine, or mycophenolate mofetil and prednisone. Routine endomyocardial biopsies were performed as recommended after HTx beginning 1 week after completion of the induction therapy with low-dose OKT3 (Orthoclone OKT3, Janssen-Cilag) or antithymocyte globulin. Based on the International Society for Heart and Lung Transplant (ISHLT) R grading system, each biopsy result was graded as 0R=0, 1R=1, 2R=2, and 3R=3.[9]

### Clinical and Demographic Data

Data collection included patient demographics (age, sex, height, and weight), donor age, CAD risk factors (hypertension, diabetes mellitus, dyslipidemia, and current smoking history), dates of IVUS procedures, and current medications. Blood pressure, cholesterol levels, blood glucose, glomerular filtration rate, and creatinine levels were also recorded. MDRD (Modification of Diet in Renal Disease) glomerular filtration rate (shown as GFR; creatinine shown as Cr) was calculated using the following formula: $GFR = 175 \times Serum\text{-}Cr^{-1.154} \times age^{-0.203} \times 1.212$ (if patient is black) $\times 0.742$ (if patient is female).[10]

### Intravascular Ultrasound Image Acquisition and Analyses

VH-IVUS examinations were performed using a 20-MHz, 2.9F phased-array IVUS catheter (Eagle Eye Gold; Volcano Corp). After intracoronary administration of 100 to 200 μg of nitroglycerin, the transducer was placed distally using a fiduciary side branch as the starting point. Automated pull back was performed at the rate of 0.5 mm/s up to the coronary ostium. Electrocardiography-gated gray-scale IVUS images and radiofrequency data were acquired at the peak of

the R-wave. Offline volumetric reconstruction was performed using Volcano Image Analysis software (version 3.1 or pcVH version 2.2; Volcano Corp) by 2 experienced observers blinded to patients' baseline characteristics. From the images acquired at initial IVUS, 3 or 4 matched coronary segments of the left anterior descending coronary artery were determined, and follow-up studies were performed on the basis of the fiducial location of distal and proximal major side branches. The length of the segment was assessed as the distance between these 2 side branches. Vessel (external elastic lamina) and lumen borders were manually contoured for all recorded frames in each coronary segment. Quantitative IVUS measurements included vessel volume, lumen volume, plaque volume (vessel−lumen), and percentage of plaque burden (plaque volume/vessel volume×100). Radiofrequency IVUS plaque components were color coded and reported as absolute plaque volume of VH-IVUS parameters (fibrous [dark green], fibrofatty [light green], necrotic core [red], and dense calcium [white]) to assess for plaque composition.[11] This approach has been validated with histological techniques in clinical studies.[12] Simpson's rule for volumetric measurements was used. To compensate for the different segment length of each analyzed artery, all volumetric data were divided by segment length and were shown as volume index ($mm^3$/mm).[13] Similarly, to compensate for variations in follow-up period, the change in plaque volume index was normalized for the length of the follow-up period.[13] Plaque progression was defined as a positive value of change in plaque volume index divided by the number of years of follow-up (a negative value was defined as plaque regression). The segment with the largest change in plaque volume index from the initial IVUS to follow-up at any matched site was used for the analysis for each patient. In a previous report, we assessed interobserver variability for virtual histology compositional data in transplant recipients.[14]

## Coronary Angiography

Based on the ISHLT guidelines, CAV was classified by coronary angiography as follows: $CAV_0$ (not significant) indicates no detectable angiographic lesion; $CAV_1$ (mild) indicates angiographic left main <50%, primary vessel with a maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction; $CAV_2$ (moderate) indicates angiographic left main <50%, a single primary vessel >70%, or isolated branch stenosis >70% in branches of 2 systems without allograft dysfunction; and $CAV_3$ (severe) indicates angiographic left main >50%, ≥2 primary vessels with >70% stenosis, isolated branch stenosis >70% in all 3 systems, or $CAV_1$ or $CAV_2$ with allograft dysfunction (defined as left ventricular ejection fraction <45%, usually in the presence of regional wall motion abnormalities).[15]

## Follow-Up Event Data

Clinical follow-up data were obtained retrospectively from patient medical records as of September 2013. The cause of death was determined by review of medical records and death certificates. Outcome data included myocardial infarction, unstable angina, hospitalization due to heart failure and arrhythmias (ventricular tachycardia, ventricular fibrillation, atrial fibrillation, and symptomatic bradycardia requiring pacemaker insertion), revascularization, retransplantation, cardiovascular (CV) death, and all-cause death. Overall outcome was defined as a combination of all of the above-mentioned outcomes.

## Statistical Analysis

All statistical analyses were performed independently using JMP 9 software (SAS Institute, Inc) by a statistician who was unaware of the study design. Continuous variables were expressed as median with interquartile range or mean±SD, as appropriate. Categorical variables were expressed in numbers and percentages. All hypotheses tested were 2-sided, and a $P$ value of <0.05 was considered statistically significant. Comparisons between 2 groups were performed using the Student $t$ test, Fisher's exact test, or the chi-square test, as appropriate. Wilcoxon signed-rank test was used to compare the changes of IVUS parameters between the initial and follow-up examinations. Univariate logistic regression analysis was performed to assess the association of all clinical variables, including ICM or non-ICM that can potentially affect plaque progression. Odds ratios were computed accordingly. To account for the confounding variables, propensity score adjustment was also performed for each patient using a logistic regression model in which the dependent variable was ICM or non-ICM and the independent variables were recipient age, sex, donor age, year of transplant, obesity, hypertension, diabetes mellitus, dyslipidemia, smoking, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, initial plaque volume index, and therapy for rejection. To further delineate the association of each studied variable on plaque progression, multivariate logistic regression analyses were performed using traditional CAD risk factors and time of HTx as independent variables, including ICM or non-ICM, and propensity score adjustment was performed.

Time-to-event data are represented by Kaplan-Meier estimates and compared between the 2 groups by means with the log-rank test. Univariate Cox proportional hazards analysis was performed to determine the association between clinical variables, including ICM and outcome. Factors that remained significant in univariate analysis and time of HTx were later entered into multivariate models to determine independence of association. Hazard ratios were calculated accordingly.

# Results

## Baseline Patient Characteristics

Table 1 summarizes baseline patient characteristics according to ICM or non-ICM. Patients in the ICM group were relatively older than those in the non-ICM group ($P<0.0001$), and 87% of the subjects in the ICM group were male compared with 66% in the non-ICM group ($P=0.006$). The ICM group had more frequent hypertension and diabetes mellitus and lower levels of high-density lipoprotein cholesterol (Table 1). Immunosuppressant and adjuvant drug use was comparable between both patient groups except for calcium channel blockers. During clinical follow-up, 22% of the patients in the ICM group were treated for significant biopsy-proven rejection compared with 14% in the non-ICM group ($P=0.246$).

On coronary angiography, 26 subjects (58%) were graded as having $CAV_0$, 16 (36%) were graded as having $CAV_1$, 2 (4%) were graded as having $CAV_2$ and 1 (2%) was graded as having $CAV_3$ in the ICM group. Similarly, in the non-ICM group, 80 (67%) were graded as having $CAV_0$, 35 (29%) were graded as having $CAV_1$, 3 (3%) were graded as having $CAV_2$, and 1 (1%) was graded as having $CAV_3$. No significant differences were observed between the groups with respect to angiographic CAV at the time of initial IVUS ($P=0.6$).

**Table 1.** Patient Characteristics

| Variable | ICM (n=46) | Non-ICM (n=119) | *P* Value |
|---|---|---|---|
| Recipient age, y | 60.1±7.8 | 51.1±13.6 | <0.0001 |
| Donor age, y | 33.0±13.9 | 29.8±13.7 | 0.164 |
| Male sex | 40 (87) | 78 (66) | 0.006* |
| BMI, kg/m$^2$ | 27.8±5.3 | 26.9±5.2 | 0.322 |
| Hypertension | 40 (87) | 86 (72.3) | 0.047* |
| Diabetes mellitus | 20 (43.5) | 23 (19.3) | 0.002* |
| Current smoking | 3 (6.5) | 4 (3.4) | 0.366 |
| Total cholesterol, mg/dL | 186.5 (163.8, 221) | 186 (160, 220) | 0.979 |
| Triglycerides, mg/dL | 167.5 (115.5, 209.3) | 135 (104, 193) | 0.149 |
| LDL-C, mg/dL | 107.8±32.5 | 105±37.6 | 0.449 |
| HDL-C, mg/dL | 50.5±17.8 | 57.2±17.5 | 0.022* |
| Cr, mg/dL | 1.4 (1.1, 1.7) | 1.3 (1.1, 1.5) | 0.170 |
| GFR, mL/min | 54.8±18.7 | 55.3±17.2 | 0.234 |
| Ischemic time, min | 174.4±48.4 | 171.8±49.3 | 0.320 |
| Rejection requiring therapy | 10 (21.7) | 17 (14.3) | 0.246 |
| Baseline drugs | | | |
| Sirolimus | 24 (52) | 54 (45) | 0.433 |
| Cyclosporin A | 18 (39) | 48 (40) | 0.887 |
| Tacrolimus | 5 (11) | 22 (19) | 0.236 |
| Azathioprine | 14 (30) | 38 (32) | 0.853 |
| MMF | 31 (67) | 76 (64) | 0.671 |
| ASA | 16 (35) | 31 (26) | 0.265 |
| CCBs | 18 (39) | 25 (21) | 0.017* |
| ACE inhibitors | 21 (46) | 42 (35) | 0.219 |
| Beta blockers | 9 (20) | 16 (14) | 0.326 |
| Diuretics | 20 (44) | 55 (46) | 0.751 |
| Statins | 40 (87) | 102 (86) | 0.836 |
| Warfarin | 4 (9) | 8 (7) | 0.662 |

ACE indicates angiotensin-converting enzyme; ASA, acetyl salicylic acid; BMI, body mass index; CCBs, calcium channel blockers; Cr, creatinine; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; ICM, ischemic cardiomyopathy; LDL-C, low-density lipoprotein cholesterol; MMF, mycophenolate mofetil; non-ICM, nonischemic cardiomyopathy.
*$P<0.05$. Data are expressed as median (interquartile range), mean±SD, or number (%).

## IVUS Results

Table 2 shows initial and follow-up VH-IVUS data for all study subjects. Median time to first IVUS since HTx and follow-up durations in both ICM and non-ICM groups were comparable. At initial IVUS, patients in the ICM group had a significantly higher plaque volume index compared with those in the non-ICM group (4.3 $mm^3$/mm [range 3.4 to 7.6 $mm^3$/mm] versus 3.8 $mm^3$/mm [range 2.6 to 5.8 $mm^3$/mm], $P$=0.040; Table 2 and Figure 2). Similar findings were observed at follow-up IVUS examination (6.5 $mm^3$/mm [range 4.5 to 9.4 $mm^3$/mm] versus 4.7 $mm^3$/mm [range 3.1 to 7.2 $mm^3$/mm], $P$=0.015; Table 2 and Figure 2). In addition, for the observed follow-up duration, change in plaque volume index was higher in the ICM group, with borderline significance, indicating a slightly higher plaque progression rate in this patient population (1.1 $mm^3$/mm [range 0.4 to 1.8 $mm^3$/mm] versus 0.5 $mm^3$/mm [range −0.1 to 1.6 $mm^3$/mm], $P$=0.063; Table 2 and Figure 2). In VH-IVUS data analyses, no significant differences were present between the groups with respect to plaque characteristics at first IVUS. For follow-up data, however, patients in the ICM group had significantly higher necrotic core ($P$=0.010), dense calcium ($P$=0.047), and fibrous tissue ($P$=0.014) compared with patients in the non-ICM group.

A subgroup analysis was performed to assess yearly patterns in initial plaque volume index within the first 5 years (Figure 3). Patients were divided into 4 groups based on their time-to-initial IVUS duration: 0 to 1 year, 1 to 2 years, 2 to 3 years, and 3 to 5 years. ICM patients within the 2- to 3-year time-to-initial IVUS group had a significantly higher initial plaque volume index compared with patients in the non-ICM group ($P$=0.002). In addition, patients with ICM in the 1- to 2-year and 3- to 5-year groups had nonsignificantly higher initial plaque volume indices than non-ICM patients ($P$=0.17 and $P$=0.17, respectively; Figure 3).

Analysis was performed to determine the prevalence of plaque progression, defined as Δ plaque volume index divided by years of follow-up, in both groups. For the observed

**Table 2.** Initial and Follow-up Virtual Histology–IVUS Data

| | ICM (n=46) | Non-ICM (n=119) | *P* Value |
|---|---|---|---|
| Time to initial IVUS, y | 2.3 (1.1, 6.3) | 2.9 (1.0, 7.0) | 0.955 |
| Follow-up duration, y | 2.9 (1.2, 3.9) | 2.7 (1.9, 3.3) | 0.907 |
| Plaque volume index, $mm^3$/mm | | | |
| Initial plaque volume index | 4.3 (3.4, 7.6) | 3.8 (2.6, 5.8) | 0.040* |
| Follow-up plaque volume index | 6.5 (4.5, 9.4) | 4.7 (3.1, 7.2) | 0.015* |
| Δ Plaque volume index | 1.1 (0.4, 1.8) | 0.5 (−0.1, 1.6) | 0.063 |
| Necrotic core index, $mm^3$/mm | | | |
| Initial NC index | 0.15 (0.01, 0.78) | 0.06 (0, 0.36) | 0.058 |
| Follow-up NC index | 0.72 (0.13, 1.35) | 0.2 (0, 0.84) | 0.010* |
| Δ NC index | 0.38±0.61 | 0.32±0.77 | 0.230 |
| Dense calcium index, $mm^3$/mm | | | |
| Initial DC index | 0.02 (0, 0.27) | 0.01 (0, 0.11) | 0.375 |
| Follow-up DC index | 0.09 (0, 0.5) | 0.02 (0, 0.26) | 0.047* |
| Δ DC index | 0.17±0.4 | 0.11±0.31 | 0.097 |
| Fibrous index, $mm^3$/mm | | | |
| Initial FI index | 0.59 (0.07, 2.31) | 0.48 (0.03, 1.48) | 0.209 |
| Follow-up FI index | 1.7 (0.54, 3.05) | 0.89 (0.13, 2.12) | 0.014* |
| Δ FI index | 0.61±1.1 | 0.68±3.4 | 0.120 |
| Fibrofatty index, $mm^3$/mm | | | |
| Initial FF index | 0.06 (0, 0.32) | 0.07 (0, 0.18) | 0.444 |
| Follow-up FF index | 0.19 (0.03, 0.41) | 0.10 (0.01, 0.25) | 0.060 |
| Δ FF index | 0±0.34 | 0±0.54 | 0.889 |

All data are expressed as volume per length of the artery analyzed ($mm^3$/mm). DC indicates dense calcium; FF, fibrofatty; FI, fibrous; ICM, ischemic cardiomyopathy; IVUS, virtual histology-intravascular ultrasound; NC, necrotic core; non-ICM, nonischemic cardiomyopathy; Δ, difference.
*$P$<0.05. Data are expressed as median (interquartile range) or mean±SD.

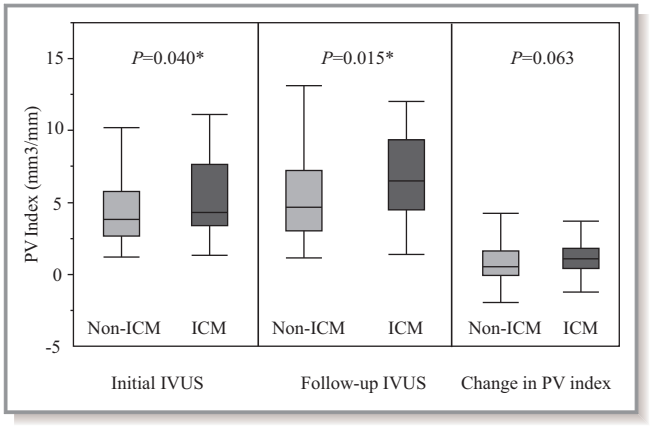


**Figure 2.** Initial and follow-up plaque volume indices. ICM group patients had significantly higher initial and follow-up plaque volume indices compared with non-ICM patients. ICM indicates ischemic cardiomyopathy; non-ICM, nonischemic cardiomyopathy; IVUS, intravascular ultrasound; PV, plaque volume.

follow-up duration of 2.9 years and 2.7 years, respectively, 40 of 46 patients (87%) in the ICM group had plaque progression compared with 71% (n=85) in the non-ICM group (*P*=0.04). In univariate logistic regression analysis (Table 3), ICM was significantly associated with plaque progression (*P*=0.029). Multivariate logistic regression analysis was performed to further delineate the association of ICM with the prevalence of plaque progression; traditional risk factors and ICM were entered as independent variables, and plaque progression was entered as a dependent variable. After adjustment, ICM was significantly associated with plaque progression (odds ratio 3.10, 95% CI 1.17 to 9.36, *P*=0.023; Table 3). Similarly, in the multivariate analysis model using propensity score adjustment, ICM was significantly associated with plaque progression (odds ratio 3.03; 95% CI 1.12 to 9.37, *P*=0.029).

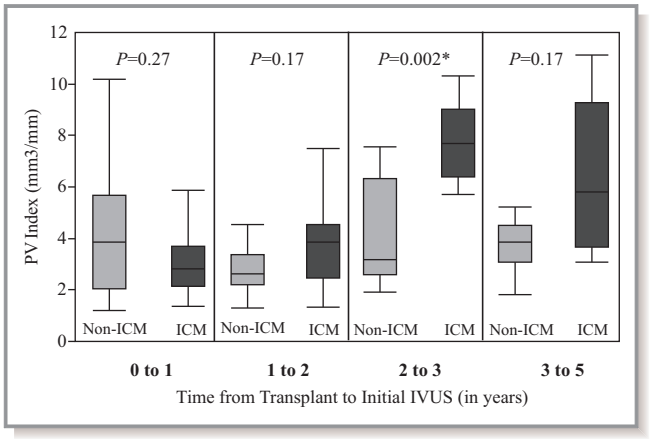


**Figure 3.** Subgroup analysis of year-by-year initial PV index. Patients with ICM in the subgroup with time-to-first IVUS between 2 and 3 years had significantly greater initial PV index than those in the non-ICM group (*P*=0.002). **P*<0.05. ICM indicates ischemic cardiomyopathy; non-ICM, nonischemic cardiomyopathy; IVUS, intravascular ultrasound; PV, plaque volume.

## Follow-Up Event Data Results

Mean duration of follow-up was 7.4±4.0 years in the ICM group and 8.9±4.8 years in the non-ICM group. Relatively greater number of ICM patients had events compared with those in the non-ICM group (35% versus 16%, *P*=0.019; Table 4). Within this event group, ICM patients had significantly greater necrotic core index ($mm^3$/mm) at both initial (*P*<0.05) and follow-up (*P*=0.030) IVUS examinations. Kaplan–Meier fraction (Figure 4) of survival at 10 years after HTx was 84% in the non-ICM group compared with 50% in the ICM group (log-rank test, *P*=0.003). In univariate Cox proportional hazards analysis, donor age, smoking, initial plaque volume index, and ICM were significantly associated with higher event rates (Table 5). In multivariate analysis, after adjustment for the above-listed variables and time of HTx, ICM, along with older donor age (*P*=0.012), was significantly associated with higher event rate after HTx (hazard ratio 2.02, 95% CI 1.01 to 4.00, *P*=0.048; Table 5).

## Discussion

The current study demonstrates that, compared with non-ICM patients, more patients in the ICM group had plaque progression and follow-up events. ICM patients had significantly greater plaque volume index at initial and follow-up VH-IVUS examinations. Our data show that ICM is independently associated with plaque progression, especially within the first 3 years after transplantation. In addition, 10 years of CV event-free survival was significantly lower in this group.

The current study indicates a differential mechanism for CAV and may have significant implications for its diagnostic evaluation and treatment. The findings from this study suggest that prior history of ischemic heart disease leading to heart failure and HTx is associated with increased risk of future coronary atherosclerosis and CV events including death. Mere replacement of a recipient heart with a new donor heart may not eliminate the systemic factors associated with disease progression in these patients. Consequently, such patients may have to be considered for close monitoring and more rigorous risk-factor control.

## Risk Factors for Coronary Artery Disease

Risk factors for CAD can be classified into causal, conditional, and predisposing. The major causal risk factors are smoking, high blood pressure, low high-density lipoprotein cholesterol,

**Table 3.** Univariate and Multivariate Logistic Regression Analysis for Plaque Progression (Adjusting for Traditional Risk Factors)

| Variable | OR [95% CI] | *P* Value | OR [95% CI] | *P* Value |
|---|---|---|---|---|
| Age, for 1 year increase | 1.01 [0.98 to 1.03] | 0.729 | 0.99 [0.96 to 1.02] | 0.68 |
| Male sex | 1.01 [0.98 to 1.04] | 0.154 | 1.48 [0.64 to 3.37] | 0.35 |
| Donor age, for 1 year increase | 1.01 [0.98 to 1.04] | 0.583 | | |
| Obesity | 1.56 [0.65 to 4.14] | 0.329 | | |
| Hypertension | 0.49 [0.17 to 1.21] | 0.126 | 0.46 [0.15 to 1.25] | 0.13 |
| Diabetes mellitus | 1.56 [0.68 to 3.92] | 0.306 | 1.41 [0.56 to 3.80] | 0.47 |
| Dyslipidemia | 0.37 [0.10 to 1.02] | 0.054 | 0.35 [0.22 to 1.07] | 0.067 |
| Smoking | 1.97 [0.32 to 37.72] | 0.507 | 1.55 [0.22 to 31.43] | 0.69 |
| Total cholesterol, for 1 mg/dL increase | 1.00 [0.99 to 1.01] | 0.967 | | |
| Triglycerides, for 1 mg/dL increase | 1.00 [0.99 to 1.01] | 0.973 | | |
| LDL-C, for 1 mg/dL increase | 1.00 [0.99 to 1.01] | 0.995 | | |
| HDL-C, for 1 mg/dL increase | 1.00 [0.98 to 1.02] | 0.891 | | |
| Rejection requiring therapy | 1.50 [0.56 to 4.73] | 0.437 | | |
| Ischemic time, for 1 minute increase | 1.00 [0.99 to 1.00] | 0.405 | | |
| Time of HTx, for 1 quartile increase | 0.78 [0.56 to 1.07] | 0.13 | 0.70 [0.49 to 0.98] | 0.036* |
| ICM | 2.67 [1.10 to 7.56] | 0.029* | 3.10 [1.17 to 9.36] | 0.023* |

Time of HTx was treated as a continuous variable. CI indicates confidence interval; HDL-C, high-density lipoprotein cholesterol; HTx, heart transplantation; ICM, ischemic cardiomyopathy; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.
*$P<0.05$.

elevated serum cholesterol, and high blood glucose[16]; however, causal risk factors do not always explain the progression of coronary atherosclerotic disease. Studies have shown that conditional and predisposing factors also contribute to atherosclerosis and CAD.[17,18] Such factors include chronic inflammatory diseases (lupus, rheumatoid arthritis), high-sensitivity C-reactive protein, chronic end-stage renal disease, metabolic syndrome, microalbuminuria, HIV infection, elevated fibrinogen, lipoprotein A, depression, socioeconomic status, physical inactivity, family history of premature CAD, insulin resistance, and obesity.[19–22] In patients with ICM, few or many of these systemic factors may act concomitantly to cause end-stage heart failure. Atherosclerotic vascular disease is a systemic disease; after HTx, these systemic factors might still contribute to progression of atherosclerotic processes in the graft coronary arteries, leading to CAV.

**Table 4.** Follow-Up Event Data

| | ICM (n=46) | Non-ICM (n=119) | Total | *P* Value |
|---|---|---|---|---|
| Patients | 16 (35) | 19 (16) | 35 (21) | 0.019* |
| Time to first event, y (range) | 5.4 (4.1 to 8.5) | 6.5 (1.7 to 11.2) | 7.6 (4.7 to 11.2) | 0.762 |
| Myocardial infarction | 1 (2) | 1 (1) | 2 (1) | 1.000 |
| Hospitalization for HF | 5 (11) | 10 (8) | 15 (9) | 0.320 |
| Hospitalization for arrhythmia | 6 (13) | 5 (4) | 11 (7) | 0.483 |
| Revascularization | 4 (9) | 6 (5) | 10 (6) | 0.739 |
| Retransplantation | 1 (2) | 1 (1) | 2 (1) | 1.000 |
| CV death | 0 (0) | 2 (2) | 2 (1) | 0.193 |
| All-cause death | 2 (4) | 7 (6) | 9 (6) | 0.121 |
| Total events per number of subjects (%) | 41 | 27 | 31 | |

CV indicates cardiovascular; HF, heart failure; ICM, ischemic cardiomyopathy; Non-ICM, nonischemic cardiomyopathy.
*$P<0.05$. Data are expressed as n (%) except as otherwise noted.

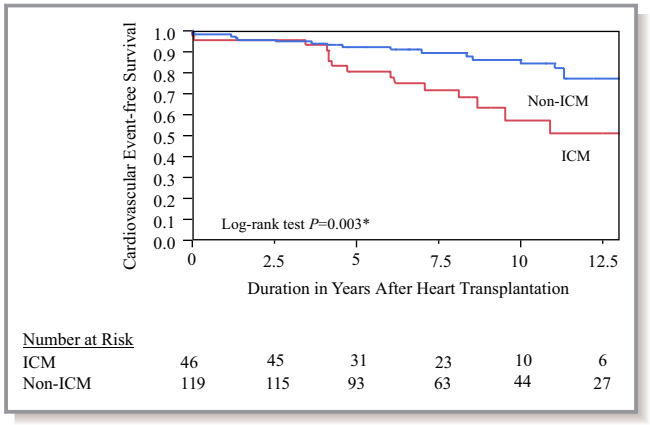


**Figure 4.** Kaplan–Meier survival curves. Ten-year cardiovascular event–free survival after HTx was 50% in the ICM group vs 84% in patients in the non-ICM group (log-rank test, $P$=0.003). *$P$<0.05. HTx indicates heart transplantation; ICM, ischemic cardiomyopathy; non-ICM, nonischemic cardiomyopathy; IVUS, intravascular ultrasound.

## Potential Mechanisms for Accelerated CAV in Patients With Ischemic Cardiomyopathy

CAV can develop at any stage after HTx with incidence of around 7% within the first year and increasing up to 50% within 10 years.[5] Pathophysiology of CAV is very complex. It appears to result from a complex interplay between immunologic and nonimmunologic factors, leading to repetitive vascular injury and a localized sustained inflammatory response. Immunologically mediated injury to the vascular endothelium appears to be important in the pathogenesis of CAV, especially during the first year after transplantation.[23] With multiple coexisting systemic risk factors for CAD, patients with HTx for ICM may be at increased risk of plaque progression and subsequent CAV than patients who had HTx for non-ICM.

Many epidemiological studies have shown a significant association between elevated high-sensitivity C-reactive protein levels and the risk of adverse CV events in patients with established CAD.[24] Studies from our group and others have shown that patients with subsequent graft failure and angiographic evidence of CAV have significantly elevated serum high-sensitivity C-reactive protein levels compared with other patients. In addition, elevated high-sensitivity C-reactive protein is an independent predictor of adverse cardiac events in transplant patients.[25–27]

Lipoprotein-associated phospholipase A2 (Lp-PLA2), a member of the phospholipase family and a proatherogenic inflammatory enzyme, is a specific marker of vascular inflammation, coronary endothelial dysfunction, and atherosclerosis.[28] Studies in nontransplant subjects have shown that elevated circulating levels of Lp-PLA2 are associated with higher risk of CAD and vascular mortality.[29] Previously, our group demonstrated that elevated levels of Lp-PLA2 independently predict progression of CAV and increased risk of CV events, including CV death, in HTx subjects.[30] We also reported that patients who underwent transplantation for ICM had higher serum Lp-PLA2 levels than patients who underwent transplantation for other reasons. This suggests that the association between elevated Lp-PLA2 and CV risk is carried forward even after HTx, contributing to pathogenesis and progression of CAV and adverse outcomes.

Periodically occurring asymptomatic mural thrombosis followed by healing has been proposed as a mechanism of plaque

**Table 5.** Univariate and Multivariate Cox Proportional Hazard Test for Follow-up Events

| | Unadjusted HR [95% CI] | *P* Value | Adjusted HR [95% CI] | *P* Value |
|---|---|---|---|---|
| Age, for 1 year increase | 1.008 [0.986 to 1.034] | 0.477 | | |
| Male sex | 1.402 [0.668 to 3.301] | 0.387 | | |
| Donor age, for 1 year increase | 1.039 [1.016 to 1.062] | <0.001* | 1.034 [1.007 to 1.059] | 0.012* |
| Obesity | 1.560 [0.736 to 3.095] | 0.235 | | |
| Hypertension | 1.105 [0.527 to 2.601] | 0.801 | | |
| Diabetes mellitus | 1.763 [0.849 to 3.473] | 0.124 | | |
| Dyslipidemia | 1.009 [0.448 to 2.699] | 0.984 | | |
| Smoking | 4.308 [1.019 to 12.43] | 0.048* | 4.083 [0.956 to 12.045] | 0.057 |
| Initial plaque volume index, for 1 $mm^3$/mm increase | 1.171 [1.032 to 1.322] | 0.015* | 1.056 [0.912 to 1.213] | 0.46 |
| Rejection requiring therapy | 1.864 [0.827 to 3.818] | 0.126 | | |
| Time of HTx, for 1 quartile increase | 1.129 [0.813 to 1.559] | 0.47 | 1.084 [0.912 to 1.214] | 0.64 |
| ICM | 2.599 [1.322 to 5.030] | 0.006* | 2.023 [1.007 to 3.999] | 0.048* |

Time of HTx was treated as a continuous variable. HR indicates hazard ratios; HTx, heart transplantation; ICM, ischemic cardiomyopathy.
*$P$<0.05. Data are expressed as hazard ratio (95% confidence interval).

progression in non-HTx CAD patients.[31] Similar findings were demonstrated by Matsuo et al in a retrospective IVUS study in HTx recipients; the authors also reported that multilayer appearance is not uncommon in asymptomatic HTx recipients and that this finding is more frequently observed in ICM patients than in non-ICM patients.[13] Patients with multilayer appearance on IVUS had higher rates of plaque progression than those without, suggesting that repeated episodes of mural thrombosis may contribute to the pathogenesis of CAV in ICM patients, especially in the early post-HTx phase.

Our current study demonstrates that at follow-up VH-IVUS, patients with ICM had significantly higher necrotic core, dense calcium, and fibrous and borderline high fibrofatty components in the plaques. Higher necrotic core and dense calcium are characteristics of vulnerable plaques (thin-cap fibroatheromas).[14] Such virtual histology–derived thin-cap fibroatheromas have been found more frequently in patients with acute coronary syndromes than those with stable angina.[32] Significantly higher necrotic core and dense calcium in patients with history of ICM in our study suggest that these patients may be at high risk for developing severe CAV.

## Therapeutic Standpoint

### *Diagnosis*

Currently the ISHLT recommends yearly coronary angiography as the imaging modality of choice to detect CAV.[33] However, the diffuse nature of CAV limits diagnostic accuracy of coronary angiography, and IVUS is now considered the gold standard for the evaluation of CAV.[2,34] Intimal changes, especially in early CAV, are best detected by IVUS.[35] Previous histopathological and IVUS studies have shown that mean intimal thickness of >0.3 mm is an independent risk factor for poor prognosis in HTx subjects.[36] Using VH-IVUS or optical coherence tomography, it is possible to accurately assess the full extent of atherosclerotic pathology, including vulnerable plaque characteristics.[37,38] In our current study, ICM patients had higher plaque volume index in the early years after transplantation. Consequently, in the early post-HTx period, use of VH-IVUS or optical coherence tomography as the routine imaging modality of choice in these patients, in addition to coronary angiography, may allow timely alterations in medical therapy and prevent disease progression to the stage at which revascularization or retransplantation is required.[8,39,40]

### *Treatment*

The definitive treatment for CAV is retransplantation; however, primary prevention by aggressive risk-factor modification and use of superior immunosuppressive agents can slow the progression of CAV. Proliferation signal inhibitors such as sirolimus and everolimus have shown promising results in attenuating CAV progression by reducing intimal hyperplasia. Consequently, in high-risk patients such as those with prior ICM, sirolimus or everolimus as primary immunosuppressants may prove beneficial if considered early after HTx.[7,8,39]

In our study, only one third of all the study subjects received aspirin after HTx (35% in the ICM group versus 26% in the non-ICM group). Multilayer appearance on IVUS is indicative of repeated episodes of thrombosis followed by healing, and such plaques are at increased risk of rupture.[13] Routine use of antiplatelet therapy may play a significant role in halting this process and, therefore, progression to CAV; however, the role of antiplatelet therapy as part of a primary preventive treatment strategy in CAV, especially in ICM patients, needs to be evaluated in large-scale multicenter randomized trials. Lp-PLA2 is another potential therapeutic target in these patients. Currently, phase II studies evaluating the therapeutic potential of Lp-PLA2 inhibition in posttransplant patients are under way.

## Limitations

Our current investigation has several limitations. First, lack of a baseline IVUS examination immediately after HTx limits accurate assessment of the temporal relationship between clinical variables and plaque progression. Second, because this study included only patients who underwent repeated IVUS examinations, inherent selection bias is a potential limitation. We lack data on patients who underwent only 1 VH-IVUS examination and those who did not undergo any VH-IVUS examinations; therefore, the results of our study should be interpreted with caution. That said, the 28th Adult Heart Transplant Report noted that ICM is a significant risk factor for increased mortality in HTx recipients.[1] Our study findings also suggest that ICM may be an important risk factor for overall CV outcome. Third, the findings of this study are based on examination of one particular segment of left anterior descending coronary artery that serves as a representative of the entire coronary vascular bed. Other arteries of the coronary tree were not assessed for plaque volume and plaque characteristics. In CAV, the morphology of coronary artery involvement tends to be diffuse[41]; therefore, we assumed that other arteries will exhibit similar behavior. Finally, this is a single-center retrospective study involving a small sample, and the results are subject to the shortcomings of all single-center studies. Consequently, the results should be regarded as exploratory.

## Conclusion

Our current study may have important clinical implications. Ischemic etiology of cardiomyopathy prior to HTx may be an

independent risk factor for plaque progression and poor prognosis after HTx. In addition, yearly surveillance with novel intravascular imaging modalities such as VH-IVUS or optical coherence tomography, in addition to coronary angiography, should be considered for these patients to allow early detection of CAV and timely pharmacological intervention.

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## Disclosures

None.

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