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Inflammatory Burden of Cardiac Allograft Coronary Atherosclerotic Plaque Is Associated With Early Recurrent Cellular Rejection and Predicts a Higher Risk of Vasculopathy Progression

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Objectives This study was designed to investigate tissue characterization of the coronary allograft atherosclerotic plaque with virtual histology intravascular ultrasound (VH-IVUS) imaging to assess the presence and predictors of vessel wall inflammation and its significance in cardiac allograft vasculopathy (CAV) progression.

Background A unique form of accelerated atherosclerosis, CAV remains the leading cause of late morbidity and mortality in heart transplant patients. The pathogenesis of CAV is not fully elucidated.

Methods A total of 86 patients with coronary allograft vasculopathy underwent VH-IVUS examination of the left anterior descending coronary artery 3.61 ± 3.04 years following cardiac transplantation. Based on the VH-IVUS plaque characteristics, coronary allograft plaque was divided on virtual histology intravascular ultrasound-derived "inflammatory" (VHD-IP) (necrotic core and dense calcium ≥30%) and "noninflammatory" plaque (VHD-NIP) (necrotic core and dense calcium <30%). Total rejection scores were calculated based on the 2004 International Society of Heart and Lung Transplantation rejection grading system.

Results In the whole study population, the mean percentage of fibrous, fibrofatty, dense calcified, and necrotic core plaques in a mean length of 62.3 ± 17.4 mm of the left anterior descending coronary artery were 50 ± 17%, 16 ± 11%, 15 ± 11%, and 18 ± 9%, respectively. Patients with a 6-month total rejection score >0.3 had significantly higher incidence of VHD-IP than those with a 6-month total rejection score ≤0.3 (69% vs. 33%, p = 0.011). The presence of VHD-IP at baseline was associated with a significant increase in plaque volume (2.42 ± 1.78 mm^3/mm vs. −0.11 ± 1.65 mm^3/mm, p = 0.010), plaque index (7 ± 9% vs. 0 ± 8%, p = 0.04), and remodeling index (1.24 ± 0.44 vs. 1.09 ± 0.36, p = 0.030) during 12 months of follow-up when compared with the presence of VHD-NIP at baseline and during follow-up.

Conclusions The presence of VHD-IP as assessed by VH-IVUS is associated with early recurrent rejection and with higher subsequent progression of CAV. A VH-IVUS assessment may add important information in the evaluation of transplant recipients. (J Am Coll Cardiol 2009;53:1279–86) © 2009 by the American College of Cardiology Foundation

Cardiac allograft vasculopathy (CAV) is a unique form of accelerated atherosclerosis and remains the leading cause of late morbidity and mortality in heart transplant patients

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accounting for 30% mortality after 5 years (1,2). Although the pathogenesis of CAV is not fully elucidated, it seems to result from a complex interplay between immunologic and nonimmunologic factors, with consequent repetitive vascular injury and a localized sustained inflammatory response (3,4).

There is a growing body of evidence supporting the major contribution of inflammatory pathways to the etiology of CAV. Elevation of systemic inflammatory markers is common in transplant recipients and associated with increased risk for CAV and worse prognosis (5–8). Focal inflammation in the vessel wall (9) and the presence of vasculitis, involving the entire coronary arterial system, was frequently shown on histopathological ex vivo examinations (10). However, the presence and predictors of local vessel inflam-

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Abbreviations and Acronyms

CAV = coronary allograft vasculopathy

hsCRP = high-sensitivity C-reactive protein

R = rejection grade

TRS = total rejection score

VHD-IP = virtual histology intravascular ultrasound-derived inflammatory plaque

VHD-NIP = virtual histology intravascular ultrasound-derived noninflammatory plaque

VH-IVUS = virtual histology intravascular ultrasound

mation and its significance in CAV progression has not been established by in vivo studies.

Grayscale intravascular ultrasound allows rapid and accurate measurement of plaque volume and assessment of the progression of coronary artery disease (11–13) but has a significant limitation in the evaluation of atherosclerotic plaque composition (Fig. 1). Recent studies have demonstrated that virtual histology intravascular ultrasound (VH-IVUS) offers a novel technology to characterize the different types of plaque morphology in vivo (e.g., fibrous, fibrofatty, dense calcium, and necrotic core) (14–16). In native coronaries, morphological composition of atherosclerotic plaque was demonstrated as a useful determinant of the plaque vulnerability (17–19) and identified plaques with a high risk of future clinical events (20–22).

The aim of the present study was to evaluate the association between different tissue characteristics of the coronary allograft plaque and risk factors for CAV and to assess its role in the progression of CAV.

Methods

From March 2005 to November 2007, a total of 119 consecutive cardiac transplant recipients without signs of infection or acute rejection underwent VH-IVUS study during routine annual coronary angiography.

Of this total cohort, 72% (86 patients, 3.61 ± 3.04 years after transplantation) had at least 1 site with atherosclerosis (intimal thickness ≥0.5 mm) and were entered into the study. Of note, no significant coronary artery disease (>70% stenosis) has been demonstrated in the donor hearts at transplantation. However, baseline post-transplant IVUS studies were not routinely performed; therefore, pre-existing mild donor disease could not be excluded.

Thirty-eight patients underwent follow-up VH-IVUS study in 1 year.

Demographic and clinical patients' data were obtained from the medical records. Maintenance immunosuppression was a triple therapy regimen based on calcineurin inhibitors or rapamycin (8,23,24) with azathioprine, or mycophenolate mofetil and prednisone.

Routine endomyocardial biopsies were performed every week for 6 weeks after transplantation beginning a week after completing Orthoclone OKT 3 (Ortho Biotech Products, Bridgewater, New Jersey) treatment, every 2 weeks from 6 weeks to 3 months, monthly from 3 to 6 months, or in 10- to 15-day intervals following any biopsy showing an International Society of Heart and Lung Transplantation rejection grade (R) ≥2 based on the 2004 guidelines. A 6-month total rejection score (TRS) was assigned as 0R = 0, 1R = 1, 2R = 2, 3R = 3 and normalized by dividing the cumulative scores for the total number of biopsies taken during the 6-month period. Because previous data (25) and our recent study (26) demonstrated the association of early recurrent rejection and subsequent development of CAV, we chose to analyze 6-month TRS in the present study.

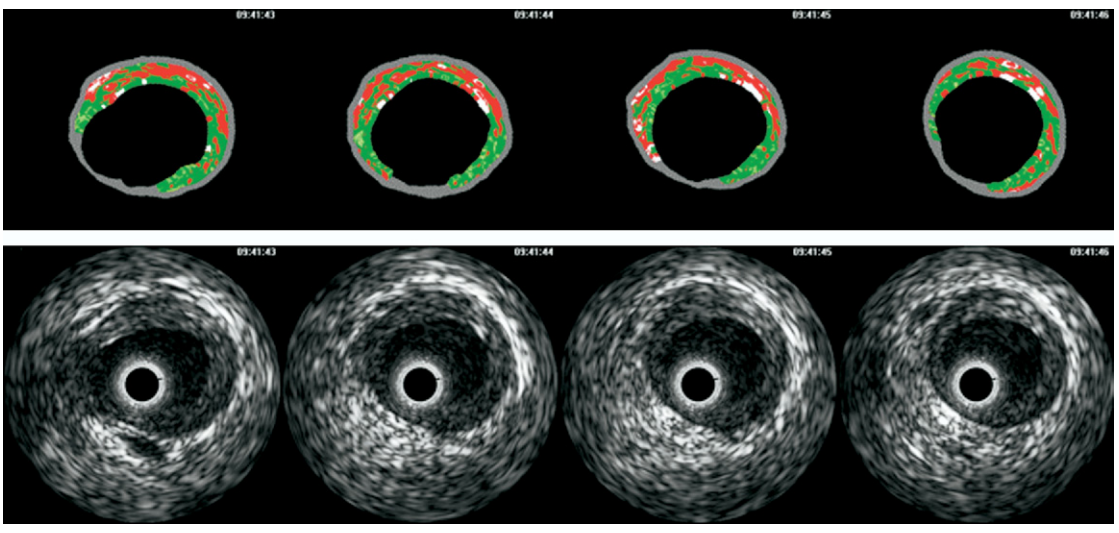

Figure 1 Grayscale IVUS Cross-Section and VH-IVUS Images

Grayscale intravascular ultrasound (IVUS) cross-section imaging **(bottom)** and corresponding virtual histology (VH)-IVUS images **(top)** from patients with VH-IVUS–derived inflammatory plaque.

Patients were stratified into 2 groups according to cumulative 6-month TRS ≤0.3 and >0.3 (26).

IVUS examination. Intravascular ultrasound was performed after intracoronary administration of 100- to 200-μg nitroglycerin. The IVUS images were recorded from the distal left anterior descending coronary artery to the left main coronary artery with a commercially available IVUS console (IVUS3 system, Volcano Therapeutics, Rancho Cordova, California) and 2.9-F, 20-MHz, phased-array IVUS catheters (Eagle Eye Gold, Volcano Therapeutics) with an automated pullback system (0.5 mm/s). The IVUS images were stored on a CD-ROM for later offline 3-dimensional volumetric and VH-IVUS analysis.

VH-IVUS analysis. Offline volumetric analysis of IVUS data was performed (Volcano Invision Gold imaging system software, Volcano Corporation, Rancho Cordova, California) by 2 experienced operators who were unaware of clinical data. After automatic border detection was corrected manually, morphometric parameters of the volume (cubic millimeters), lumen, and plaque in the examined vessel segment were obtained and calculated as previously described (27). The Simpson rule for volumetric measurement was used. Each measured volume (vessel volume, lumen volume, plaque volume) was normalized to the examined segment length (cubic millimeters per millimeter) to compensate for differences in examined vessel segment length. A plaque index was calculated as: (plaque volume/vessel volume) × 100%. The volumetric remodeling index was calculated as: follow-up vessel volume/baseline vessel volume.

Each plaque segment was classified following 4 types of characteristics (fibrous, fibrofatty, dense calcium, and necrotic core) according to the radiofrequency signal processing of VH-IVUS technology (14). They were color-coded and displayed on the IVUS console: fibrous as green, fibrofatty as light green, dense calcium as white, and necrotic core as red. This approach has been validated with histological techniques (14,15,28). Because necrotic core is characterized histologically by a high level of lipids, necrotic cells, remnants of lymphocytes, and microcalcification, which presents a by-product of dead cells, we followed the approach of Nair et al. (14) and combined necrotic core and dense calcium into a single group that presumably reflects the inflammatory burden of the cardiac allograft atherosclerotic plaque. Thus, based on the VH-IVUS plaque characteristics, the patients were divided as those with virtual histology intravascular ultrasound-derived "inflammatory plaque" (VHD-IP) (necrotic core and dense calcium ≥30%) or "noninflammatory plaque" (VHD-NIP) (necrotic core and dense calcium <30%). We selected this cutoff value based on previous pathological and in vivo VH-IVUS findings in a nontransplant population (16,29–31).

For the random samples of 41 patients, intraobserver analysis was performed at least 2 weeks apart, and interobserver analysis was performed by 2 experienced, independent observers. Intraobserver reliability of the percentage of necrotic core and dense calcium was 92.7%.

Statistical analysis. Data are described by mean ± SD or counts and percentages, as appropriate. Analysis to compare for different demographic and clinical data between the groups was performed using the *t* test for continuous data and the chi-square test for categorical data. The Pearson correlation coefficient and univariate linear regression were used to describe associations between plaque characteristics assessed by VH-IVUS and risk factors for CAV. Correlation coefficients of high-sensitivity C-reactive protein (hsCRP) level, for which the distribution was heavily skewed, and 3-dimensional IVUS findings were calculated according to Spearman rank correlation. Differences from baseline to 12-month follow-up within groups were compared using a paired *t* test. Multivariable regression was used to assess independent predictors of plaque progression. A value of $p < 0.05$ was considered to be statistically significant.

Results

Our study population represents a cross section of transplant recipients studied at various time intervals after transplantation. Eighty-six patients (mean age: 49.1 ± 15.9 years, mean donor age: 30.1 ± 13.7 years) underwent the VH-IVUS study at 3.6 ± 3.0 years after transplantation (Table 1).

VH-IVUS plaque composition in heart transplant patients. In the whole study population, a mean length of 62.3 ± 17.4 mm of the left anterior descending coronary artery was analyzed. The mean percentage of fibrous, fibrofatty, dense calcified, and necrotic core plaques were 50 ± 17%, 16 ± 11%, 15 ± 11%, and 18 ± 9%, respectively (Table 2).

Correlation of VH-IVUS findings with 6-month TRS. Patients were stratified into 2 groups according to cumulative 6-month TRS ≤0.3 (n = 34) and TRS >0.3 (n = 52). There were no significant differences between the groups with regard to recipient's sex, reason for transplantation, cold ischemic time, cytomegalovirus infection, conventional atherosclerosis risk factors, and treatment (Table 1). There was no difference in volumetric plaque characteristics between the groups (Table 2).The percentage of necrotic core was significantly higher in patients with 6-month TRS >0.3. There was a significantly higher incidence of VHD-IP in the group of patients with 6-month TRS >0.3.

Correlation of VH-IVUS findings with other risk factors for CAV. Time after transplantation positively correlated with plaque index ($r = 0.23$, $p = 0.034$), but there were no significant correlations between the time after transplantation and plaque volume or any element of plaque composition.

Linear-regression analysis revealed a direct correlation between the donor age and the total amount ($r = 0.43$, $p < 0.001$) or percentage of fibrous plaque tissue ($r = 0.23$, $p = 0.022$).

There were no significant correlations between the plaque composition and lipid levels or body mass index.

Table 1 Patients' Demographic, Clinical, and Laboratory Characteristics Divided by TRS at 6 Months

	Overall N = 86	TRS ≤0.3 n = 34 (40%)	TRS >0.3 n = 52 (60%)	p Value
Recipient age, yrs	49.08 ± 15.85	51.95 ± 14.32	47.30 ± 17.38	0.24
Time after transplant, yrs	3.91 ± 3.84	3.85 ± 3.69	4.95 ± 3.97	0.25
Recipient male sex, n (%)	55 (64%)	21 (63%)	34 (66%)	0.71
Reason for transplant, n (%)				
Ischemic CMP	29 (31%)	9 (27%)	21 (40%)	0.64
Dilated CMP	27 (37%)	11 (32%)	16 (31%)	
Other	29 (30%)	14 (41%)	15 (29%)	
Donor age, yrs	31.10 ± 13.69	32.30 ± 14.67	30.28 ± 14.34	0.60
Cold ischemic time, min	172.30 ± 48.05	163.04 ± 49.00	173.95 ± 47.66	0.40
BMI at transplantation, kg/m^2	26.23 ± 5.58	27.00 ± 7.63	25.92 ± 4.41	0.54
Triglycerides, mg/dl	162.09 ± 85.05	176.00 ± 93.07	153.31 ± 75.28	0.31
HDL cholesterol, mg/dl	58.75 ± 19.71	57.31 ± 18.99	58.90 ± 18.84	0.74
LDL cholesterol, mg/dl	105.57 ± 35.25	106.96 ± 38.38	101.21 ± 32.85	0.35
Hypertension, n (%)	70 (81%)	31 (91%)	39 (78%)	0.12
Diabetes mellitus, n (%)	17 (20%)	6 (17%)	11 (21%)	0.73
Cytomegalovirus viremia, n (%)	10 (12%)	4 (12%)	6 (12%)	0.98
ACE inhibitors, n (%)	36 (42%)	16 (48%)	20 (39%)	0.52
Calcium-channel blocker, n (%)	26 (30%)	12 (35%)	14 (26%)	0.45
Statin, n (%)	78 (91%)	31 (91%)	47 (90%)	0.89
CNI/sirolimus, n (%)	56 (65%)/30 (35%)	22 (65%)/12 (35%)	34 (66%)/18 (34%)	0.98
Azathioprine/MMF, n (%)	41 (48%)/45 (52%)	18 (52%)/16 (48%)	23 (45%)/29 (55%)	0.57

ACE = angiotensin-converting enzyme; BMI = body mass index; CMP = cardiomyopathy; CNI = calcineurin inhibitor; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MMF = mycophenolate mofetil; TRS = total rejection score.

The hsCRP level was available in 43 patients and was increased in the VHD-IP group, but the difference was not significant (2.96 ± 2.94 mg/l, n = 21 vs. 1.62 ± 1.78 mg/l, n = 22; p = 0.07). There was significant correlation between hsCRP level and the percentage of necrotic core (r_s = 0.32, p = 0.03).

Association between plaque morphology and CAV progression. Of the total cohort, 38 patients underwent follow-up VH-IVUS examinations in 12 months. Overall mean change in plaque volume (change in plaque volume/segment length) was 0.78 ± 2.43 mm^3/mm and mean change in plaque index was 4 ± 11%. Mean remodeling

Table 2 3-Dimensional and VH-IVUS Characteristics Divided by TRS at 6 Months

	Overall N = 86	TRS ≤0.3 n = 34 (40%)	TRS >0.3 n = 52 (60%)	p Value
Volumetric characteristics				
SL, mm	62.33 ± 17.36	63.86 ± 14.12	62.20 ± 19.33	0.67
VV/SL, mm^3/mm	17.53 ± 4.62	18.25 ± 4.79	16.66 ± 4.59	0.21
LV/SL, mm^3/mm	12.35 ± 3.44	13.04 ± 3.13	11.53 ± 3.59	0.10
PV/SL, mm^3/mm	5.18 ± 2.14	5.22 ± 2.57	5.13 ± 2.05	0.89
Plaque index, %	29 ± 9	28 ± 9	31 ± 9	0.20
Tissue type				
Fibrotic, mm^3/mm	0.93 ± 1.19	1.23 ± 1.53	0.86 ± 1.12	0.33
Fibrofatty, mm^3/mm	0.27 ± 0.41	0.37 ± 0.49	0.26 ± 0.35	0.36
Dense calcium, mm^3/mm	0.20 ± 0.21	0.14 ± 0.14	0.24 ± 0.25	0.07
Necrotic core, mm^3/mm	0.29 ± 0.30	0.22 ± 0.23	0.33 ± 0.35	0.16
Fibrotic, %	50 ± 17	55 ± 19	47 ± 15	0.07
Fibrofatty, %	16 ± 11	18 ± 13	16 ± 10	0.56
Dense calcium, %	15 ± 11	12 ± 11	17 ± 12	0.08
Necrotic core, %	18 ± 9	14 ± 8	21 ± 8	0.004
VHD-IP/VHD-NIP	47 (55%)/39 (45%)	11 (33%)/23 (67%)	36 (69%)/16 (31%)	0.011

LV = lumen volume; Plaque index = percent plaque volume; PV = plaque volume; SL = segment length; VHD-IP = virtual histology intravascular ultrasound-derived inflammatory plaque; VHD-NIP = virtual histology intravascular ultrasound-derived noninflammatory plaque; VH-IVUS = virtual histology intravascular ultrasound; VV = vessel volume; other abbreviations as in Table 1.

index at 12 months was 1.02 ± 0.46. There were no significant changes in plaque composition during the 12-month period (Table 3).

In the patients with VHD-IP in the baseline VH-IVUS study (n = 20), there was significant subsequent increase in plaque volume (2.42 ± 1.78 mm^3/mm vs. −0.11 ± 1.65 mm^3/mm, p = 0.01) and plaque index (7 ± 9 vs. 0 ± 8, p = 0.04) during the 1-year follow-up compared with those with VHD-NIP (n = 18). There was significant increase in remodeling index in the patients with VHD-IP compared with those with VHD-NIP (1.24 ± 0.44 vs. 1.09 ± 0.36, p = 0.03) (Fig. 2).

Covariates that could influence plaque progression, including recipient's sex and age at transplantation, reason for transplantation, cold ischemic time, body mass index, lipid levels, 6-month TRS, and donor age, were examined, and only lower high-density lipoprotein cholesterol level was significant when added to the model in the presence of the plaque type. When corrected for high-density lipoprotein cholesterol, the presence of the VHD-IP remained a significant factor for changes in plaque volume and plaque index.

Discussion

The current study demonstrates that the presence of inflammatory plaque as assessed by VH-IVUS is associated with early recurrent rejection and with subsequent progression of CAV. This study supports a role of interaction between the immune basis for onset and late inflammatory modulation in the progression of CAV and suggests that VH-IVUS may be a useful tool in studying the mechanism of and for predicting the progression of CAV.

Coronary artery plaque composition assessed by VH-IVUS. Coronary artery disease of human cardiac allograft is a multifactorial phenomenon with variable morphologic features. Previous histological ex vivo studies described 2 microscopic types of coronary allograft lesions (32). One type of lesion is confined to the proximal region of epicardial arteries and is indistinguishable from ordinary atherosclerosis of native vessels. The second type is characterized by the presence of vasculitis, involves the entire coronary arterial system, and has been suggested to represent the immune-mediated vessel injury (10). A dichotomous pattern of coronary allograft vasculopathy was also previously suggested by grayscale IVUS (33). The current study extends these previous observations and reports the tissue characterization and the heterogeneity of coronary plaque composition following heart transplantation assessed by VH-IVUS.

Table 3 Volumetric Assessment of Vascular Geometry and Progression of Allograft Vasculopathy During 12-Month Follow-Up (n = 38)

	First 3D VH-IVUS	Second 3D VH-IVUS	p Value
SL, mm	54.22 ± 18.10	58.14 ± 15.86	0.024
VV/SL, mm^3/mm	16.32 ± 5.80	16.58 ± 5.23	0.26
LV/SL, mm^3/mm	11.58 ± 3.99	11.06 ± 4.39	0.08
PV/SL, mm^3/mm	4.74 ± 2.59	5.52 ± 2.37	0.025
Plaque index, %	28 ± 10	32 ± 13	0.010
Fibrotic, mm^3/mm	0.93 ± 0.65	0.98 ± 0.56	0.75
Fibrolipid, mm^3/mm	0.26 ± 0.41	0.19 ± 0.4	0.46
Dense calcium, mm^3/mm	0.20 ± 0.21	0.17 ± 0.28	0.48
Necrotic core, mm^3/mm	0.20 ± 0.30	0.29 ± 0.24	0.37
Fibrotic, %	49 ± 15	52 ± 16	0.57
Fibrolipid, %	16 ± 12	15 ± 13	0.43
Dense calcium, %	15 ± 10	14 ± 12	0.74
Necrotic core, %	19 ± 9	21 ± 11	0.32

3D = 3-dimensional; IVUS = intravascular ultrasound; other abbreviations as in Table 2.

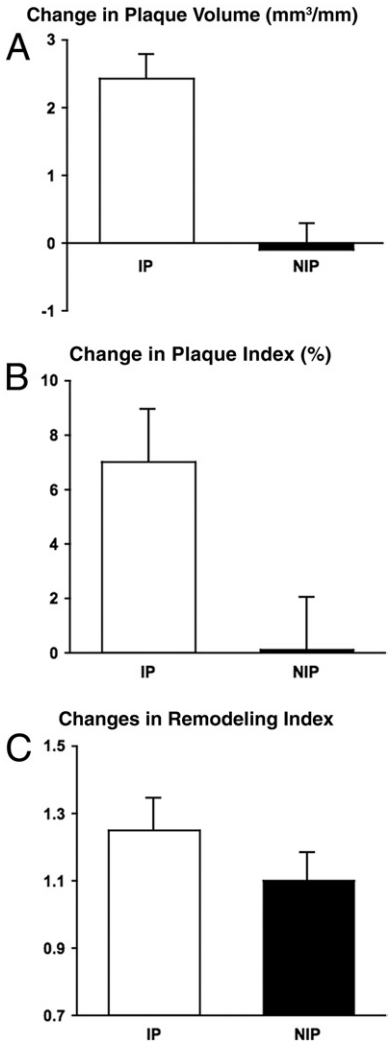

Figure 2 Progression in Plaque Volume, Plaque Index, and Remodeling Index in IP and NIP Groups

A shows the progression in plaque volume in the inflammatory plaque (IP) and noninflammatory plaque (NIP) groups: virtual histology intravascular ultrasound-derived inflammatory plaque (VHD-IP) (n = 21): 2.42 ± 1.78, virtual histology intravascular ultrasound-derived noninflammatory plaque (VHD-NIP) (n = 17): −0.11 ± 1.65; p = 0.01. **B** shows the progression in plaque index in the VHD-IP and VHD-NIP groups: VHD-IP (n = 21): 7 ± 9, VHD-NIP (n = 17): 0.1 ± 8; p = 0.04. **C** shows the remodeling index in the VHD-IP and VHD-NIP groups: VHD-IP (n = 21): 1.24 ± 0.44, VHD-NIP (n = 17): 1.09 ± 0.36; p = 0.03.

Early rejection, systemic inflammation, and inflammatory plaque burden. Cardiac allograft vasculopathy is associated with an injury of the coronary vessel endothelium that may be initiated by a variety of immunologic factors. It has been demonstrated that early immunological events surrounding engraftment lead to an inflammatory process in the vascular endothelium (34–41). Although CAV may develop at any stage after transplantation, events during the first year, resulting most likely from initial and ongoing immunologically mediated injury to the vascular endothelium, appear to be important in CAV pathogenesis (42). Several clinical studies demonstrated a relationship between immune events and an increase in systemic inflammatory markers following heart transplantation (7,43). The present study suggests that the association between early recurrent cellular rejection and inflammatory burden of cardiac allograft atherosclerotic plaque supports an immune basis of the inflammatory process. In line with a study of a nontransplant population that demonstrated that elevated plasma hsCRP level is associated with necrotic core volume in patients with acute coronary syndromes (44), our study demonstrated the association between hsCRP level and necrotic core of cardiac allograft coronary plaque. The predominant VH-IVUS examination was performed late (nearly 4 years) after transplantation, indicating that systemic and vascular inflammation tend to persist throughout the course of transplantation.

Inflammatory plaque and CAV progression. The evidence that chronic inflammation may be a central event in cardiac allograft vasculopathy is gaining acceptance. Several studies demonstrated that elevated systemic levels of the inflammatory markers are predictive not only of cardiac allograft vasculopathy but also of allograft failure (5–7,43,45). The present study suggested that VH-IVUS can be used to identify patients with increased burden of inflammatory plaque following heart transplantation and showed that the focal inflammation as assessed by VH-IVUS is associated with subsequent progression of CAV.

In addition, the coronary arteries with VHD-IP showed positive remodeling in the present study. These data are consistent with previous findings from a nontransplant population, which showed that necrotic core and inflammation are associated with expansion of the internal elastic lamina, and positive remodeling closely correlates with plaque vulnerability (46,47).

Fibrotic plaque. Grayscale IVUS studies found that the pattern of atherosclerosis in many proximal segments appeared similar to conventional atherosclerosis with eccentric focal plaques, often located near branching points and with predominantly fibrotic morphology, and demonstrated that the incidence of donor-derived coronary atherosclerosis is positively related to the donor age (33). It was shown in a recent VH-IVUS study (48) that fibrotic and fibrofatty tissues were predominant within 2 months following cardiac transplantation and associated with donor-derived coronary artery disease. Although there was a weak linear correlation, the present study demonstrated significantly increased donor age in recipients with predominant fibrotic plaque tissue even late after transplantation and suggests the association of noninflammatory plaque with donor transmitted disease.

In the 2007 International Society of Heart and Lung Transplantation registry, older donor age is an independent risk factor for early CAV. Donor coronary artery disease can serve as a starting point for CAV (2); however, the impact of native vessel atherosclerosis on CAV progression remains controversial. Several studies found no significant difference in the rate of intimal thickening between patients with donor hearts having pre-existing CAD and those without (49,50). Our study demonstrated relatively slow progression of CAV in the group of patients with fibrous plaque.

Study limitations. The predictive accuracies for VH-IVUS demonstrated the potential of this imaging tool for analyzing plaque vulnerability in a nontransplant population. This approach, however, has not been validated with histological techniques in heart transplant patients. Although we speculated that necrotic core and dense calcium represent the inflammatory burden of the coronary allograft plaque, it is not clear if the inflammatory activity of the plaque can be directly visualized by VH-IVUS. Study of a large cohort of patients is justified to evaluate the association between plaque characteristics and systemic inflammatory markers following heart transplantation. Our study, however, showed an association between the VH-IVUS–assessed plaque characteristics, early recurrent rejection, and subsequent progression of CAV.

Conclusions

Coronary angiography has a high specificity of 97.8% but only moderate sensitivity of 79.3% in CAV detection (51). The intimal changes in CAV are best detected by IVUS, which has become the gold standard for the early diagnosis of CAV (12,52,53). Simultaneous assessment of virtual histology with IVUS may add important information in the clinical evaluation of heart transplant recipients. The association of necrotic core and spotty dense calcification assessed by VH-IVUS as a parameter of an inflammatory plaque with higher score for early recurrent rejection confirms the dual etiology for transplant coronary artery disease. Early stratification of these high-risk lesions is desirable and may shed light not only on the mechanism of CAV but also on development of a novel therapeutic approach. The association of early recurrent rejection, inflammation, and the changes in the plaque burden suggests an interaction between the immune basis for onset and inflammatory modulation for progression of CAV. Patients with an inflammatory plaque composition pattern that suggests possible rapid progression of CAV may be scheduled for more frequent observations and augmentation of immunosuppressive or anti-inflammatory therapy early after transplantation.

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