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Myocardial Ischemic-Fibrotic Injury After Human Heart Transplantation Is Associated With Increased Progression of Vasculopathy, Decreased Cellular Rejection and Poor Long-Term Outcome

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OBJECTIVES We sought to assess the influence of peritransplant ischemia and fibrosis on the development of allograft vasculopathy, acute cellular rejection and long-term outcome.

BACKGROUND Allograft vasculopathy is a common long-term complication of cardiac transplantation. One of the potential risk factors is peritransplant allograft ischemia.

METHODS One hundred forty heart transplant recipients had baseline and one-year intravascular ultrasound analysis done to assess the progression of allograft vasculopathy. Serial endomyocardial biopsies were evaluated for cellular rejection, vascular rejection, ischemia and fibrosis. Based on histology, patients were classified into one of the following groups: nonischemic (n = 32), ischemia (n = 24), fibrosis (n = 62) or vascular rejection (n = 22). Three-color flow cytometry crossmatching (FCXM) was used to assess donor-specific human lymphocyte antigens (HLA) sensitization. Long-term outcome of patients in each group was assessed by estimating incidence of graft failure or deaths over a seven-year follow up.

RESULTS Patients in the fibrosis group had the lowest incidence of donor-specific HLA sensitization (40%, $p = 0.008$) and lowest average episodes of cellular rejection (1.7 ± 1.4, $p = 0.04$), but they had increased coronary vasculopathy progression (change in coronary intimal thickness = 0.59 ± 0.28 mm, $p < 0.0001$) and poor seven-year event-free survival (49%, $p = 0.01$).

CONCLUSIONS The development of fibrosis after cardiac transplantation is associated with advanced coronary vasculopathy, although a low incidence of acute cellular rejection is noted, suggesting the presence of nonimmune mechanisms in mediating the pathogenesis of allograft vasculopathy. (J Am Coll Cardiol 2002;39:970–7) © 2002 by the American College of Cardiology Foundation

Allograft vasculopathy is a significant long-term complication of cardiac transplantation. Angiographically evident allograft vasculopathy affects up to half of the heart transplant recipients who survive five years after transplantation (1). Necropsy and intravascular ultrasound (IVUS) studies have demonstrated that angiography underestimates transplant coronary artery disease (2–4). Donor and recipient age, serum triglyceride and cholesterol levels, major histocompatability mismatch, alloantigen-dependent cellular and vascular rejection, cytomegalovirus infection and ischemia time have all been suggested as risk factors for the development of allograft vasculopathy, but the role of these risk factors has not been fully established (1,5–11).

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Ischemia-induced myocardial injury is a well-defined histopathological pattern seen in endomyocardial biopsies soon after transplantation. Graft ischemia time, peritransplant hemodynamic status of the donor, inotropic support required by the donor, myocardial damage due to reperfusion and the quality of graft preservation during transportation play a role in the pathogenesis of ischemic injury (12–14). Ischemic injury to the heart at the time of transplantation might influence the development of accelerated allograft atherosclerosis through a number of mechanisms, including endothelial cell injury and promotion of cellular and vascular rejection through the release of donor antigens (15). Myocardial fibrosis after ischemia may also influence the allograft. The purpose of this study was to evaluate the impact of peritransplant myocardial ischemic injury on allograft vasculopathy and long-term survival in heart transplant recipients.

METHODS

Patient population. Between December 1992 and December 1997, a total of 422 patients underwent heart transplantation at The Cleveland Clinic Foundation. One hundred forty of these transplant recipients had a baseline IVUS study at one month of transplant and participated in a prospective 12-month study. All patients gave informed consent. Information regarding donor and recipient age, the etiology of heart failure in the recipient, the mode of donor

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Abbreviations and Acronyms

CMIT = change in maximal intimal thickness
FCXM = flow cytometry cross match
HLA = human lymphocyte antigens
IVUS = intravascular ultrasound

death, ischemia time and use of left ventricular assist device was obtained from The Cleveland Clinic Foundation Cardiac Transplant Database. The patients were followed for a period of 67 ± 19 months after transplantation to assess the incidence of graft failure, retransplantation and death.

IVUS. Intravascular ultrasound was performed in 294 coronary vessels in 140 patients (2.1 ± 0.6 arteries/patient). The methods of IVUS imaging have been previously reported in detail (16). Briefly, the ultrasound catheter was passed over an angioplasty guidewire to the most distal position that could be safely reached, and the distal site was documented by cineangiography. Ultrasound images were recorded on a super VHS tape during a slow distal to proximal pull back. When necessary, a repeat imaging was performed to concentrate on specific regions of interest, and contrast was injected to confirm the location of the imaging site to enable precise matching on a follow-up study. Before the one-year follow-up examination, the cineangiograms and IVUS images from the baseline study were reviewed by operators to duplicate the imaging study. Coronary intimal thickness was measured at baseline (1.0 ± 0.1 months) and one year (12.0 ± 1.0 months) after transplantation (Fig. 1). Paired analysis of matched sites (10 sites/patient) at one year measured the change in maximal intimal thickness (CMIT). Intimal thickening of >0.3 mm was considered pathological, based on reported values of intimal thickness in the young adult population (17,18). Development of coronary vasculopathy progression was defined as an increase in CMIT >0.3 mm at any site in one year.

Endomyocardial biopsies. An average of 13 biopsies was performed in each patient during the first year after transplantation as part of the routine endomyocardial biopsy protocol to monitor for acute rejection. During each procedure, four or five tissue specimens were usually obtained. The tissues were evaluated for ischemic injury, cellular and vascular rejection, and for development of interstitial fibrosis (Fig. 2). Ischemic injury related to transplantation was identified by areas of myocyte necrosis occurring in the immediate post-transplant period with an absence of infiltration by activated lymphocytes (12–14). Ischemia was noted within two weeks of transplantation. Biopsies that showed scarring consistent with old biopsy site in the absence of interstitial fibrosis were not considered part of

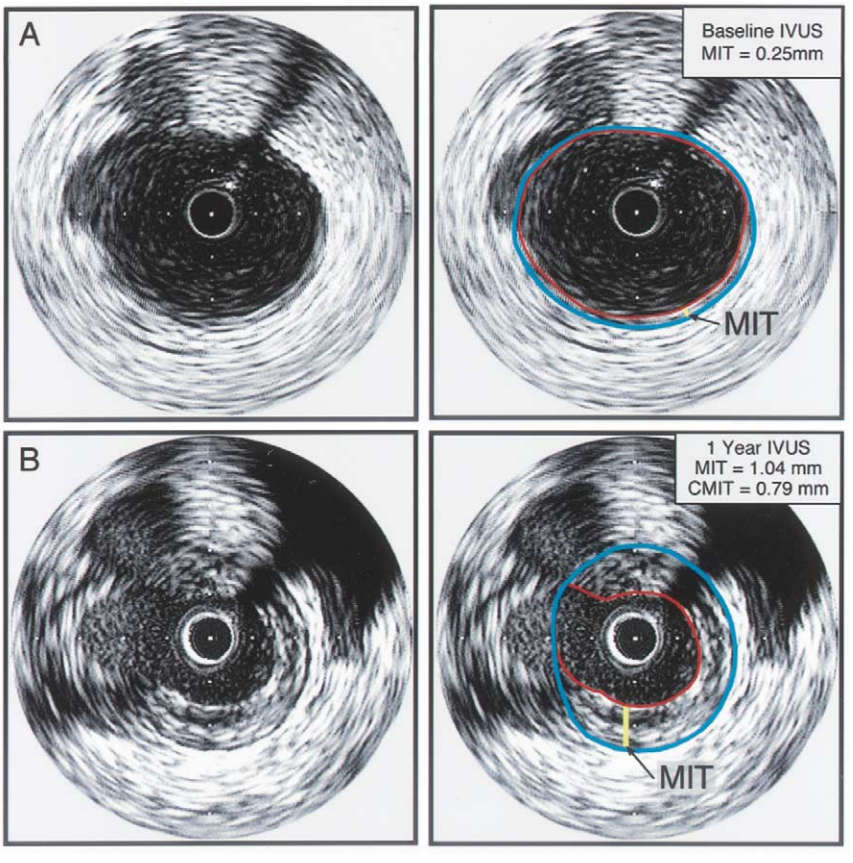

Figure 1. In vivo intravascular ultrasound images of left anterior descending artery of a cardiac allograft at a branching site at baseline **(A)** and one year after transplantation **(B)** showing severe intimal progression. CMIT = change in maximal intimal and medial thickness over one year; IVUS = intravascular ultrasound; MIT = maximal intimal thickness.

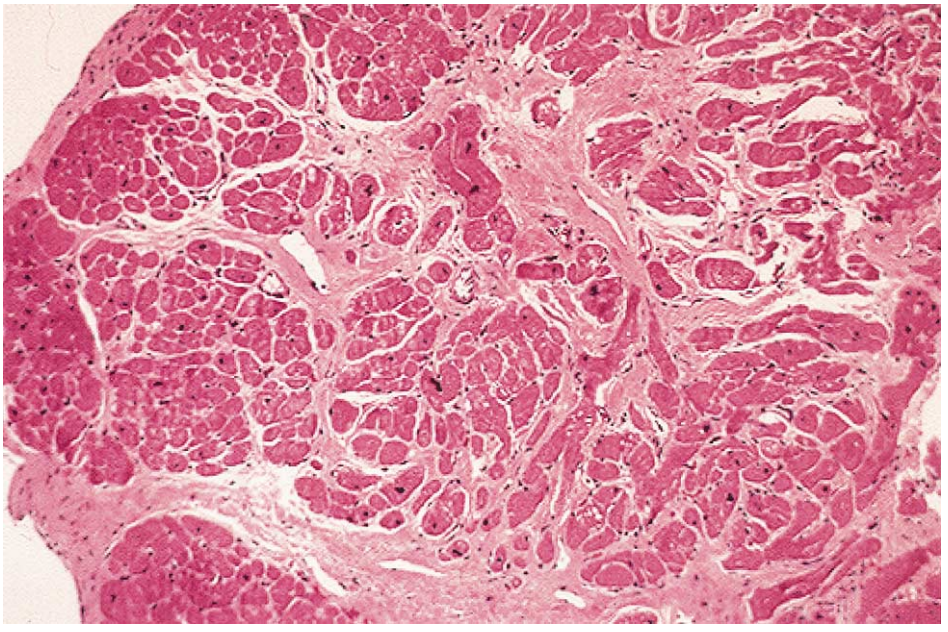

Figure 2. A section of the myocardium (H&E stain) from a patient with ischemic injury complicated by the development of interstitial fibrosis.

the fibrosis group. Acute vascular rejection is characterized by a cascade of inflammatory reactions associated with myocardial ischemic necrosis, vascular endothelial injury and intravascular immune complex formation with deposition of immunoglobulin, usually IgM, as well as complements such as C1q or C3 (19). Based on the histology findings, the study group of 140 patients was divided into the following four groups:

1. Ischemia group (n = 24): patients who developed peritransplant ischemia uncomplicated by fibrosis or vascular rejection (negative immunofluorescence).
2. Fibrosis group (n = 62): patients who developed peritransplant ischemia followed by interstitial fibrosis in the absence of vascular rejection (negative immunofluorescence).
3. Vascular group (n = 22): patients with evidence of acute vascular rejection confirmed by immunofluorescence; ischemic/fibrotic injury was evident in 82% (18/22) of these patients.
4. Nonischemic group (n = 32): patients with no evidence of peritransplant ischemia, fibrosis or vascular rejection.

Average biopsy score was calculated in each patient as the sum of numerical values assigned to each International Society of Heart and Lung Transplantation grade of rejection, divided by the total number of biopsies during the first year after transplantation.

Quantitative flow cytometry crossmatching. Using pretransplant sera, three-color flow cytometry crossmatching (FCXM) was performed as previously described (20) to quantitate antidonor IgG reactions against donor B and T lymphocytes. All reactions were compared with normal control sera. A shift from control values of >500 molecules of equivalent soluble fluorochrome was considered positive for T-cell reactions and >2,000 molecules of equivalent soluble fluorochrome was considered positive for B-cell reactions. Positive reactions against both T and B cells were considered to be against class I antigens, and positive reactions against B cells only was considered to be against human lymphocyte antigens (HLA) class II antigens.

Immunosuppressive treatment. All patients were maintained on prednisone. The maintenance immunosuppressive regimens are shown in Table 1. Twenty percent of grade 2 and all grade ≥3A rejection episodes were treated with steroid pulse therapy.

Statistical analysis. Quantitative data are presented as mean ± SD. The analysis of variance (ANOVA) or the chi-square test was used to find significant differences among the different groups. To account for potential deviations from normal distribution, nonparametric testing using Kruskal-Wallis test was used when appropriate. Time-related analysis was conducted using the method of Kaplan and Meier, and the log-rank (Mantel-Cox) test was used to test the equality of freedom from a combined end point of death, retransplantation and graft failure in the four groups stratified by findings on endomyocardial biopsy described previously. Cox proportional hazards regression was used to identify the risk factors for the combined end point. Results were reported as hazard ratio, 95% confidence intervals and p values. A p value <0.05 was considered to be significant for all analyses.

RESULTS

The characteristics of the 140 patients in four groups are displayed in Table 1. The donor age was significantly

Table 1. Baseline Characteristics

	Ischemia	Fibrosis	Nonischemic	Vascular	p Value
n =	24	62	32	22	
Donor age (yrs)	27 ± 10	37 ± 11	29 ± 12	29 ± 11	<0.001
Recipient age (yrs)	49 ± 11	53 ± 11	48 ± 11	52 ± 8	0.08
CNS-donor death	9 (38%)	30 (48%)	8 (25%)	5 (23%)	0.06
Etiology					
Dilated CM	11 (46%)	22 (35%)	15 (47%)	9 (41%)	NS
Ischemic CM	13 (56%)	40 (65%)	17 (53%)	13 (59%)	NS
LVAD	6 (25%)	15 (24%)	9 (28%)	3 (14%)	NS
Ischemia time (min)	143 ± 48	145 ± 50	136 ± 46	142 ± 43	NS
Immunosuppression					
AZA/CSA/pred	11 (46%)	26 (42%)	12 (38%)	7 (32%)	NS
MMF/CSA/pred	9 (38%)	33 (53%)	17 (53%)	10 (45%)	NS
FK/MMF/pred	4 (16%)	3 (5%)	3 (9%)	5 (23%)	0.09

AZA = azathioprine; CM = cardiomyopathy; CNS = donor death caused by brain injury; CSA = cyclosporine; FK = tacrolimus; LVAD = left ventricular assist device as a bridge to transplant; MMF = mycophenolate mofetil; NS = not significant; pred = prednisone.

greater in the fibrosis group of patients than in the other groups. Brain injury was more likely to be the cause of donor death in the fibrosis group than in the other groups. The recipient age, etiology of heart disease in the recipient, the use of left ventricular assist device and ischemia time were similar in the four groups of patients. Tacrolimus-based therapy tended to be more commonly used in the vascular rejection group than in any other.

Development of allograft vasculopathy. The progression of vasculopathy in the four groups of patients as measured by the change in maximal intimal and medial thickness (CMIT) is represented in Figure 3. Compared with patients in the nonischemic group, patients in the fibrosis group had a significant increase in intimal thickness, which was comparable to that in patients with vascular rejection (vascular group).

Long-term outcome. During a mean follow-up period of 67 ± 19 months, 16% (23/140) of the patients died and 8% (12/140) developed graft failure, with one of these patients requiring a retransplant. Patients with graft failure had left ventricular dysfunction with symptomatic heart failure and a mean left ventricular ejection fraction of 28 ± 8%. The majority of deaths were related to allograft vasculopathy. In a univariate Cox regression, recipient age, histopathological groups, donor age, ischemia time, donor cause of death and HLA crossmatch were tested, and histopathological group was found to be the only significant factor in determining morbidity and mortality. The Kaplan-Meier seven-year event-free survival in the different histopathological groups is shown in Figure 4. The patients in the fibrosis group had a poor outcome. Risk of death or allograft failure for patients in the fibrosis group was almost four times higher compared with that for patients in the nonischemic group (hazard ratio = 3.8; CI 1.14 to 12.8; p = 0.03) and five times higher than for patients in the ischemia group (hazard ratio = 4.95; CI 1.16 to 21.3; p = 0.03).

Cellular rejection. Patients in the fibrosis group had the lowest average episodes of grade ≥3A rejection (Fig. 5) and

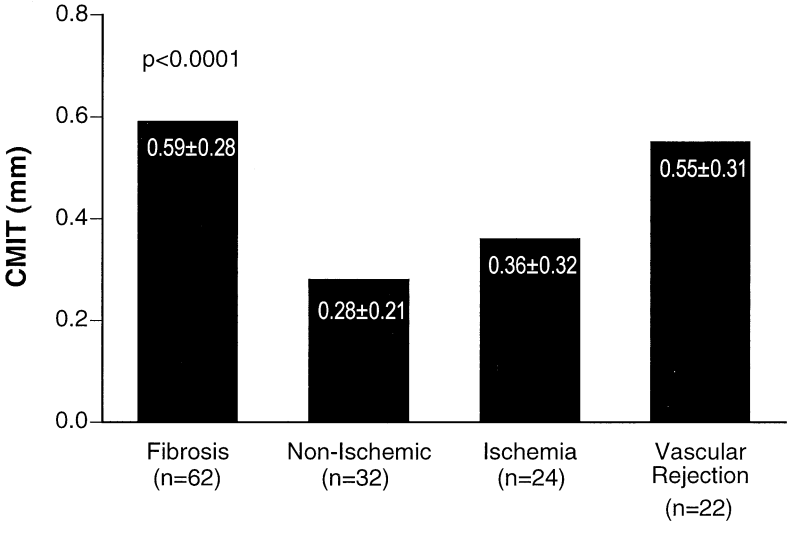

Figure 3. Bar diagram showing extent of progression of coronary vasculopathy in the first year after transplantation (as indicated by the change in maximal intimal and medial thickness, CMIT) in the different patient groups.

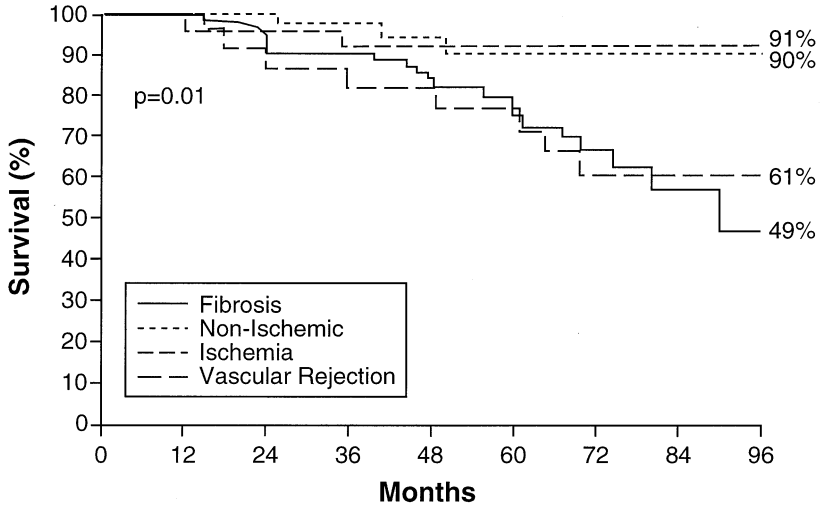

Figure 4. Kaplan-Meier seven-year event-free survival in the different patient groups.

the lowest average biopsy score (Fig. 6) compared with the other groups. Patients with vascular rejection, as expected, had the highest incidence of cellular rejection episodes.

Donor-specific FCXM. The fibrosis group had the lowest incidence of positive HLA (class I or class II) donor-specific cross matches (Fig. 7) and tended to have reduced amounts of IgG binding to T- (Fig. 8) and B- (Fig. 9) cell lymphocytes from the donors.

Coronary angiography. Among patients who survived beyond three years after transplant and who were able to undergo cardiac catheterization (depending on renal function), coronary angiography data were available on 109 patients. Advanced coronary vasculopathy (>50% obstruction) was more common in the fibrosis group than in any other (Table 2).

DISCUSSION

Early endomyocardial fibrosis has been described in transplant animal models and human allograft recipients and was linked to peritransplant ischemia (21,22). In a recent study on serial endomyocardial biopsies on 50 cardiac transplant patients followed over five years, Armstrong and his colleagues (23) showed that myocardial fibrosis develops early and remains modestly elevated two months after transplant, indicating that peritransplant factors might be responsible for this fibrotic process. Pickering et al. (22) showed that cardiac allograft fibrosis may be identified shortly after transplantation and is dependent on the total ischemia duration. In our study, 61% (86/140) of transplant recipients showed evidence of ischemic injury on their endomyocardial biopsies soon after transplantation, and 72% (62/86) of these patients developed fibrosis on successive biopsies (within one to four weeks of ischemia). We studied the relationship of ischemia and fibrosis to development of coronary vasculopathy, acute cellular rejection and the impact of this ischemia and fibrosis on long-term survival in heart transplant recipients.

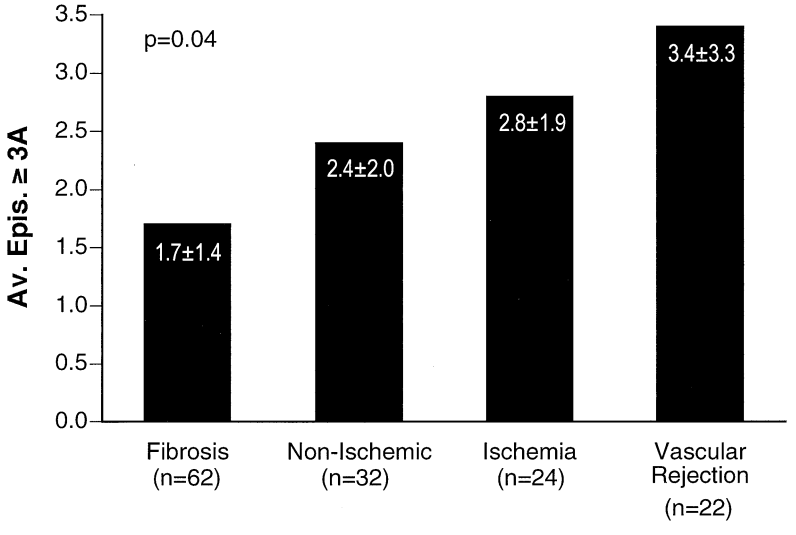

Figure 5. Bar diagram showing average episodes of acute cellular rejection ≥3A (during the first year of transplantation) in the different patient groups.

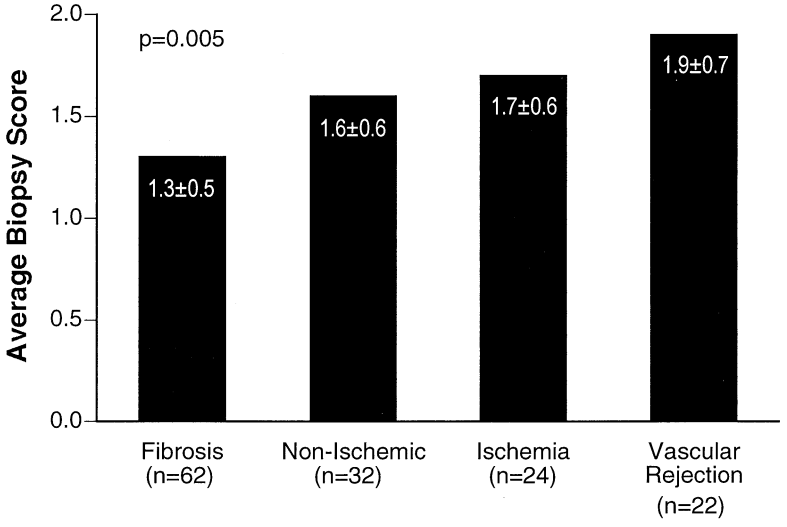

Figure 6. Bar diagram showing average biopsy score (during the first year of transplantation) in the different patient groups.

Our results indicate that patients with peritransplant myocardial ischemia followed by fibrosis clearly showed an increased incidence of progression of coronary vasculopathy confirmed by IVUS (at one year) and subsequent cardiac catheterization. Surprisingly, these patients had the least cellular rejection and antidonor HLA presensitization, indicating factors other than an antiallograft immune response are responsible for the progression of vasculopathy. Peeters and colleagues (24) found an inverse relationship, similar to our findings, between acute cellular rejection and portal fibrosis in pediatric liver transplant patients.

Ischemia at the time of transplantation has been associated with direct endothelial injury. Billingham et al. (25) compared the histological findings at the time of transplantation in hearts procured distantly (mean ischemia time 154 min) and hearts procured locally (mean ischemia time 49 min) and found severe capillary endothelial cell damage in the distantly obtained donor hearts, compared with almost no endothelial cell damage in the on-site donor hearts. In an experimental model of rat renal allograft (26), prolonged ischemia was associated with chronic rejection (vasculopathy) that was not due to the increased intensity of antiallograft immune response. Injured endothelial cells could, in turn, promote atherosclerosis through a number of mechanisms, including the adherence of platelets, release of growth factors and cytokines, expression of adhesion molecules and proliferation of vascular smooth muscle cells (27–29).

Our study identified a subgroup of patients with peritransplant ischemia complicated by fibrosis who had rapid

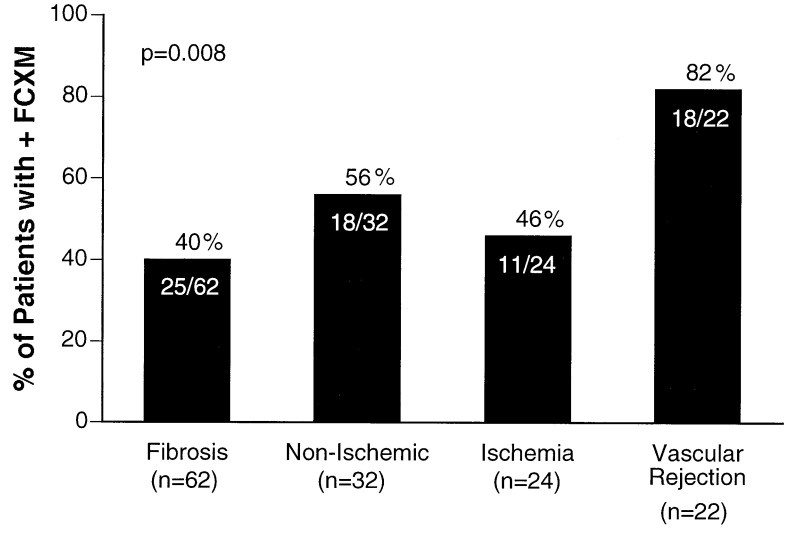

Figure 7. Bar diagram showing percentage of patients with positive human lymphocyte antigens crossmatch in the different patient groups. FCXM = flow cytometry cross match.

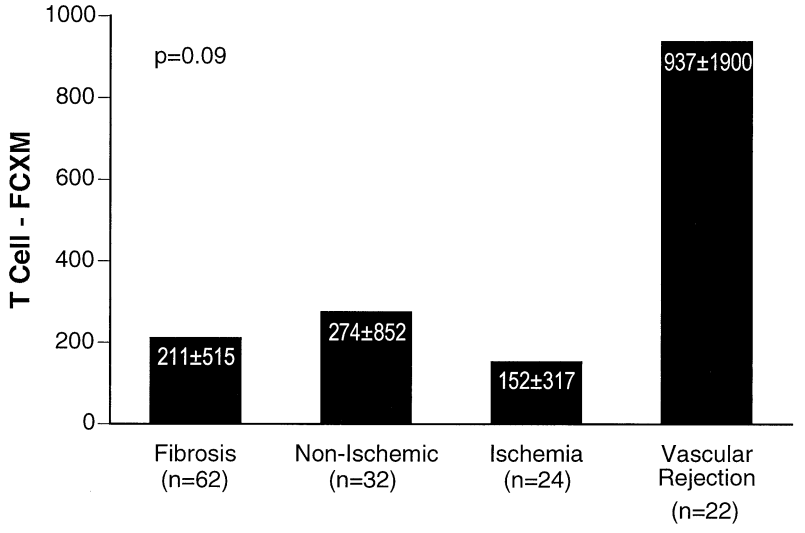

Figure 8. Bar diagram showing quantitative T-cell flow cytometry in the different patient groups. FCXM = flow cytometry cross match.

progression of vasculopathy, a decreased rate of cellular rejection and a poor seven-year event-free survival. Compared with the other three groups, the fibrosis group was associated with higher donor age, and the donor cause of death was more likely to be related to brain injury. The mechanism is not clear. Increased donor age (1) has been shown to be associated with the development of severe coronary vasculopathy. Brain-injury related donor cause of death has also been shown to influence the outcome in heart transplants (30). In our study there was no difference in ischemia times among the groups, highlighting the fact that graft ischemia time may not be the best predictor of peritransplant ischemic injury.

Study limitations. We used IVUS to assess the extent of progression of vasculopathy. Our study was based on matching site analysis and thus may be subject to selection bias. Although volumetric analysis with motorized pull back would be the most suitable approach to compare serial changes (31), our study was conducted with manual pull back, and thus volumetric analysis could not be applied.

Another limitation of the study is that the design has an internal selection bias for outcome because only patients who completed IVUS study at one year were evaluated; hence, only patients who survived the first year after transplantation were followed. Therefore, the mortality does not reflect the natural course of the different categories since the time of transplant.

Conclusions. We conclude that myocardial ischemia in the peritransplant period complicated by fibrosis is associated with increased progression of allograft coronary vasculopathy and a poor long-term outcome. This effect may be mediated by factors other than an increase in the intensity of

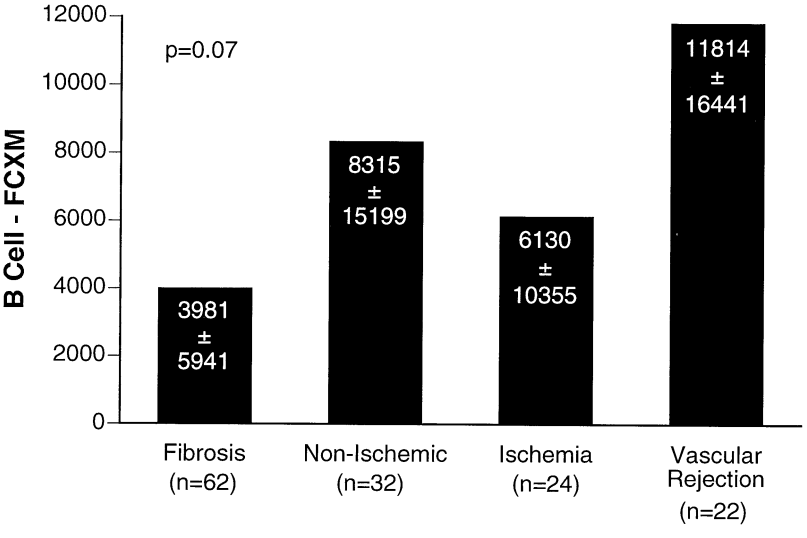

Figure 9. Bar diagram showing quantitative B-cell flow cytometry in the different patient groups. FCXM = flow cytometry cross match.

Table 2. Cardiac Catheterization Data

	Ischemia	Fibrosis	Nonischemic	Vascular	p Value
n =	22	47	25	15	
Advanced vasculopathy	2 (9%)	15 (32%)	0 (0%)	1 (6%)	0.001
Moderate		8	0	0	
Severe	2	7	0	1	
Mild vasculopathy	6 (27%)	10 (21%)	12 (48%)	7 (47%)	NS
Normal coronaries	14 (64%)	22 (47%)	13 (52%)	7 (47%)	NS

NS = not significant.

allograft immune response because the incidence of humoral presensitization and acute cellular rejection was low in this group of patients.

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