Correlation of Donor Characteristics With Transplant Coronary Artery Disease as Assessed by Intracoronary Ultrasound and Coronary Angiography

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The mechanisms responsible for transplant coronary artery disease (CAD) and its predisposing factors remain incompletely understood. The influence of donor characteristics as predisposing factors has not been studied systematically. We examined the correlation of donor demographic, clinical, and immunologic parameters with transplant CAD assessed by both intracoronary ultrasound (ICUS) and coronary angiography in 116 heart transplant recipients (age 44.7 ± 12.0 years) studied 3.4 years (range 1.0 to 14.6) after transplantation. Quantitative ultrasound data were obtained by calculating mean intimal thickness from several distinct coronary sites. Coronary angiograms were categorized visually as normal or showing any transplant CAD. By multivariate regression analysis, donor undersize of >20% of recipient weight (p <0.02) and duration after transplantation (p <0.005) were independently correlated with the amount of ICUS intimal thickness (r = 0.36, p = 0.0007), and older donor age with angiographic evidence for the disease (r = 0.34, p <0.006). In a subgroup analysis of the 39 patients studied 1 year after transplantation, white donor race (p <0.05), fewer human leukocyte antigen-DR mismatches (p <0.002), shorter ischemic time (p <0.04), and donor smoking history (p <0.02) were independent predictors for severity of ICUS intimal thickening (r = 0.92, p = 0.0009); higher donor age (p <0.006) and higher arterial partial pressure of oxygen (p <0.003) were independent predictors for angiographic disease (r = 0.67, p <0.002). In conclusion, donor characteristics may contribute to the probably multifactorial pathogenesis of transplant CAD.

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An accelerated form of coronary intimal thickening in the transplanted heart (transplant coronary artery disease [CAD]) has emerged as the major factor contributing to long-term morbidity and mortality in heart transplant recipients.[1–3] The pathophysiologic mechanisms involved in transplant CAD are incompletely understood and are probably multifactorial.[4] Whether donor factors could predispose to transplant CAD has not been studied systematically to date. Because of the unique morphology of transplant CAD with generally concentric and longitudinal arterial narrowing,[5] its severity is generally underestimated by visual assessment of coronary angiograms. This fact has been demonstrated by pathology-angiography correlation studies,[6] and confirmed by recent experience with intracoronary ultrasound (ICUS).[7] This new imaging modality overcomes the limitations of angiography by providing images of the blood vessels in cross section, allowing delineation of intimal thickness and morphology and quantitation of luminal dimensions.[8,9] The diagnostic value, reproducibility, and safety of ICUS in heart transplant recipients is well established.[10–12] To test the hypothesis that donor factors may contribute to the development of transplant CAD, we examined the correlation of demographic, clinical, and immunologic donor factors with the severity of intimal thickness in the transplanted heart as measured by ICUS, and with angiographic evidence of transplant CAD.

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METHODS

Study patients: The study population consisted of 116 heart transplant recipients (mean age 44.7 ± 12.0 years [27 women and 89 men]) who consented to undergo ICUS during their routine annual coronary angiography 3.4 ± 2.7 years (range 1.0 to 14.6) after transplantation. The medical records of these patients' donors were reviewed retrospectively to identify potential predisposing factors for transplant CAD.

The recipients were managed with standard maintenance immunosuppressive regimens including cyclosporine, prednisone, and azathioprine, except for 2 patients studied 13.0 and 14.6 years after transplantation who did not receive cyclosporine.

Given the wide range of duration after transplantation in the population, a subgroup of patients examined 1 year after transplantation (n = 39) was analyzed separately to evaluate whether different donor parameters predict transplant CAD present 1 year after transplantation versus later in their course.

The study protocol was approved by the Committee for the Protection of Human Subjects in Research at

Stanford University Medical Center and all subjects gave written informed consent before inclusion in the study.

Clinical data: The donor information examined as potential dependent variables for transplant CAD was categorized as demographic factors, clinical factors pertaining to the donor, and potential donor immunologic parameters. Donor demographic characteristics and clinical and immunologic factors are listed in Tables I to III. To determine whether any donor factors were independent predictors of transplant CAD, the following post-transplant variables were also recorded for multivariate analyses: duration after transplantation at the time of ICUS and angiography; number of treated rejection episodes; fasting plasma lipoprotein measurements (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides); average weight; average daily doses of corticosteroids, cyclosporine, and azathioprine; cytomegalovirus serostatus/infection; and use of calcium channel blocking drugs and lipid-lowering agents.

Coronary angiography: Coronary angiography was performed from the percutaneous femoral approach using standard angiographic techniques. After sublingual nitroglycerin premedication, multiple projections of the right and left coronary arteries were obtained. Arteriograms were assessed visually by 2 independent experienced angiographers not aware of the clinical and ICUS data. For the purpose of this study, patients were categorized as having no angiographic evidence of transplant CAD versus any angiographic evidence (any luminal stenosis or diffuse pruning of distal vessels).

Intracoronary ultrasound: The procedure for ICUS image acquisition and analysis at this institution has been described previously in detail.[7] Up to 4 distinct locations, separated by ≥1 cm, were selected for ultrasound measurements. The largest vessel lumen at end-diastole was used for analysis. The lumen-vessel interface and, in the presence of intimal thickening, the external border of the intimal layer (intima-media interface) were traced by planimetry, and mean intimal thickness was calculated from the intimal area. Measurements from all sites were averaged for each study. Intimal thickening of >0.3 mm was considered significant based on prior work from this laboratory[13] and pathologic observations in 164 unselected subjects aged 21 to 35 years.[14]

TABLE I Donor Demographic Characteristics in the Total Population

	Intimal Thickness		
	>0.3 mm (n = 37)	≤0.3 mm (n = 79)	p Value
Age (yr)	25.0 ± 8.2	26.0 ± 9.2	<0.6
Dr.–rec. age difference (yr)	17.9 ± 11.7	19.5 ± 14.5	<0.6
Female gender	6 (16)	17 (22)	<0.6
Dr.–rec. gender difference	6 (16)	16 (20)	<0.5
Male dr. to female rec.	3 (8)	11 (14)	<0.4
Female dr. to male rec.	3 (8)	7 (8)	<0.9
Height (cm)	177.4 ± 7.8	177.4 ± 10.0	<1
Dr.–rec. height difference (cm)	−3.0 ± 7.4	−3.5 ± 10.8	<0.9
Weight (kg)	76.3 ± 13.9	76.0 ± 12.6	<0.9
Dr.–rec. weight difference (kg)	−1.1 ± 13.5	−4.3 ± 12.9	<0.3
Dr. >20% oversized	6 (16)	18 (23)	<0.6
Dr. >20% undersized	4 (11)	3 (4)	<0.1
BSA (m^2)	2.0 ± 0.2	1.9 ± 0.2	<0.5
Dr.–rec. difference BSA (m^2)	−0.03 ± 0.15	−0.07 ± 0.20	<0.3
Donor race*			<1
White	27 (82)	54 (81)	
Hispanic	3 (9)	7 (10)	
Black	2 (6)	5 (8)	
Asian	1 (3)	1 (1)	
Dr.–rec. race difference	10 (30)	20 (30)	<1

*Donor race was known for 33 patients with intimal thickening >0.3 mm, and for 67 patients with intimal thickening ≤0.3 mm.
Data are expressed as mean ± SD or as number of patients (%).
BSA = body surface area; Dr. = donor, rec. = recipient.

TABLE II Donor Clinical Characteristics in the Total Population

	Intimal Thickness		
	>0.3 mm (n = 37)	≤0.3 mm (n = 79)	p Value
Cause of death			<0.8
Vehicular accident	61	49	
Gunshot	15	20	
Other trauma	6	7	
Cerebrovascular	15	18	
Anoxic brain death	0	1	
Domino donor	3	1	
Other	0	4	
Duration of hospitalization (d)	3.5 ± 4.0	2.4 ± 1.7	<0.08
Ischemic time (min)	130 ± 61	146 ± 79	<0.3
Dopamine treatment	73	74	<1
Dopamine dose (μg/min)	7.9 ± 4.7	7.1 ± 3.4	<0.5
Cardiac arrest	9	10	<1
Positive CMV serostatus	42	42	<1
Diabetes mellitus	0	5	<0.9
Arterial hypertension	5	11	<0.8
Positive CAD family history	5	0	<0.7
Smoking	37	25	<0.6
Serum sodium (μmol/L)	144 ± 10	144 ± 9	<0.8
Serum potassium (μmol/L)	4.0 ± 0.6	3.9 ± 0.7	<0.8
Serum creatinine (μmol/L)	1.2 ± 0.3	1.2 ± 0.4	<0.7
Hematocrit (%)	36.0 ± 6.8	36.1 ± 6.9	<1
White blood count (10^9/L)	13.2 ± 5.1	15.5 ± 6.8	<0.2
Arterial pH	7.4 ± 0.1	7.5 ± 0.1	<0.5
Arterial PO_2 (mm Hg)	175 ± 119	148 ± 85	<0.3
Duration after transplantation (y)	4.5 ± 3.1	2.9 ± 2.4	<0.005*

*$p < 0.05$.
CAD = coronary artery disease; CMV = cytomegalovirus; PO_2 = partial pressure of oxygen.
Data are expressed as mean ± SD or as percentage of patients.

Statistical analysis: Data are expressed as mean ± 1 SD or as number of patients (%) for continuous and categorical variables, respectively. Two methods were used to examine the association of donor factors with the outcome measures of transplant CAD. First, intimal thickness was expressed as a dichotomous variable, >0.3 vs

TABLE III Donor Immunologic Characteristics in the Total Population

	Intimal Thickness		
	>0.3 mm (n = 37)	≤0.3 mm (n = 79)	p Value
Blood group			<0.9
A	16 (43)	33 (42)	
B	2 (5)	6 (8)	
O	15 (41)	35 (45)	
AB	2 (5)	3 (4)	
No. of HLA-A mismatches	1.2 ± 0.7	1.4 ± 0.7	<0.07
No. of HLA-B mismatches	1.6 ± 0.6	1.7 ± 0.5	<0.3
No. of HLA-A + B mismatches	2.8 ± 0.9	3.2 ± 0.9	<0.08

HLA = human leukocyte antigen.
Data are expressed as mean ± SD or as number of patients (%).

≤0.3 mm; each dependent variable was then compared in patients with intimal thickness >0.3 versus ≤0.3 mm, using the unpaired Student's *t* test for continuous variables and the chi-square test for categorical variables. Second, the correlation between donor factors and ICUS or angiographic findings was explored by univariate analysis using a simple regression model. To determine whether any donor factors found to be significantly associated with transplant CAD by univariate analysis were indeed independently correlated, multiple regression analysis was performed using a model that included post-transplant variables. In all analyses, statistical significance was assigned to 2-sided p values <0.05.

RESULTS

Relation of donor demographic characteristics, clinical factors, and immunologic parameters to intracoronary ultrasound intimal thickness >0.3 vs ≤0.3 mm: TOTAL POPULATION: Tables I to III compare the dependent variables in patients with intimal thickness >0.3 versus ≤0.3 mm. None of the factors examined differed significantly in patients with intimal thickening >0.3 versus ≤0.3 mm.

SUBGROUP OF PATIENTS STUDIED 1 YEAR AFTER TRANSPLANTATION: Donor demographic characteristics were not significantly different when comparing patients with intimal thickness >0.3 versus ≤0.3 mm. Donors of patients with an intimal thickness >0.3 mm had received significantly higher doses of dopamine (12.0 ± 1.8 vs 7.9 ± 3.1 mg/min, p <0.03), were more often smokers (100% vs 22%, p <0.05), and had significantly fewer human leukocyte antigen-DR (HLA-DR) mismatches between donor and recipient (1.0 vs 1.7 ± 0.5, p <0.006) than donors of recipients with an intimal thickness ≤0.3 mm.

Correlation of dependent variables with outcome measures of transplant coronary artery disease: TOTAL POPULATION: The donor parameters examined by univariate analysis for correlation with intimal thickening by ICUS, and coronary stenosis by angiography, are listed in Table IV.

Intracoronary ultrasound disease: The significant univariate correlates of intimal thickening were donor age and donor undersize of >20%. After entering these variables in a multiple regression model, which also included the post-transplant factors listed in the Methods section, donor undersize of >20% (p <0.02) and longer duration after transplantation (p <0.005) remained independent predictors of ICUS intimal thickening (r = 0.36, p = 0.0007). Post-transplant average fasting plasma triglyceride levels (p <0.006) and weight (p <0.01) also were independently correlated with intimal thickening.

Angiographic disease: Univariate correlates of angiographic disease included donor age and post-transplant average fasting plasma triglyceride levels. By multiple regression analysis, including post-transplant factors, higher donor age (p <0.02) and higher average fasting plasma triglyceride levels (p <0.01) remained as independent correlates of angiographic transplant CAD (r = 0.34, p <0.006).

SUBGROUP STUDIED 1 YEAR AFTER TRANSPLANTATION: The donor parameters examined by univariate analysis for correlation with intimal thickening by ICUS, and coronary stenosis by angiography, in the subset of patients studied 1 year after transplantation are delineated in Table V.

Intracoronary ultrasound disease: By univariate analysis, significant correlates of intimal thickening included Caucasian race, donor–recipient race difference, shorter graft ischemic time, donor smoking history, and a lower frequency of HLA mismatch. By multivariate regression analysis, including post-transplant factors, white donor race (p <0.05), fewer HLA-DR mismatches (p <0.002), shorter ischemic time (p <0.04), donor smoking history (p <0.02), and post-transplant average fasting plasma triglyceride levels emerged as independent correlates of intimal thickness in patients 1 year after transplantation (r = 0.92, p = 0.0009).

Angiographic disease: By univariate analysis, higher donor age (p <0.006) and higher arterial partial pressure of oxygen (p <0.003) were significantly correlated with angiographic evidence of transplant CAD. Multivariate analysis, including post-transplant factors, revealed none of the factors to be independently correlated with angiographic disease.

Other post-transplant factors examined, including rejection incidence, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering drugs, and calcium channel blockers, were not independently correlated with intimal thickening or coronary artery stenosis.

DISCUSSION

Conflicting results regarding the risk factors for transplant CAD have been published.[2,3,15–24] Donor factors that could potentially influence the development of transplant CAD have not been evaluated to date in a systematic fashion. The results of the present study suggest that some donor parameters may play an important role in the development of transplant CAD.

Predisposing factors for transplant coronary artery disease: In the present study, donor undersize of >20% was independently correlated with ICUS severity of intimal thickness even after inclusion of significant post-transplant factors, such as duration after transplantation, average fasting plasma triglyceride levels, and weight in the multivariate analysis. Older donor age was the only factor independently correlated with angiographic evidence for the disease. In the subgroup of patients studied 1 year

after transplantation, white donor race, fewer HLA-DR mismatches, shorter ischemic time, and donor smoking history all were independently correlated with more severe ICUS intimal thickness. Higher donor age and donor arterial partial pressure of oxygen were independently associated with angiographic transplant CAD in this subgroup. In accordance with the donor factors that consistently and independently predicted transplant CAD, post-transplant average fasting plasma triglycerides and weight were found to be independently correlated with both intimal thickening and coronary artery stenosis. However, none of the other post-transplant factors examined independently predicted transplant CAD when assessed in the multivariate model that included donor factors. This observation suggests that donor factors play an important role in transplant CAD, and seriously challenges the current hypothesis implicating the alloimmune response as the primary mediator of the disease.

Donors and recipients are conventionally matched for size within 20% of body weight because of concerns of acute right ventricular failure after transplantation in the setting of pulmonary hypertension in the recipient. However, in a recent analysis,[25] undersizing of donor hearts was not detrimental to allograft function and recipient survival, and the use of undersized donor organs was advocated as a strategy to maximize the use of scarce donor organs. Our observation of a correlation of donor undersize with more severe intimal thickness suggests that this approach cannot be generally recommended.

Donor age has been identified previously as a risk factor for transplant CAD by our group[1,2] and Sharples et al,[18] but not by others.[3,20] In the present study, donor age was an independent predictor of angiographic transplant CAD in the total population but not in the subgroup 1 year after transplantation. Although higher donor age correlated with intimal thickening by univariate analysis, it did not emerge as an independent predictor in the total population or in the subset of patients studied 1 year after transplantation. This observation raises the possibility of at least 2 distinct pathways for the development of transplant CAD. Diffuse intimal thickening typical of early transplant CAD may reflect the proliferative response to alloimmune injury, whereas coronary stenosis typically seen in non-transplant atherosclerosis may indicate accelerated progression of native CAD, which was unrecognized at the time of transplantation. One possible explanation for this observation is that more severe stages of conventional CAD (e.g., atherosclerotic plaque) were transplanted with older, not younger, donor hearts, and that progression of these lesions distinct from transplant

TABLE IV Correlation of Potential Predisposing Donor Factors With Transplant Coronary Artery Disease as Assessed by Intracoronary Ultrasound and Coronary Angiography in the Total Population

	ICUS		Angiography	
	r	p Value	r	p Value
Demographic Characteristics				
Age	−0.04	<0.8	0.26	<0.006*
Dr.–rec. age difference	−0.08	<0.4	−0.14	<0.2
Gender	0.09	<0.4	0.03	<0.8
Dr.–rec. gender difference	−0.08	<0.5	−0.04	<0.7
Male dr. to female rec.	−0.08	<0.5	−0.13	<0.9
Female dr. to male rec.	−0.02	<0.9	−0.05	<0.7
Height	0.08	<0.5	0.12	<0.3
Dr.–rec. height difference	−0.10	<0.4	−0.22	<0.04*
Weight	0.003	<1	0.14	<0.2
Dr.–rec. weight difference	0.17	<0.07	0.01	<1
Dr. >20% oversized	−0.04	<0.06	−0.04	<0.7
Dr. >20% undersized	0.25	<0.01*	0.10	<0.4
BSA	0.08	<0.5	0.19	<0.08
Dr.–rec. difference BSA	0.11	<0.4	−0.10	<0.4
Donor race				
White	0.11	<0.3	0.13	<0.2
Hispanic	−0.07	<0.5	−0.06	<0.6
Black	−0.09	<0.4	−0.12	<0.3
Asian	0.03	0.8	−0.09	<0.4
Dr.–rec. race difference	−0.001	<1	0.003	<1
Clinical Characteristics				
Cause of death				
Brain death	−0.15	<0.2	0.03	<0.8
Trauma	0.15	<0.2	−0.03	<0.8
Duration of hospitalization	0.06	<0.7	0.10	<0.4
Ischemic time	−0.11	<0.3	−0.10	<0.3
Dopamine treatment	−0.07	<0.5	0.01	<0.9
Dopamine dose	0.12	<0.5	0.08	<0.6
Cardiac arrest	−0.03	<0.9	−0.15	<0.3
Positive CMV serostatus	−0.02	<0.9	−0.07	<0.5
Diabetus mellitus	−0.03	<0.9	−0.08	<0.6
Arterial hypertension	−0.14	<0.3	0.01	<1
Positive CAD family history	0.05	<0.7	−0.06	<0.7
Smoking	0.12	<0.4	0.08	<0.6
Serum sodium	0.07	<0.5	−0.19	<0.08
Serum potassium	0.07	<0.6	−0.04	<0.8
Serum creatinine	0.16	<0.2	−0.14	<0.3
Hematocrit	−0.01	<1	0.08	<0.5
White blood count	−0.04	<0.8	0.20	<0.07
Arterial pH	−0.19	<0.08	0.07	<0.6
Arterial PO_2	0.14	<0.3	0.17	<0.2
Immunologic Characteristics				
Blood group				
A	0.01	<1	0.15	<0.2
B	0.02	<0.9	−0.12	<0.2
O	−0.03	<0.8	−0.05	<0.6
AB	0.02	<0.9	−0.10	<0.4
No. of HLA-A mismatches	−0.08	<0.5	−0.09	<0.4
No. of HLA-B mismatches	−0.03	<0.8	−0.01	<1
No. of HLA-A + B mismatches	−0.06	<0.6	−0.03	<0.8
Duration post-transplantation	0.30	0.001*	0.07	<0.5

*p <0.05.
ICUS = intracoronary ultrasound; other abbreviations as in Tables I to III.

TABLE V Correlation of Potential Predisposing Donor Factors With Transplant Coronary Artery Disease as Assessed by Intracoronary Ultrasound and Coronary Angiography in the Subgroup of Patients Studied One Year After Transplantation (n = 39)

	ICUS		Angiography	
	r	p Value	r	p Value
Demographic Characteristics				
Age	−0.04	<0.9	0.32	<0.05*
Dr.–rec. age difference	−0.01	<1	−0.10	<0.6
Gender	−0.15	<0.4	−0.07	<0.7
Dr.–rec. gender difference	0.04	<0.9	−0.14	<0.5
Male dr. to female rec.	−0.10	0.6	−0.10	<0.6
Female dr. to male rec.	0.18	<0.3	−0.08	<0.7
Height	−0.10	<0.6	−0.05	<0.8
Dr.–rec. height difference	−0.004	<1	−0.32	<0.07
Weight	−0.03	<0.9	0.05	<0.8
Dr.–rec. weight difference	−0.11	<0.6	−0.05	<0.8
Dr. >20% oversized	−0.07	<0.7	0.05	<0.8
Dr. >20% undersized	−0.19	<0.3	−0.07	<0.7
BSA	−0.08	<0.7	0.03	<0.9
Dr.–rec. difference BSA	0.15	<0.4	−0.21	<0.3
Donor race				
White	0.35	<0.05*	0.13	<0.5
Hispanic	−0.05	<0.2	−0.10	<0.6
Black	−0.16	<0.4	−0.06	<0.8
Asian	0.03	<0.9	−0.09	<0.4
Dr.–rec. race difference	−0.36	<0.04*	0.12	<0.6
Clinical Characteristics				
Cause of death				
Brain death	−0.10	<0.6	0.11	<0.6
Trauma	0.12	<0.5	−0.11	<1
Duration of hospitalization	−0.23	<0.3	−0.22	<0.3
Ischemic time	−0.34	<0.04*	−0.16	<0.4
Dopamine treatment	−0.10	<0.6	0.17	<0.4
Dopamine dose	0.15	<0.6	−0.14	<0.6
Cardiac arrest	−0.05	<0.3	−0.10	<0.7
Positive CMV serostatus	0.24	<0.2	−0.01	<1
Diabetes mellitus	0.13	<0.6	−0.09	<0.7
Arterial hypertension	−0.26	<0.3	−0.11	<0.6
Positive CAD family history	0.24	<0.3	−0.07	<0.8
Smoking	0.50	<0.03*	0.12	<0.7
Serum sodium	0.09	<0.7	−0.20	<0.3
Serium potassium	0.14	<0.5	−0.004	<1
Serum creatinine	0.10	<0.6	−0.08	<0.7
Hematocrit	−0.17	<0.4	0.31	0.1
White blood count	−0.14	<0.5	0.29	<0.2
Arterial pH	−0.20	<0.3	0.04	<0.9
Arterial PO_2	0.02	<1	0.46	<0.03*
Immunologic Characteristics				
Blood group				
A	0.17	<0.4	0.07	<0.7
B	−0.17	<0.4	−0.08	<0.7
O	−0.15	<0.4	−0.02	<1
AB	0.12	<0.5	−0.05	<0.8
No. of HLA-A mismatches	0.05	<0.8	0.10	<0.6
No. of HLA-B mismatches	0.10	<0.6	0.03	<0.9
No. of HLA-A + B mismatches	−0.01	<1	0.20	<0.3
No. of HLA-DR mismatches	−0.46	<0.03*	−0.06	<0.8
Total no. of HLA mismatches	−0.19	<0.4	0.05	<0.9

*p <0.05.
Abbreviations as in Tables I to IV.

CAD led to isolated luminal stenoses visible by angiography. In support of this hypothesis, Schüler et al[26] found a higher incidence of focal CAD in transplant patients with hearts from older donors.

In the present study, an inverse correlation of the number of HLA-DR mismatches, but not of HLA-A or HLA-B mismatches with ICUS intimal thickness, was found in the group studied 1 year after transplantation. Similar results have been obtained by Narrod et al,[16] whereas some groups found no[21–23] and others a positive[3,27] correlation between number of HLA-DR mismatches and transplant CAD. Conflicting results have also been reported for the association of number of HLA-A and HLA-B mismatches with transplant CAD.[3,16,21–23,27,28] Interestingly, a negative correlation of the number of HLA-A mismatches with the "vanishing bile duct syndrome" was described in liver transplant recipients, and it was hypothesized that matching at the HLA-A locus facilitates the interaction of antigen-presenting cells with inducer/effector cells and the transduction of positive signals resulting in T-cell activation.[29]

Except for hyperlipidemia,[12,15,18,20,24] no studies to date have shown a relation between transplant CAD and conventional CAD risk factors. Our results provide evidence for the first time that a donor smoking history predisposes to more intimal thickness by ICUS 1 year after transplantation. This early intimal thickening probably reflects a predisposition to myointimal proliferation mediated by smoking, which is then accelerated following the initiation of the alloimmune response. Alternatively, preexisting intimal thickening in these donor hearts may have been present before heart transplantation. The impact of donor hyperlipidemia cannot be assessed because these data were not available. However, post-transplant hypertriglyceridemia and weight were found to be independent predictors of intimal thickening and coronary artery stenosis. This observation supports an important role for dyslipidemia in the development of transplant CAD, and suggests that mechanisms distinct from the alloimmune response may be involved.

Study limitations: Several limitations have to be taken into account when interpreting the results of this study. First, analysis of the donor characteristics was performed retrospectively. Second, the study population represented a selected group of transplant patients consenting to undergo ICUS and angiography rather than a consecutive series of transplant recipients, and there was a wide range of duration after transplantation at the time of the study. Because ICUS was introduced into clinical use only in the late 1980s, results in large consecutive

series of patients studied at different time intervals after transplantation will not be available for several years. Because duration post-transplantation was an independent predictor of ICUS transplant CAD, the subgroup of patients studied 1 year after transplantation was analyzed separately. Third, the many variables evaluated in this study raise the possibility of finding significant correlations by chance, and positive correlations must therefore be interpreted carefully. Fourth, the reported measurements of intimal thickness represent the disease process in a limited number of sites along the proximal ⅔ of the left anterior descending or left circumflex coronary artery. Given the predominantly diffuse nature of transplant CAD,[5] these selective measurements likely reflect the overall extent of the disease. Finally, the lack of baseline assessment of transplant CAD precludes determination of whether the disease was preexisting at the time of transplantation, or whether donor factors accelerated the post-transplant cause of an alloimmune-mediated phenomenon. This intriguing question needs to be addressed through a prospective experimental design.

Conclusions: The observations of this retrospective analysis suggest that donor factors may contribute significantly to the development of transplant CAD. In particular, the observation that donor age and smoking were predictors of transplant CAD, independent of post-transplant factors, suggests that a predisposition for transplant CAD may exist in the donor heart. This predisposition may relate to endothelial injury as a consequence of conventional risk factors such as smoking, age, or dyslipidemia. Data from this study suggest that such donor predisposition to transplant CAD is further propagated by hypertriglyceridemia and obesity after transplantation. These results do not support donor/recipient immunologic differences as primary factors for the development of transplant CAD in the current clinical setting.

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