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ORIGINAL ARTICLE

Risk factors for the development of coronary artery disease of a grafted heart as detected very early after orthotopic heart transplantation

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Summary

Orthotopic heart transplantation (OHTx) represents a well established method of end-stage heart failure treatment. Allograft coronary artery disease (CAD) still remains to be one of the most important limiting factors for OHTx recipients' long-term survival. Unfortunately, allograft CAD can be detected very early after OHTx. Our study was designed to identify risk factors for early allograft CAD development. Eighty-three OHTx recipients (18 females, 65 males, mean age 50.55 ± 11.04 years) with coronary intravascular ultrasound examination performed early after OHTx (29.81 ± 12.45 days) formed the study population. The impact of a number of pre-, peri- and early post-transplant possible risk factors on early allograft CAD development was studied. By multivariate analysis, only higher donor age ($P < 0.001$) and higher recipient's body mass index ($P = 0.003$) were found to represent risk factors for the early development of allograft CAD.

Introduction

Orthotopic heart transplantation (OHTx) represents a well-established method of end-stage heart failure treatment. Despite huge progress in transplantation medicine, allograft vasculopathy still remains to be one of the most important limiting factors for OHTx recipient's long-term survival [1]. Unfortunately, based on coronary intravascular ultrasound examinations, morphological abnormalities of the graft's coronary arteries can be detected very early after OHTx in a number of cases [2,3]. Despite its negative prognostic impact on OHTx recipients' outcome, the etiology of the graft's coronary artery pathology detected early after OHTx still remains to be speculative. Based on morphological characteristics and the short time after the procedure, they are thought to be of donor origin [4] but no proof exists so far. Surprisingly, little data are available on the risk factors for the development of the graft's coronary artery pathology detected very early after OHTx. Risk factor knowledge could help us to understand its etiology and more importantly to identify the OHTx recipients in risk of early development of the graft's coronary artery disease (CAD).

Therefore, we have designed a retrospective study in order to identify the risk factors for the very early development of the graft's CAD as detected by coronary intravascular ultrasound examination (cIVUS).

Study group

Our study population was recruited from 165 OHTx performed at the Center of Cardiology IKEM between January 1999 and July 2003.

From this large cohort, 83 OHTx recipients (18 females, 65 males, mean age 50.55 ± 11.04 years) with cIVUS performed early after OHTx (29.81 ± 12.45 days) formed the study population. Pretransplant diagnoses were as follows: ischemic cardiomyopathy 34, dilated

cardiomyopathy 38, restrictive cardiomyopathy 1, hypertrophic cardiomyopathy 1, congenital heart disease 4, valvular heart disease 5.

All enrolled patients were in good clinical condition at the time of the cIVUS, i.e., no signs of acute rejection (Banff >1B), no signs of infection, and acceptable renal function (serum creatinine <150 μmol/l).

The remaining 82 OHTx recipients were not enrolled in the study for different reasons. There were 15 deaths within the fourth week after OHTx. There were two cases of pediatric transplantations and one case of combined heart and kidney transplantation. Another two recipients were excluded from the study because of adverse clinical status at week 4 after the procedure, and another two of the recipients were followed up in another center after successful OHTx. Furthermore, five cases were excluded from the study because of known donor CAD as proved by coronary angiography prior to the harvesting. In 55 cases, we failed to obtain recipients' informed consent with the coronary angiography and intravascular coronary ultrasound examinations at week 4 after successful OHTx.

Heart transplantation management

Donor evaluation

Potential heart donors must meet the generally accepted medical criteria (i.e. age: male <50 years, female <55 years, donor/recipient weight mismatch <0.8, good graft function, left ventricle ejection fraction >50% with no left ventricle wall motion abnormality as assessed by echocardiography and/or left ventriculography), no history of cardiopulmonary resuscitation or prolonged circulatory instability, no need for advanced pharmacological circulatory support, freedom from any infection or malignancy (except some primary brain tumors) and legal criteria (clinical signs of brain death accompanied by angiographically proven brain death). From a CAD point of view, all older potential heart donors (i.e. male >45 years and female >50 years) or donors in suspicion of suffering from CAD (history, risk factors, noninvasive tests) are to be referred to coronary angiography prior to harvesting, which is available for everyone 24 h a day in our country. Only patients without angiographically apparent significant CAD can be accepted as heart donors. Donors with significant CAD that is suitable for complete coronary revascularization (either surgical or percutaneous) can be accepted only for super urgent recipients.

Immunosuppressive therapy

All patients received induction therapy with anti-CD3 antibody/antithymocyte globulin until reaching the therapeutic target cyclosporine A (CyA) plasma levels. The basic immunosuppressive regimen consisted of CyA with target plasma levels of 300–400 ng/ml, azathioprine (1–2 mg/kg/day) and prednisone (starting doses 1 mg/kg/day with subsequent dose reduction to 0.22 ± 0.08 mg/kg/day at week 4 after OHTx) – see Table 1.

Other medication

All patients were treated with pravastatin (10 mg/day or more depending on their plasma cholesterol levels) and ASA 100 mg/day. Other medication (mostly anti-hypertensive drugs and anti-diabetics) was given depending on the patient's clinical status. Medication is summarized in Table 2.

Acute rejection surveillance program

Regularly performed endomyocardial biopsies were used as a screening method in the acute rejection surveillance program, with the first one being performed on the seventh day after OHTx followed by another three every week. The Banff classification was used in evaluating endomyocardial biopsies.

Management of acute rejection treatment

Clinically silent cellular acute rejections of grade >1B (Banff classification) were treated by i.v. steroids (methylprednisolone, 3 g). On-going clinically silent cellular acute rejections were treated by i.v. steroids and basic immunosuppressive regimen switch (CyA to tacrolimus and/or AZA to MMF). Clinically apparent (echocardiographically proven graft dysfunction, clinically apparent graft failure,

Table 1. Immunosuppressive medication.

Medication	Cases (*n*)	Dose	%
Cyclosporin (Neoral)	83	–	100
Azathioprin	80	1 mg/kg/day	96
Mycophenolate mofetil	3	3 g/day	4
Prednisone*	83	0.22 ± 0.08 mg/kg/day	100

*Doses at week 4 after orthotopic heart transplantation.

Table 2. Other medication.

Medication	Cases, *n*(%)
β-blockers	49 (59)
Angiotensin-converting enzyme inhibitors/angiotensin receptor C (ACEI/AT)$_{blockers}$	23/1 (29)
Ca-antagonists	12 (14)
Diuretics	32 (39)
Anti-diabetics	3 (4)
Insulin	16 (19)

arrhythmias) cellular acute rejections of grade >1B were treated by anti-CD3/antibody/antithymocyte globulin therapy and basic immunosuppressive regimen switch (CyA to tacrolimus and/or AZA to MMF). No acute humoral rejections were observed in this study population.

CMV prophylaxis and CMV infection management

No cytomegalovirus (CMV) prophylaxis is given in our center. Only clinically apparent CMV infections are treated with ganciclovir therapy.

Allograft CAD surveillance program

Neither invasive (coronary angiography or cIVUS) nor noninvasive tests are routinely performed at our center to screen the allograft CAD presence. These tests are generally performed only in the case of clinical suspicion in the presence of allograft CAD, or as a part of study protocols after obtaining recipients informed consent with the procedure.

Methods

cIVUS examination

All enrolled patients underwent cIVUS on week 4 after OHTx (mean time 29.81 ± 12.45 days). After routine coronary angiography, a 30 MHz 2.9F ultrasound catheter (Jomed/Endosonic Avanar F/X, Jomed Inc., Rancho Cordova, CA, USA, cat. no REF 85700) was passed over an angioplasty-guiding catheter into the most distal location in the left anterior descending and right coronary artery or ramus circumflexus (depending on artery dominance). Ultrasound images were recorded on a CD during a distal to proximal manual pullback. Recorded ultrasound images were analyzed using an image processing computer (Endosonics Jomed, Rancho Cordova, CA, USA; in-vision gold V4.0.1). The vessel lumen and lamina elastica externa borders were manually traced and the manual measurements of maximum plaque thickness were performed. Any focal arterial wall thickness in the cIVUS image with a plaque thickness of ≥0.5 mm was regarded as a pathologic lesion, a criterion consistent with previously published studies [4].

Risk factors for early detected graft's CAD

A number of potential risk factors concerning the recipient [age, gender, pretransplant diagnosis, body mass index (BMI), cholesterolemia, triglycriidemia, urgent status, pretransplant nonpharmacological circulatory support], the donor (age, gender, weight, BMI, CMV status, cause of death, history of smoking, history of hypertension, history of diabetes, history of hyperlipidemia, unknown history), immunology (pretransplant panel reactive antibodies, HLA mismatch, gender mismatch), the peri-transplant period (cold ischemia time, CMV mismatch) and the early (first 4 weeks) post-transplant period [incidence of acute rejection Banff >1B, the incidence of clinically apparent acute rejection (i.e. echocardiographically proven graft dysfunction, clinically apparent graft failure, arrhythmias), acute rejection score, graft dysfunction, infection, CMV infection, presence of hypertension, diabetes, and hyperlipidemia] were evaluated in relation to the presence of an early detected graft's CAD.

Statistics

Continuous variables (data) are expressed as mean ± SD. Univariate analysis [using *t*-test or Mann–Whitney for continuous variables and the Chi-square test (with Yates correction) for categorical variables] and multivariate analysis (logistic regression) were performed in order to identify the risk factors for early detected graft's CAD. A *P*-value of <0.05 was considered as statistically significant.

Results

Incidence of graft's CAD

Allograft CAD was detected in 37 cases (i.e. 45%) early (mean time 29.81 ± 12.45 days) after OHTx.

Risk factors for early detected graft's CAD

Influences of every single possible risk factor on the early development of graft's CAD are summarized in Table 3 (univariate analysis) and in Table 4 (multivariate analysis). By univariate analysis, the higher recipient's BMI (25.63 ± 4.04 vs. 23.39 ± 3.5, $P = 0.008$), the higher donor's age (40.67 ± 9.38 vs. 27.74 ± 9.59, $P < 0.0001$), the donor's cause of death – typical intracranial hemorrhage (13% vs. 0%, $P = 0.01$), and the donor's history of hypertension (16% vs. 0%, $P = 0.008$) were found to represent a risk factors for the allograft CAD early development.

By multivariate analysis, only the higher donor age ($P < 0.001$) and higher recipients' BMI ($P = 0.003$) were found to represent risk factors for early development of allograft CAD. Although a strong statistical significance of donor history of hypertension was found in univariate analysis, the history of donor hypertension was not found to be an independent risk factor in multivariate analysis due to its dependency on donor age.

Using a logistic regression model, donors' age and recipients' BMI can predict cIVUS early detected allograft CAD (EDACAD) with a sensitivity of 89%, specificity

Table 3. Risk factors for early detectedallograft coronary artery disease (EDACAD) development – univariate analysis.

Risk factor	EDACAD+	EDACAD–	*P*-value
Recipient			
Gender (male/female)	32/5	33/13	0.1
Age (years)	51.67 ± 9.17	49.65 ± 12.37	0.79
PreTx dg (DCM/ICM/other)	17/17/3	21/15/10	0.48
Diabetes mellitus	5	7	0.83
Cholesterolemia (mmol/l)	4.58 ± 1.38	4.6 ± 1.26	0.45
Triglycidemia (mmol/l)	1.54 ± 0.6	1.33 ± 0.79	0.37
Weight (kg)	81.66 ± 14.18	73.7 ± 11.9	0.01
BMI	25.63 ± 4.04	23.39 ± 3.5	0.008
Urgent status	20	29	0.41
Nonpharmacological support	0	0	1.0
Pretransplant panel reactive antibodies (PRA) (%)	0.24 ± 0.78	0.18 ± 0.72	0.76
Donor			
Gender (M/F)	28/9	39/7	0.29
Age (years)	40.67 ± 9.38	27.74 ± 9.59	<0.001
BMI	25.78 ± 2.83	24.55 ± 4.67	0.15
CMV status	13/24	18/27	0.65
Cause of death (typical intracranial hemorrhage/other)	5/32	0/46	0.01
Smoking	1	0	0.26
Hypertension	6	0	0.005
Diabetes mellitus	0	0	1.0
Hyperlipidemia	0	0	1.0
Unknown history	12	11	0.4
Recipient/donor			
HLA mismatch	5.07 ± 1.1	5 ± 0.97	0.84
Gender mismatch	6	11	0.4
CMV mismatch	0/37	1/44	1.0
Transplantation			
Cold ischemic time (min)	148.9 ± 36.71	148.7 ± 49.2	0.98
Post-transplant period			
Incidence of acute rejection >1B	23	15	0.11
Acute rejection score	0.71 ± 0.64	0.56 ± 0.5	0.22
Incidence of clinical apparent acute rejection	4	0	0.08
Graft dysfunction	1	0	0.27
CMV infection (seven cases)	1	0	1.0
Other infections	2	4	0.55
Hypertension	25	23	0.11
Diabetes mellitus	19	14	0.05
Cholesterolemia (mmol/l)	5.57 ± 1.36	5.18 ± 0.98	0.19
Triglycidemia (mmol/l)	1.84 ± 0.93	1.76 ± 0.68	0.68
Steroids above basic immunosuppression (g/patient)	1.1 ± 1.44	0.58 ± 1.4	0.12

DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; BMI, body mass index.

75%, positive predictive value 90%, and negative predictive value 75% (Fig. 1).

Discussion

The main result of our study is that only a higher donor age and a recipient's higher BMI represent the independent risk factors for the early development of allograft CAD. Univariate analysis shows the possible impact of the donor's history of hypertension and cause of death on early allograft coronary artery pathology development. Very importantly, neither any peri- nor post-transplant possible risk factor including incidence and severity (significance) of acute rejection or CMV infections was found to have any impact on early allograft coronary artery pathology development in our study population. Taking the results of our study and the epidemiology of asymptomatic coronary artery pathology in general population

Table 4. Risk factors for early detected allograft coronary artery disease (EDACAD) development – multivariate analysis.

Risk factor	EDACAD+	EDACAD–	*P*-value
Recipient			
Gender (male/female)	32/5	33/13	NS
Age (years)	51.67 ± 9.17	49.65 ± 12.37	NS
PreTx dg (DCM/ICM/other)	17/17/3	21/15/10	NS
Diabetes mellitus	5	7	NS
Cholesterolemia (mmol/l)	4.58 ± 1.38	4.6 ± 1.26	NS
Triglycidemia (mmol/l)	1.54 ± 0.6	1.33 ± 0.79	NS
Weight (kg)	81.66 ± 14.18	73.7 ± 11.9	NS
BMI	25.63 ± 4.04	23.39 ± 3.5	0.003
Urgent status	20	29	NS
Nonpharmacological support	0	0	NS
Pretransplant PRA (%)	0.24 ± 0.78	0.18 ± 0.72	NS
Donor			
Gender (M/F)	28/9	39/7	NS
Age (years)	40.67 ± 9.38	27.74 ± 9.59	<0.0001
BMI	25.78 ± 2.83	24.55 ± 4.67	NS
CMV status			NS
Cause of death (typical intracranial hemorrhage/other)	5/32	0/46	NS
Smoking	1	0	NS
Hypertension	6	0	NS
Diabetes mellitus	0	0	NS
Hyperlipidemia	0	0	NS
Unknown history	12	11	NS
Recipient/donor			
HLA mismatch	5.07 ± 1.1	5 ± 0.97	NS
Gender mismatch	6	11	NS
CMV mismatch			NS
Transplantation			
Cold ischemic time (min)	148.9 ± 36.71	148.7 ± 49.2	NS
Posttransplant period			
Incidence of acute rejection >1B	23	15	NS
Acute rejection score	0.71 ± 0.64	0.56 ± 0.5	NS
Incidence of clinical apparent acute rejection	4	0	NS
Graft dysfunction	1	0	NS
CMV infection (seven cases)	1	0	NS
Other infections	2	4	NS
Hypertension	25	23	NS
Diabetes mellitus	19	14	NS
Cholesterolemia (mmol/l)	5.57 ± 1.36	5.18 ± 0.98	NS
Triglycidemia (mmol/l)	1.84 ± 0.93	1.76 ± 0.68	NS
Steroids above basic immunosuppression (g/patient)	1.1 ± 1.44	0.58 ± 1.4	NS

DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; BMI, body mass index.

[5–9] all together, these data strongly support the crucial role of donor characteristics in the early development of allograft coronary artery pathology.

As being the most important limiting factor for OHTx recipients' long-term survival, a large number of studies have tried to identify the risk factors for the allograft CAD development. Surprisingly, despite a number of persuading data showing allograft CAD to be detected very early after OHTx in a large number of cases [2,3], almost all previously published studies have evaluated the risk factors for later (1 year and later after OHTx) development of the allograft CAD or for the progression of EDACAD. Very surprisingly, there is only one previously published study identifying the risk factor for EDACAD development [2]. Tuzcu *et al.* [2] have found only donor's age, recipient's age, and donor's gender to be independent risk factors for the presence of EDACAD. The current study differs in many ways

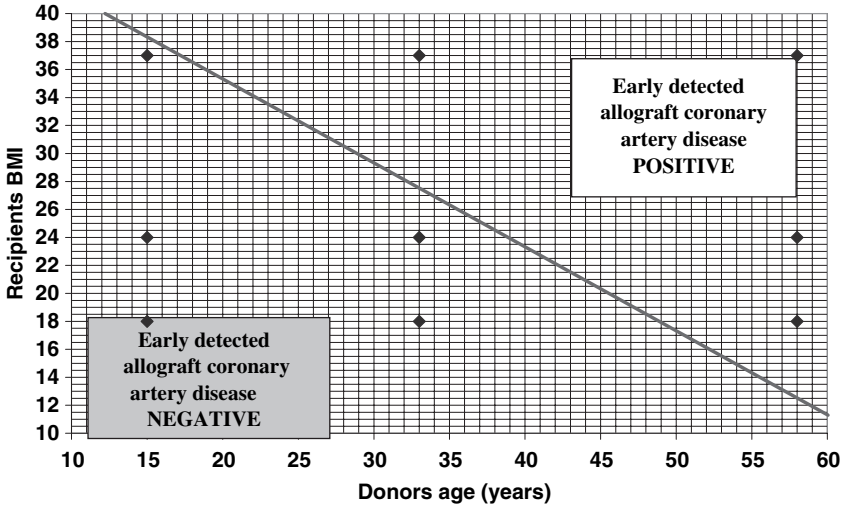

Figure 1 Predictive model for early detected allograft coronary artery disease presence (logistic regression model, sensitivity 89%, specificity 75%, positive predictive value 90%, negative predictive value 75%).

from the cited one: a larger study cohort (83 OHTx recipient in our study versus 50 OHTx recipients), earlier cIVUS examinations (4.47 ± 1.6 weeks after OHTx in our study versus 4.6 ± 2.6 weeks), a little bit lower incidence of EDACAD (45% in our study versus 56%), and a higher number of tested possible risk factors. In contrast to Tuzcu *et al.*, we failed to prove the recipient's age to be a risk factor for EDACAD development. On the other hand, despite a more comprehensive approach, we were unable to identify any other risk factor for early allograft CAD development except the recipients BMI and, similar to Tuzcu *et al.*, donor age. Similar to Tuzcu *et al.*, we failed to prove any post-transplant factors including classical risk factors, CMV infection and acute rejection to be an independent factor for EDACAD development.

Our study demonstrates that a donor's characteristics play a crucial role in the early allograft CAD development. Age and hypertension represent both generally well-accepted risk factors for endothelial dysfunction and atherosclerosis development. As these are related only to the donor, the results of our study strongly support the theory of donor *in vivo* developed coronary artery pathology caused by classical atherosclerotic risk factors.

In contrast, other classical atherosclerotic risk factors possibly affecting coronary arteries before harvesting – donor gender, donors' history of diabetes, hyperlipidemia or smoking – were found not to be risk factors for early developed CAD. The main reasons for these findings are as follows: the majority of donors were males (males 81%, females 19%); furthermore, male donors were significantly younger than females (donor males age 31.58 ± 10.77, donor females age 40.94 ± 11.63, $P = 0.004$). Therefore, from a gender point of view, the donor population is not ideal and this is probably the reason for the possibility of underestimating the male donor as a risk factor for the early development of allograft CAD in our study. Incidence of donor diabetes mellitus and hyperlipidemia was also found not to represent a risk factor for allograft coronary artery early development. In our retrospective manner of the study, the low incidence of documented donor history of diabetes (0%), hyperlipidemia (0%) and smoking (1%) was highly the probable reasons for these findings. There are three major reasons for such low incidence of traditional atherosclerotic risk factors within our donor population. The first one is the donor population mean age of 33.51 ± 11.45 years, which makes the donor population quite young with lower probability of the manifestation of diabetes and hypertension. Second, donor population generally represents previously healthy individuals usually dying of sudden accidents (trauma, cerebrovascular catastrophe). Individuals suffering from any atherosclerotic risk factors (or any other disease) were further evaluated through the donor evaluation procedures and might be excluded from the program due to the CAD. Therefore, the accepted heart donors represent quite a selected population from the point of atherosclerotic risk factors and its possible vascular complications. Third, this study was designed as a retrospective one. Only the data collected and available at the time of the donor evaluation process were analyzed. No retrospective completions of the donor history data were performed for ethical reasons. Therefore, the history data (especially the history of smoking) might be incomplete in some cases, which may lead to the underestimation of some classical atherosclerotic risk factors within our donor population.

In contrast, donor gender, age, the cause of death, and the CMV status are well-documented data, easy to document and analyze.

Any of the recipient's pretransplant characteristics were found not to have any influence on allograft CAD early development except of recipient's BMI. The reasons for this finding remain speculative. Based on the knowledge of clinical practice (recipient/donor weight mismatch <0.8), one could expect the recipient's BMI to be correlated with a donor's BMI – recipient with higher BMI requires a donor with corresponding anthropologic parameters. Thus, the recipient's BMI could (through donor's BMI) influence the allograft coronary artery status. Surprisingly, no such observation – donor and recipient BMI correlation – was made in our study ($r = 0.2$, $P = 0.07$). The main reason for this observation is probably an inaccurate donor's BMI measurement, as donor BMI value is obtained from donor weight and height estimation (the clinical practice in our country) and not from an accurate measurement (as in the case of recipient's BMI). A possible coincidence of a higher recipient's BMI and higher incidence of donor history of hypertension ($P = 0.54$), diabetes ($P = 1.0$), hyperlipidemia ($P = 1.0$) or smoking ($P = 1.0$), which is based on the above-described thesis, might also explain the impact of the recipient BMI on the early development of the allograft CAD was not observed.

Concerning the close peri-transplant and early post-tranplant period, a number of factors – both immunologic and non-immunologic ones – have been tested as possible risk factors for early allograft CAD development. Neither any classical atherosclerotic nor immunologic factors have been found to represent an independent risk factor for the early allograft coronary artery development. This is of interest, especially because acute rejections and CMV infection are speculated to play an important role in allograft coronary artery pathology development.

Concerning acute rejections, neither the incidence of higher grades of acute rejection, acute rejection score (biopsy score) nor incidence of clinically apparent acute rejection was found to be a risk factor for early allograft CAD development in our study. Similar to the number of previously published studies addressing the issue of allograft CAD development, the incidence and severity of acute rejections (as expressed by incidence of grade >1B acute rejections, incidence of clinically apparent acute rejections, a rejection score in our study) were chosen as a surrogate marker for anti-donor immune system activity. If a level of a recipients' immune system (re)activity against donor antigens is graded by the incidence and/or severity of acute rejections (as it is in almost all studies addressing the issue of allograft CAD development, including current study), the impact of anti-donor immunity on EDACAD development was not observed. There is a definite need for a better surrogate marker of anti-donor recipient immune system reactivity, to be able to definitely exclude or prove the impact of anti-donor immune system activity on EDACAD development.

Our study also failed to find any correlation between the CMV infection and early allograft CAD development. In fact, the incidence of CMV infection, both primoinfection and reinfection/reactivation, was very low in our study cohort, in spite of our center's approach of not using CMV prophylactic therapy. Neither the clinically apparent CMV infection (signs of possible CMV infection in combination with CMV-IgM positivity and/or CMV early antigen PCR detection) nor CMV primoinfection (CMV-IgM switch in pretransplant CMV IgM and IgG negative recipients) were observed within the study population. Only seven cases of reinfection/reactivation were documented (pretransplant CMV-IgM negative and CMV-IgG positive recipients), and only one recipient out of these seven cases suffered from EDACAD. Therefore, our study shows that EDACAD can develop in a large number of cases even in the cohort of recipients with low incidence of CMV infection despite not using CMV prophylactic therapy. These results might be in contrast to expected ones and also to results of the Valantine *et al.* study [9], which has demonstrated the positive impact of CMV prophylactic therapy on allograft CAD development. In fact, the Valantine *et al.* study addressed the impact of CMV prophylactic therapy on the later development of allograft CAD only in a group of high-risk recipients (i.e. seronegative recipient and seropositive donor), and no data of CMV prophylactic therapy impact on EDACAD were presented. Therefore, no proof for CMV infection or CMV prophylactic therapy influence on early allograft CAD development exists so far.

It is important to stress that not proving acute rejections, CMV infections, post-transplant diabetes, hypertension, and hyperlipidemia impact on early allograft CAD development does not exclude these possible risk factors from having any influence on the later allograft CAD development as demonstrated in a number of other studies. The differences in risk factors for the early and later allograft CAD development might represent some 'time factor', which different risk factors need to cause allograft coronary arteries to become diseased.

Study limitations

The authors are aware of some study limitations. The first one is the retrospective manner of the study. As discussed before, the retrospective manner of the study has influenced especially the impact of some donor characteristics on the early allograft CAD development. On the other hand, this possible underestimation surely does not have an impact on the ' results' of all peri- and post-transplant risk factors. If any positive correlation between another

Table 5. Basic demographic and clinical data of enrolled and not enrolled recipients.

	Study population	Not enrolled population	*P*-value
Number of recipients	83	80 (+2 children)	
Age (years)	50.55 ± 11.04	48.84 ± 12.31	0.34
Sex (female/male)	18/65	15/65	0.78
PreTx dg (DCM/ICM/other)	38/34/11	36/33/11	0.96
Body mass index	24.40 ± 3.89	25.28 ± 4.37	0.22
Diabetes mellitus	33	22	0.67
Hypertension	49	41	0.57
Cholesterolemia (mmol/l)	5.35 ± 1.16	5.47 ± 1.29	0.63
Triglycidemia (mmol/l)	1.80 ± 0.79	1.81 ± 0.96	0.96
Incidence of acute rejection >1B (per patient)	0.47 ± 0.82	0.24 ± 0.68	0.08
Acute rejection score	0.62 ± 0.57	0.42 ± 0.82	0.02

DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy.

donor characteristics (diabetes, hypertension, hyperlipidemia, smoking) and the early allograft CAD development was observed, this would only confirm the importance of donor characteristics on the early allograft CAD development. Second, there is no doubt that this is a single center study. Its results are limited due to potential differences in routine management of both donor and recipient populations (donor evaluation criteria, induction theraphy, chronic immunosuppressive protocols, nonimmunosuppressive medication, CMV prophylaxis etc.) between our and other centers.

Third, mainly due to our center policy (see Allograft CAD surveillance program) we were able to enroll only 83 recipients from the whole cohort of 165 OHTx performed at our center between January 1999 and July 2003. As there were no significant differences in basic demographic data or clinical status (except for acute rejection (AR) score – study population with a higher AR score) between study population and the rest of recipients (Table 5), the study population can be regarded as a representative sample. Fourth, despite high statistical significance, our study cannot directly prove the donor origin of early detected allograft coronary artery pathology as no cIVUS examinations of graft were performed prior to harvesting. Three possible ways of how donor characteristics can dramatically influence the incidence of EDACAD are to be discussed. The presence of coronary arteriosclerosis developed before and transmitted through the OHTx is the first one. The presence of coronary endothelial dysfunction developed prior to graft harvesting and transmitted through OHTx is the second way. Finally, the donor-determined susceptibility (including genetics) of donor coronary arteries to different endothelial injuries must be taken into consideration as a third way. Unfortunately, the setting of our study has not allowed us to answer this issue.

Conclusions

Our study proves a high incidence of EDACAD. More importantly, our study clearly shows that the donor age and recipient's BMI represent independent risk factors for early allograft CAD development. This conclusion, together with the results of the univariate analysis, strongly supports the theory of the crucial role of donor characteristics on early allograft coronary artery development. Neither any immunologic factor nor CMV infection was found to represent a risk factor for the early allograft CAD development.

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