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Heart Transplantation and Risk of Cardiac Vasculopathy Development: What Factors Are Important?

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Background: The aim of this study was to find the main risk factors for development of cardiac allograft vasculopathy (CAV), especially factors identified before the surgical procedure and factors related to the recipient profile and the medical history of the donor.

Material/Methods: There were 147 patients who had heart transplantation (HT) included in this study: mean age was 45.8 ± 15.3 years. All study patients had coronary angiography after HT. Analyzed risk factors were: non-immunologic recipient risk factors (age of transplantation, smoking, hypertension, lipids, diabetes, obesity and weight gain after HT), immunologic recipient risk factors (acute cellular rejection (ACR), acute humoral rejection (AMR), cytomegalovirus (CMV) episodes), and donor-related risk factors (age, sex, catecholamine usage, ischemic time, compatibility of sex and blood groups, cause of death, cardiac arrest).

Results: CAV was recognized in 48 patients (CAV group); mean age 53.6 ± 13.6 years. There were 99 patients without CAV (nonCAV group); mean age 48.3 ± 15.5 years. A univariate Cox analysis of the development of coronary disease showed statistical significance ($p < 0.05$) for baseline high-density lipoprotein (HDL), ACR, AMR, CMV, and donor age. Multivariate Cox regression model confirmed that only baseline HDL, episodes of ACR, donor age, and CMV infection are significant for the frequency of CAV after HT.

Conclusions: Older donor age is highly associated with CAV development. Older donor age and low level of HDL in heart recipients with the strongest influence of immunologic risk factors (ACR, CMV infection) were linked with development of CAV.

MeSH Keywords: Coronary Artery Disease • Heart Transplantation • Risk Factors

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Background

Cardiac transplantation is a lifesaving therapy for patients with end-stage heart disease. Remarkable progress has been made in terms of controlling acute rejection of the transplanted heart. Nevertheless, three years after the transplantation, cardiac allograft vasculopathy (CAV), malignancy, and renal failure become common causes of death [1]. For this reason, the task of decreasing the burden of CAV in transplanted hearts has become one of the main goals of care in the transplantology arena. Prophylactic strategies have demonstrated significant improvements in long-term prognosis. These include control of classical risk factors for vascular disease (e.g., hyperlipidemia, obesity, hypertension, smoking, and diabetes) as well as controlling immunological risk factors: treatment of acute rejection and cytomegalovirus (CMV) infection, and type of immunosuppression therapy. Donor-related risk factors constitute a separate group of risk factors and encompass donor age, cause of brain death, and ischemia time.

The aim of this study was to find the main risk factors for development of CAV, especially factors identified before the surgical procedure and related to the recipient profile and the medical history of the donor. This study was conducted in one medical center in Poland.

Material and Methods

This study included 147 patients included who had heart transplantation (HT) at our center, and had complete data (including donor history): mean age was 45.8 ± 15.3 , 119 patients were males. All study patients were examined at least once by coronary angiography after HT. The routine protocol included a baseline coronary angiography within one year after HT, and thereafter, once every two years and in all cases when it was clinically indicated. Coronary angiography was performed using standard techniques. All angiograms were examined and each patient's CAV status was classified in accordance with the International Society for Heart and Lung Transplantation (ISHLT) recommended nomenclature as follows: not significant (CAV 0), mild (CAV 1), moderate (CAV 2), severe (CAV 3) [2]. CAV ≥ 1 was classified as CAV disease. Myocardial biopsies were conducted to acute cellular rejection (ACR) and acute humoral rejection (AMR). Biopsies were done according to study protocol: during the first year at two, three, four, six, and eight weeks, in the third month, and then every three months. In the second year after HT, biopsies were performed every six months, followed by once a year and always in all cases when it was clinically indicated.

ACR was classified according to the modified 2004 ISHLT criteria [3]. Cellular rejection ≥ 2 was considered significant and

methylprednisolone pulses were administered. We examined C4d retrospectively as a marker of AMR according to ISHLT nomenclature 2004 [4]. Immunohistochemical staining with polyclonal antibody against C4d was performed for all samples. Staining with antibody against CD68 (macrophages marker) was not performed. AMR 0 was recognized as negative for humoral rejection while AMR 1 was positive for humoral rejection. AMR 1 was diagnosed when more than 50% of capillaries showed strong C4d positive staining. The test for DSA (donor specific antibodies) was not performed, thus antibody-mediated rejection was established based on C4d positivity.

The following recipient risk factors were assessed as well: smoking (pack years of smoking), hypertension (time of treatment), fraction of cholesterol levels, diabetes (years of disease, insulin use), body mass and weight gain after HT.

CMV prophylaxis was given when there was a donor +/-recipient-mismatch or in cases of induction therapy and during high-dose steroids rejection treatments [5]. CMV infection during the study period was also taken into account and was based on clinical symptoms and laboratory tests. We used the CMV pp65 antigenemia test or the quantitative nucleic acid testing (QNAT) for CMV (real-time PCR method) specific diagnosis. Treatment with valganciclovir or intravenous ganciclovir every 12 hours was continued until viral eradication was achieved on one or two assays after a minimum of two weeks.

Triple immunosuppressive therapy was applied and comprised of steroids, cyclosporine or tacrolimus (TAC), mycophenolate mofetil (MMF) or azathioprine or everolimus/sirolimus.

Patients after HT had been receiving anti-thymocyte globulin intravenously or daclizumab (to year 2009) and basiliximab. The initial immunosuppressive regimen consisting of cyclosporine A (CSA) and azathioprine was replaced by CSA and MMF in 2001 and by TAC and MMF in 2009. Additionally, mammalian target of rapamycin (mTOR) inhibitors (everolimus/sirolimus) were used from 2005. The oral dose of CSA was titrated to reach the target through level of 60–250 ng/mL depending on time after HT: <0.5 years after HT, 200–250 ng/mL; 0.5–1 years after HT, 150–200 ng/mL; >1 year after HT, 80–150 ng/mL. The MMF target through level was 1.5–3.0 mg/L. The TAC target through level ranged from 3–20 ng/mL depending on time after HT: <0.5 years after HT, 15–20 ng/mL; >0.5–1 years after HT, 10–15 ng/mL; >1 year after HT, 6–10 ng/mL; >2 years after HT, 5–7 ng/mL. Oral mTOR inhibitor therapy was titrated to achieve the target through level of 3–8 ng/mL (<2 years, 5–8 ng/mL; >2 years, 3–6.5 ng/mL). Steroids were weaned off whenever possible 12 months after HT.

Patients were given statins and acetylic acid in the first month after HT according to our center standards. Donor-related

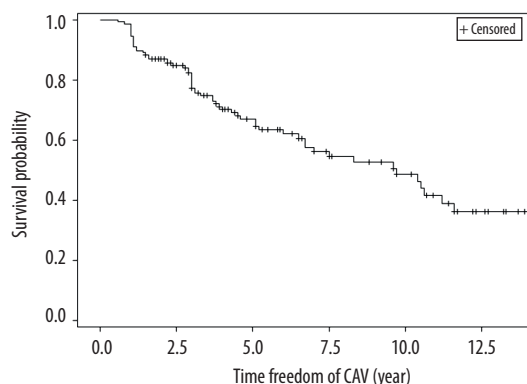


Figure 1. The probability of survival without CAV after HT.

variables were: sex, age, cause of death, catecholamine use (dobutamine $>10 \mu\text{g}/\text{kg}/\text{min}$, dopamine $8\text{--}15 \mu\text{g}/\text{kg}/\text{min}$, adrenal-in $0.06\text{--}0.3 \mu\text{g}/\text{kg}/\text{min}$), blood group matching, ischemia time, and cardiac arrest. Risk factors were divided into three groups: donor-related factors, non-immunologic recipient-related factors, and immunologic recipient-related factors. Either the day of the recognition of coronary artery changes or the date of December 31, 2014 were considered as the end point of the observation period.

Statistical analysis

Continuous variables were presented as median and quartiles, categorical variables were presented as n (%). Wilcoxon rank sum test, chi-square test or Fisher's exact test were used for analysis of patient characteristics as appropriate. Cox proportional hazard models were used to evaluate the risk factors of the development of coronary artery disease after orthotopic HT. The following factors were thought to affect the hazard of CAV: recipient age and sex, baseline values of recipient cholesterol LDL, HDL, TG, BMI, level of catecholamine, and ischemic time during transplantation, compatibility of sex and blood groups between donor and recipient, donor age, sex, and cause of death, sudden cardiac arrest, status of hypertension, diabetes and smoking, immunological factors such as ACR, AMR, and CMV.

The univariable Cox proportional hazards models were developed for each covariate and the final multivariable regression model, which was based on HDL, ACR, CMV, and donor age.

All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and a p -value <0.05 was considered statistically significant.

The proportional hazard assumption was checked using Schoenfeld's residuals, martingale residuals, and cumulative

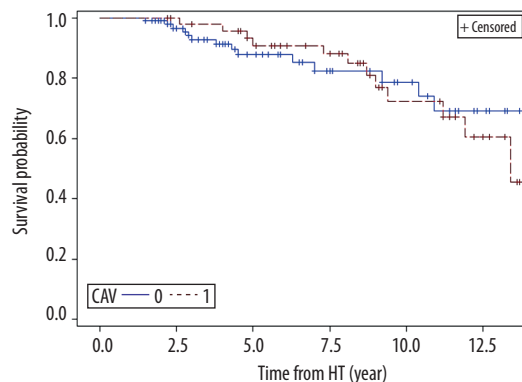


Figure 2. Patient survival curve with regards to having or not developing CAV.

martingale residuals in PROC PHREG. The p -value for all covariates in the supremum test for proportional hazards assumption were greater than 0.05. This confirmed that proportional hazards assumption was not violated and there were no time-dependent covariates in the model. Also the p -value for continuous variables in supremum test for functional form were greater than 0.05.

Results

Among 147 patients included into the study, CAV was identified in 48 patients (39 men), mean age 53.6 ± 13.6 years (the CAV group). Patients without CAV (the nonCAV group) included 99 patients (80 men), mean age 48.3 ± 15.5 years. Patients in the CAV group were older than patients in the nonCAV group, $p=0.0029$. The mean time of observation was 6.6 ± 3.8 years. The time lag between transplantation and CAV was 9.7 years (7.7; 11.6 years), Figure 1.

There was no significant difference between patient survival and developing CAV (log-rank test chi-squared=0.0021 $p=0.963$), Figure 2.

Coronary disease risk factors were compared for the CAV group and the nonCAV group.

Donor-related parameters were measured. In the CAV group, donors were significantly older (38 years versus 30 years, $p=0.0038$). There were no significant differences between groups in the following: catecholamine use, cause of brain death, ischemic time, episodes of cardiac arrest, and blood group identity.

Non-immunologic recipient risk factors were measured. No significant differences were found between the CAV group and

the nonCAV group in the following: frequency of arterial hypertension, new onset of diabetes, smoking, and weight gain. There were also no statistically significant differences in LDL, HDL, and TG levels between the two groups.

Immunologic recipient risk factors were measured. ACR, AMR, and CMV infection were analyzed. Comparing the CAV group versus the nonCAV group, we found a significantly higher proportion of ACR (39.6% versus 18.2%, $p=0.0051$) and AMR (22.9% versus 7.1%, $p=0.0060$). Significant differences were also observed in CMV infection frequency (18.8% versus 7.1%, $p=0.0330$). Table 1 presents the baseline characteristics of patients.

A univariate analysis of the influence of separate factors on the development of coronary disease was conducted. It showed statistical significance ($p<0.05$) for baseline HDL, ACR, AMR, CMV, and donor age.

A multivariate regression model for all risk factors was applied. We discovered that only baseline HDL concentration, episodes of ACR, age of donor, and CMV infection were significant for the frequency of CAV after HT (Table 2). The estimated survivor function curves of freedom from CAV according to the presence or absence of immunological factors (ACR, CMV) or their combination, for average HDL-level (1.43 mmol/L) and donor age (32.2 years) are presented in Figure 3. The combination of the presence of ACR episodes and CMV infection was linked with the worst chance of freedom of CAV for heart transplant patients. Each of those factors deteriorates prognosis separately, but CMV infection had the most negative influence.

Discussion

According to the latest ISHLT report, within the period of five years following a HT, coronary disease is recognized among approximately 30% of patients [6]. In our study group, coronary disease was recognized among 32.7% of the patients (CAV ≥ 1 according to the ISHLT scale). We did not find significant differences in survival between the CAV group and the nonCAV group. One of the reasons for our finding is probably the fact that CAV develops late after HT (9.7 years). The second reason is routine use of drug-eluting stents (DES). DES are safe and effective in the suppression of neointimal hyperplasia after percutaneous coronary intervention for CAV, resulting in significantly lower rates of late lumen loss and target lesion revascularization and reduced rate of cardiac death [7,8].

Other authors have analyzed the risk factors related to the recipient (after HT), or risk factors linked to the donor and to the HT itself (ischemia time) separately. Our goal was to analyze all known risk factors together and link them with development

of CAV to identify which of the risk factors might influence the HT procedure. We evaluated the typical risk factors influencing the development of arteriosclerosis such as hypertension, smoking, obesity and weight gain, lipid abnormalities, donor-related variables (sex, age, cause of death, catecholamine use, blood group matching, ischemia time, donor cardiac arrest) and post transplantation history (CMV infections, ACR and AMR incidents).

Among the donor-related factors, only the donor age significantly influenced the CAV frequency in all the analyses we conducted in our study. It has been reported that the more advanced age of the donor, the more likely the incidence of CAV [9,10]. Among the patients in our study group, the age of the oldest donor was 56 years. The aforementioned studies suggested that the donor's maximum age should not exceed 50 years. However, it is not always possible to match young recipient with young donor in everyday practice. So other risk factors for CAV should be well-controlled, especially when the donor is of an older age.

Other donor-related factors, such as sex, cause of brain death, type of treatment (including catecholamine usage) or cardiac arrest did not influence the development of coronary disease among our patients.

Among the typical risk factors in the recipients group, in both univariate and multivariate analyses, only decreased HDL level had significant impact on the development of CAV. Hypercholesterolemia has been reported to be common after HT and is a well-known risk factor, confirmed by the fact that ISHLT recommends the use of statins [11]. The anti-atherogenic function of HDL is considered an important mediator of reverse cholesterol transport, a process that involves the transfer and uptake of free cholesterol from the peripheral tissues, such as the arterial wall. HDL has been shown to have anti-inflammatory, anti-oxidative, and fibrinolytic effect, which may prevent atherosclerosis development [12,13].

In heart transplant recipients, early initiation of statins results in lower rates of CAV [14]. In our center, we administer statins early after HT. However, its use has an influence on HDL level only to some degree.

Other classical risk factors did not affect the CAV frequency in our study. Acute cellular and humoral rejections are related to increased risk of CAV [15,16]. According to different studies, AMR occurs among approximately 6% of the patients with a transplanted heart, yet some authors have indicated that the AMR frequency is higher, reaching up to 20%. If immunohistopathological changes are considered among patients with minimal clinical symptoms, the AMR might reach up to 40% [17–19]. The AMR frequency was about 12.2% among our patients and

Table 1. Patients characteristics.

Variable	NonCAV		CAV		p-Value
Recipient					
Age [years], ME (IQR)	48.3	(30.7–55.2)	53.6	(48.2–60.3)	0.003
Male, n (%)	80	(80.8)	39	(81.3)	0.949
Non-immunologic factors					
Hypertension, n (%)	57	(57.6)	32	(66.7)	0.290
Diabetes, n (%)	28	(28.3)	17	(35.4)	0.379
Smoking, n (%)	20	(20.2)	8	(16.7)	0.609
Tchol [mmol/l], ME (IQR)	4.70	(4.10–5.51)	4.17	(3.75–4.96)	0.027
LDL [mmol/l], ME (IQR)	2.62	(2.15–3.24)	2.29	(1.85–2.98)	0.121
HDL [mmol/l], ME (IQR)	1.42	(1.16–1.70)	1.33	(1.08–1.60)	0.119
TG [mmol/l], ME (IQR)	1.46	(1.11–2.05)	1.69	(1.17–2.31)	0.395
BMI [kg/m ²], ME (IQR)	23.7	(21.1–26.4)	24.8	(21.6–27.7)	0.186
Immunologic factors					
ACR, n (%)	18	(18.2)	19	(39.6)	0.005
AMR, n (%)	7	(7.1)	11	(22.9)	0.006
CMV, n (%)	7	(7.1)	9	(18.8)	0.033
Death, n (%)	14	(14.1)	12	(25.0)	0.106
Donor					
Donor's age [years], ME (IQR)	30.0	(21.0–39.0)	38.0	(29.0–43.0)	0.004
Male, n (%)	68	(68.7)	33	(68.8)	0.994
Compatibility of sex, n (%)	67	(67.7)	30	(62.5)	0.534
Brain death					
Tumor, n (%)	1	(1.0)	2	(4.2)	0.249
Trauma, n (%)	58	(58.6)	27	(56.2)	0.788
Haemorrhagia, n (%)	32	(32.3)	18	(37.5)	0.534
Other, n (%)	8	(8.1)	1	(2.1)	0.272
Compatibility of blood groups, n (%)	92	(92.9)	46	(95.8)	0.718
Catecholamine use, n (%)	53	(53.5)	28	(58.3)	0.583
Cardiac arrest, n (%)	11	(11.1)	4	(8.3)	0.774
Ischemia time [min], ME (IQR)	183	(146–212)	189	(149–217)	0.577

ME – median; IQR – interquartile range; Tchol – total cholesterol; LDL – low-density lipoprotein, HDL – high-density lipoprotein; TG – triglycerides; BMI – body mass index; ACR – acute cellular rejection; AMR – antibody mediated rejection; CMV – cytomegalovirus infection.

Table 2. Cox proportional hazard models for development of CAV in post-heart transplant patients.

Variable	Univariate results		p-Value	Multivariate results		p-Value
	HR	95% CI		HR	95% CI	
HDL	0.479	(0.246–0.931)	0.0299	0.388	(0.199–0.757)	0.0055
ACR	2.216	(1.320–3.720)	0.0026	1.910	(1.102–3.310)	0.0212
AMR	2.477	(1.332–4.608)	0.0042	–	–	–
CMV	2.916	(1.561–5.445)	0.0008	2.117	(1.096–4.088)	0.0255
Donor's age	1.044	(1.017–1.070)	0.0010	1.039	(1.012–1.068)	0.0052

HR – hazard ratio; CI – confidence interval; HDL-high-density lipoprotein; ACR-acute cellular rejection; AMR-antibody mediated rejection; CMV-cytomegalovirus infection.

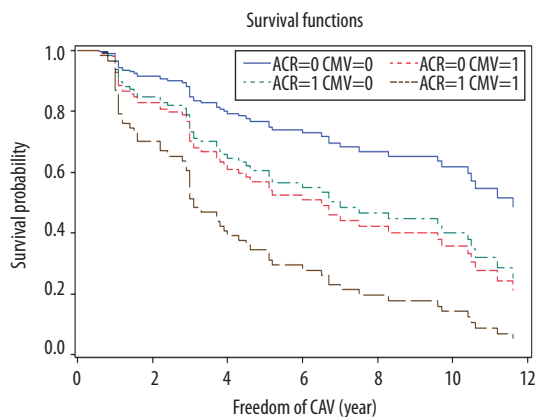


Figure 3. Estimated survivor function plot of risk factors according to the model of multivariate analysis. HDL and donor's age assumed as average values (1.43 mmol/L and 32.2 years). 1 – presence of ACR or CMV, 0 – absence of ACR or CMV.

it was related to a significantly increased CAV incidence in our univariate analysis. Early recognition of AMR is crucial, since the treatment should also be initiated among patients who do not show any symptoms; this might lead to the CAV incidence reduction [15]. In our study group, the AMR evaluation was conducted retrospectively in most cases and for this reason the treatment was not possible. ACR was also related to the significantly increased CAV incidence; a fact which previous studies have confirmed [19].

Another important risk factor for CAV is CMV infection [20,21]. CMV infection might act directly and indirectly in HT patients. The direct effects of CMV disease are related to viral burden and the indirect effects are independent and related to high levels of CMV. A direct effect is the destruction and cell lysis due to viral replication and activation of the host immune response. In the indirect effect, CMV could act by altering growth

factors and cytokine expression and cause upregulation of pro-inflammatory and adhesion molecules [22,23]. Clinical manifestations of indirect effects of CMV infections are heterogeneous and may lead to an accelerated coronary vasculopathy, secondary infections, cancer development, diabetes, lymphoproliferative disorders. The consequence of this is a reduction of graft function and patient survival [24]. Our study confirmed the influence of CMV infection on CAV development, suggesting that anti CMV prophylactic should be applied especially among recipients of older donor heart.

Lipid abnormalities, particularly low HDL, and the fact that the recipient received the heart from an older donor constitute risk factors for vasculopathy. If incidents of ACR and CMV infection accompany these risk factors, the risk rises significantly. It is clear that typical atherosclerosis risk factors play a role in the process of CAV development. In our study, patients were treated with statins and the concentration of plasma lipids was within normal limits (although in terms of LDL, especially in the CAV group, LDL should be kept low). The average BMI in both groups in our study did not indicated obesity [25–27].

Limitations

This study was retrospective in terms of AMR incidence analysis (C4d) and for this reason most patients did not receive AMR treatment. Other host immune factors, including HLA mismatch and the presence of anti-HLA class I or class II antibodies, were not analyzed. We could not define the impact of immunosuppression on vasculopathy.

In the years 2001–2008 cyclosporine A was the basic immunosuppression treatment. Since 2009, TAC has been used. Additionally, mTOR inhibitors (everolimus/sirolimus) were used starting in 2005. Patients with CAV or cancer were given mTOR instead of MMF. This change in therapy made assessment of CAV in relation to used drugs difficult.

According to this study, older donor age plays an important role in the risk of CAV, especially in connection with immunologic factors such as ACR and CMV infections. It has become very clear that this specific group of patients should be under close scrutiny for CAV after HT.

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Conclusions

In conclusion, 1) older donor age is highly associated with CAV development, and 2) older donor age and low level of HDL in heart recipients with the strongest influence of immunologic risk factors (ACR, CMV infection) are linked with development of CAV.

Conflict of interest

None.