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Graft coronary vasculopathy in cardiac transplantation – evaluation of risk factors by multivariate analysis

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Abstract The development of coronary vasculopathy is the main determinant of long-term survival in cardiac transplantation. The identification of risk factors, therefore, seems necessary in order to identify possible treatment strategies. Ninety-five out of 397 patients, undergoing orthotopic cardiac transplantation from 10/1985 to 10/1992 were evaluated retrospectively on the basis of perioperative and postoperative variables including age, sex, diagnosis, previous operations, renal function, cholesterol levels, dosage of immunosuppressive drugs (cyclosporin A, azathioprine, steroids), incidence of rejection, treatment with calcium channel blockers at 3, 6, 12, and 18 months postoperatively. Coronary vasculopathy was assessed by annual angiography at 1 and 2 years postoperatively. After univariate analysis, data were evaluated by stepwise multiple logistic regression analysis. Coronary vasculopathy was assessed in 15 patients at 1 (16%), and in 23 patients (24%) at 2, years. On multivariate analysis, previous operations and the incidence of rejections were identified as significant risk factors ($P < 0.05$), whereas the underlying diagnosis had borderline significance ($P = 0.058$) for the development of graft coronary vasculopathy. In contrast, all other variables were not significant in our subset of patients investigated. We therefore conclude that the development of coronary vasculopathy in cardiac transplant patients mainly depends on the rejection process itself, aside from patient-dependent factors. Therapeutic measures, such as the administration of calcium channel blockers and regulation of lipid disorders, may therefore only reduce the progress of native atherosclerotic disease in the posttransplant setting. [Eur J Cardio-thorac Surg (1996) 10: 1–5]

Key words Coronary vasculopathy · Cardiac transplantation evaluation · Risk factors

Introduction

The development of coronary vasculopathy in cardiac allografts represents one of the most important determinants of long-term outcome [1–3, 5, 9, 10, 12, 23, 24, 26, 33]. As outlined by the registry of the International Society for Heart Transplantation a steady decline in the actuarial survival can be expected following the 1st year after trans-plantation [15]. The attrition rate is mainly attributed to coronary vasculopathy and comparable to the long-term outcome following kidney transplantation. Despite advances of follow-up investigations in the clinical setting, only annually performed coronary angiographies or intracoronary ultrasound may help to detect the disease [20, 21, 28–32]. Today only cardiac retransplantation represents a viable treatment option. Various factors have been discussed to modulate the incidence and progress of the under-

lying pathomechanism [7, 11, 13, 17]. However, despite positive single center experiences with prohibitive drugs including calcium channel blockers, heparin, somatostatin analogues and others, no definite treatment could be introduced into clinical practice [7, 8, 18, 19, 22, 27]. In addition, it is still a matter of discussion, which factors might have an impact on the development of coronary vasculopathy [25, 38].

It was the aim of this retrospective investigation to identify predictors in cardiac allograft recipients by comparing preoperative, perioperative, and postoperative variables in patients with or without the presence of the disease.

Patients and methods

The retrospective analysis was performed in a cohort of 95 out of 397 patients, who underwent cardiac transplantation at Hannover Medical School, Germany, from October 1985 to July 1992. Patients with retransplantations were excluded, while a previous cardiac operation was not an exclusion criterion. Patients had to have complete data documentation including preoperative, perioperative, and postoperative data to be included in the study cohort.

The mean age of the patients was 46 ± 10 years. Eighty-three patients were male, while 12 were female. The underlying diagnosis was dilative cardiomyopathy in 73 patients and ischemic heart disease in 22. Fourteen out of the 95 patients had been previously operated upon with the application of cardiopulmonary bypass: five for coronary artery bypass grafting, three for valve replacement, two with aneurysmectomy and one with endocardial resection. The remaining three patients underwent automatic cardioverter defibrillator implantation using sternotomy and supportive extracorporeal circulation for testing of the defibrillation thresholds. Transplantations were performed using standard cardiopulmonary bypass with aortal and bicaval cannulation and hypothermia of $28-30\,^\circ$C. Donor hearts were preserved with 1.5 l of St. Thomas[1], hospital cardioplegia followed by storage in Ringer's solution.

Preoperative data included the Ig-G- and Ig-M-cytomegalievirus status of the recipient. All patients were screened for cytotoxic antibodies. If positive, a direct crossmatch was performed prior to transplantation.

Perioperative data were analyzed with regard to bypass times, aortic cross-clamp times and cold ischemia times. All patients received triple drug immunosuppression including cyclosporin A (CYA) 3–10 mg/kg, azathioprine 1–2.5 mg/kg, and prednisolone 0.5–0.1 mg/kg, as described previously [34, 36, 37]. After release of the aortic cross-clamp all patients were given 500 mg methylprednisolone as well as three subsequent doses 125 mg every 12 h thereafter. From day 1 to day 4 all patients received antithymocyte globulin 1 5 mg/kg (ATG). Immunosuppression was analyzed at 1, 3, 6, 12, and 18 months postoperatively and the dosages of drugs administered compared. All patients underwent routine endomyocardial biopsy according to a fixed schedule as outlined earlier [35]. All biopsies were scored according to the International Society for Heart Transplantation [14]. Rejections were treated with methylprednisolone 500 or 1000 mg for 3 subsequent days based on weight (500 mg for patients <75 kg). Patients with severe rejections were given either ATG 1.5 mg/kg for 3 days or OKT III· 10 mg/kg per day for 10 days [4]. Rejections per patient were counted according to the postoperative period, which was divided into periods 0–1 months, 2–6 months, 7–12 months, 13–18 months, and 19–24 months. The postoperative course of the patients was analyzed by review of the records from outpatient department visits. All patients were followed by angiography performed on an annual basis. Coronary arteries were an-

alyzed by biplane angiography. The presence of coronary graft vasculopathy was assessed at either 1 or 2 years, and patients subsequently defined positive for the disease. The patients were divided into two groups according to the presence or absence of graft vasculopathy and all variables were compared between these groups. Aside from the parameters mentioned above, the following variables were compared using univariate analysis, as patient dependent variables: patient – age, – sex, – survival, previous cardiac operations, and underlying diagnosis. In terms of immunosuppressive variables, it was verified whether patients had had an induction treatment with ATG. The number of rejections were counted according to the postoperative period, as outlined. Immunosuppressive drug dosages administered which were compared included cyclosporin A, azathioprine and prednisolone at 1, 3, 6, 12, and 18 months. Serum parameters included creatinine at 1, 3, 6, 12, 18, and 24 months as well as cholesterol and triglyceride levels. In addition, treatment for hypertension with either nifedipine or diltiazem was checked independently from the drug dosage administered at 6, 12, and 18 months. Diastolic blood pressure was recorded at 1, 3, 6, 12, and 18 months.

All patients dying throughout the investigation underwent postmortem analysis, either at the local hospital, where the patient was admitted, or at Hannover Medical School. In any case, the heart was investigated secondarily at Hannover Medical School and the presence of transplant vasculopathy was assessed macroscopically.

On statistical analysis, all values were given as mean±one standard deviation. The results were first compared by univariate analysis including Student's t-test or Fisher's exact-test, as appropriate. Prior to the Student's t-test, the normal distribution of the continuous variables was assessed. A probability value of 0.05 was considered significant. Thereafter step-wise logistic regression analysis was performed including all variables showing a P-value of less than 0 10 in the univariate analysis. For statistical evaluation, the SPSS software, version 5.1, was used.

Results

A total of 13 patients died throughout the entire observation period to March 1994. While two patients died early due to graft failure, six other patients died within the 1st, and five others in the 2nd year. The causes of late deaths were infections in three patients, liver dysfunction in one patient, acute rejection in one patient each. The other late deaths were due to bronchial carcinoma, epilepsia, sepsis, kidney failure in one each, and multiorgan damage in two, patients. Transplant vasculopathy was ruled out in all cases by pathological evaluation at Hannover Medical School.

The mean survival was 1683 ± 950 days. Actuarial survival was calculated as $85 \pm 4.8\%$ at 1, and $80 \pm 5.7\%$ at 2, years. At 1 year coronary vasculopathy was found in 15 patients (16%) and in 23 (25%) at 2 years. These 23 patients were named TVP positive and compared to the TVP negative ($n = 72$).

No significant differences between the groups were found for mean survival, ischemic times and all operative times (bypass time, aortic cross-clamp time). Cytotoxic antibodies also revealed no differences in being positive: in 1/23 as compared to 2/72 ($P = $NS). After univariate analysis, significant differences were observed for age, underlying diagnosis before transplantation, presence of previ-

Patient-dependent	TVP negative	TVP positive	*P*-value
Age	46.3 ± 8.29	45.9 ± 11.9	0.079
Previous operation	9/72	5/23	0.002
Diagnosis			
DCM	54/72	14/23	
ICM	17/72	8/23	0.064
Other	1/72	1/23	
CMV-IGM antibody pos.	1/72	1/23	0.030
Creatinine at 3 months	112 ± 43	123 ± 29	0.042
Cholesterol at 1 months	6.10 ± 1.70	5.77 ± 1.20	0.045
Diltiazem at 6 months	0.12 ± 0.34	0.05 ± 0.23	0.073
AZA at 12 months	121 ± 35	117 ± 41	0.086
Rejections 19–24 months	0.25 ± 0.45	0.03 ± 0.19	<0.000

Table 1 Univariate analysis (significant variables) variables investigated (mean SD) (*TVP* transplant vasculopathy; *DCM* dilative cardiomyopathy; *ICM* ischemic cardiomyopathy; *CMV* cytomegalovirus; *AZA* azathioprine)

Variable	Regression coefficient	Standard error	Odds ratio	Chi square	*P*-value
Previous operation	1.910	0 860	6.77	4.88	0.027
Age	−0.330	0.030	0.96	1.02	0.310
CMV	−1.050	0.650	0.34	2.59	0.107
CYA	−0.001	0.003	0.99	0.40	0.525
Diagnosis	0.917	0.480	2.50	3.59	0.058
Cholesterol	−0.044	0.009	0.81	0.56	0.654
Azathioprine	0.050	0.004	0.91	0.65	0.562
Rejections	1.100	0.440	3.02	0.01	0.013

Table 2 Results of the stepwise multilogistic regression analysis. (*CMV* cytomegalovirus; *CYA* cyclosporin A)

ous operations and a positive CMV-IGM antibody in the recipient. From the other parameters analyzed, azathioprine dosage, cholesterol level, creatinine, and numbers of rejections were found significant (Table 1). Rejections showed a tendency to be more prone throughout all time intervals in the group presenting more vasculopathy, however statistical significance was reached only in the time interval 19–24 months.

The other perioperative variables, including CMV-IGG antibody status, immunosuppression including ATG as induction therapy, immunosuppressive therapy including CYA, prednisone, and azathioprine drug therapy, were not significant for the rejection courses at 0–18 months.

Postoperative treatment-dependent variables, including diastolic blood pressure, creatinine at 1 and 12/24 months, cholesterol 6/24 months, and triglycerides as well as diltiazem treatment at 12, and 18 months, and nifedidipine treatment at 6, 12, and 18 months, were also not significant ($P<0.1$). Stepwise multiple regression analysis revealed that previous operations, underlying diagnosis (borderline, $P=0.058$), and number of rejections significantly enhanced the risk of coronary vasculopathy (Table 2).

Discussion

The major cause of death following cardiac transplantation in the long-term course is accelerated coronary vas-

culopathy [1–3, 16, 31, 32]. It occurs in about 30–60% of patients within 5 years following cardiac transplantation [1–3]. A comparable incidence was found in our patient population with 16% in the 1st year and a 10% increase per year [15]. Transplant vasculopathy is generally thought to be a chronic immunological problem, probably caused by an endothelial injury of the graft [9, 13]. A lot of factors, including age, sex, presence of cytotoxic antibodies, HLA compatibility, preoperative diagnosis, previous operations and pregnancies, cholesterol, estrogen levels, cytomegalovirus status, rejection, and infection numbers, amount of calcium channel blockers taken postoperatively as well as cyclosporin A have been discussed as interfering with the development of the disease, however, substantial data are still missing [6–8, 16, 17, 19, 25, 32, 38]. Reviewing the literature, several attempts have been made to counteract transplant vasculopathy. Calcium channel blockers as well as heparin have been discussed as being beneficial in the treatment of either the development or progression of the disease [7, 8, 13, 18, 26]. It was the aim of this retrospective analysis to identify variables which may interfere with the problem. Our study cohort was selected out of all the patients transplanted in our department. Selection was based on the completness of the data set necessary for analysis. This may lead to a certain selection of well investigated or hospital-followed patients, since all patients with incomplete catheterization data, "which live well", have been missed. However, after comparison of the demographic data of the cohort with data reported from the Inter-

national Society, the study group is a precisely comparable group, based on death, survival, and demographics [15]. In addition, demographic and survival data are comparable to the results presented by our group in general, as published previously [4, 14, 35–37]. The variables chosen for the univariate analysis were based on the experience reported in the literature. Data on HLA compatibility could not be included in the analysis, which certainly represents a major limitation. But, HLA-dependent cardiac transplantation is currently limited by the ischemic tolerance of the graft and therefore may only be a theoretic option with future perspective. It was demonstrated that the patient–dependent variables underlying diagnosis, previous operations and rejections were significantly important predictors for graft vasculopathy at 2 years, as demonstrated by the results of the univariate analysis. Underlying diagnosis as a risk factor showed a borderline impact in the multivariate analysis, however, previous cardiac operations and more rejections tended to identify patients developing more transplant vasculopathy. Comparable results have been achieved by other groups, demonstrating that a previous operation may lead to the development of cytotoxic antibodies [5, 23, 24]. However, in our patient group a comparable distribution on a positive screen for cytotoxic antibodies was assessed, therefore this did not have any impact in our study.

Advanced age and underlying diagnosis as predisposing factors are known to be related to the rejection process itself, therefore perhaps also modulating the chronic rejection process by interference with acute rejection. However, no reverse argumentation regarding patient selection can be concluded based on our results, since excellent therapeutic results are achieved with transplantation even in this subgroup, when compared to conventional treatment. As a consequence, more molecular research has to identify the background of the underlying pathomechanism in order to overcome the limitation in the subgroup of old patients with previous operations for coronary heart disease.

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