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Long-term outcome of cardiac allograft vasculopathy: Importance of the ISHLT angiographic grading scale --Manuscript Draft--

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Abstract:	<p>BACKGROUND. Cardiac allograft vasculopathy (CAV) is a major complication limiting long-term survival after heart transplantation (HTx). However, long-term outcome data of HTx recipients with detailed information on angiographic severity are scarce.</p> <p>METHODS. The study included 501 HTx recipients with angiographic follow-up up to 20 years post-transplant. All coronary angiograms were classified according to the International Society for Heart and Lung Transplantation (ISHLT) grading scale.</p> <p>RESULTS. CAV prevalence increased over time after transplantation, reaching 10% at 1 year, 44% at 10 years and 59% at 20 years. Older donor age (hazard ratio (HR) 1.38 per 10 years, 1.20–1.59, $p<0.001$), male donor gender (hazard ratio 1.86, 1.31–2.64, $p<0.001$), stroke as donor cause of death (HR 1.47, 1.04–2.09, $p=0.03$), recipient pretransplant hemodynamic instability (HR 1.79, 1.15–2.77, $p=0.01$), post-transplant smoking (HR 1.59, 1.06–2.39, $p=0.03$) and first-year treated rejection episodes (HR 1.49, 1.01–2.20, $p=0.046$) were independent risk factors for CAV. Baseline antimetabolite drug use (HR 0.57, 0.34–0.95, $p=0.03$) and more recent transplant date (HR 0.78 per 10 years, 0.62–0.99, $p=0.04$) were protective factors. Compared to patients without CAV, the hazard ratio for death or retransplantation was 1.22 (0.85–1.76, $p=0.28$) for CAV 1, 1.86 (1.08–3.22, $p=0.03$) for CAV 2 and 5.71 (3.64 – 8.94, $p<0.001$) for CAV 3.</p> <p>CONCLUSIONS. CAV is highly prevalent in HTx recipients, and is explained by immunological and non-immunological factors. Higher ISHLT CAV grades are independently associated with worse graft survival.</p>

LONG-TERM OUTCOME OF CARDIAC ALLOGRAFT VASCULOPATHY: IMPORTANCE OF THE ISHLT ANGIOGRAPHIC GRADING SCALE

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Abstract

Background. Cardiac allograft vasculopathy (CAV) is a major complication limiting long-term survival after heart transplantation (HTx). However, long-term outcome data of HTx recipients with detailed information on angiographic severity are scarce.

Methods. The study included 501 HTx recipients with angiographic follow-up up to 20 years post-transplant. All coronary angiograms were classified according to the International Society for Heart and Lung Transplantation (ISHLT) grading scale.

Results. CAV prevalence increased over time after transplantation, reaching 10% at 1 year, 44% at 10 years and 59% at 20 years. Older donor age (hazard ratio (HR) 1.38 per 10 years, 1.20–1.59, $p<0.001$), male donor gender (hazard ratio 1.86, 1.31–2.64, $p<0.001$), stroke as donor cause of death (HR 1.47, 1.04–2.09, $p=0.03$), recipient pretransplant hemodynamic instability (HR 1.79, 1.15–2.77, $p=0.01$), post-transplant smoking (HR 1.59, 1.06–2.39, $p=0.03$) and first-year treated rejection episodes (HR 1.49, 1.01–2.20, $p=0.046$) were independent risk factors for CAV. Baseline antimetabolite drug use (HR 0.57, 0.34–0.95, $p=0.03$) and more recent transplant date (HR 0.78 per 10 years, 0.62–0.99, $p=0.04$) were protective factors. Compared to patients without CAV, the hazard ratio for death or retransplantation was 1.22 (0.85–1.76, $p=0.28$) for CAV 1, 1.86 (1.08–3.22, $p=0.03$) for CAV 2 and 5.71 (3.64 – 8.94, $p<0.001$) for CAV 3.

Conclusions. CAV is highly prevalent in HTx recipients, and is explained by immunological and non-immunological factors. Higher ISHLT CAV grades are independently associated with worse graft survival.

Introduction

Cardiac allograft vasculopathy (CAV) is a major complication limiting long-term survival after heart transplantation (HTx)(1). CAV is characterized by intimal proliferation of the transplant vasculature, causing diffuse narrowing of coronary arteries(2). Its pathophysiology involves a complex interplay of donor and recipient risk factors and allo-immunity. Known risk factors include older donor age(3, 4), recipient dyslipidemia(5), acute cellular rejection episodes(6) and donor-specific HLA antibodies (DSA)(7), whereas statin use(8) and mammalian target of rapamycin (mTOR) based immunosuppression(9, 10) have been shown to be beneficial.

CAV can lead to graft failure, arrhythmia and sudden cardiac death(2). Angina is typically absent due to allograft denervation. Therefore, surveillance by invasive coronary angiography is recommended(11). Angiographic diagnosis can be challenging because of the diffuse and concentric nature of CAV, as opposed to the focal and eccentric pattern of nontransplant coronary artery disease. In order to standardize angiographic scoring of CAV, in 2010, the International Society for Heart and Lung Transplantation (ISHLT) published guidelines for terminology(12), based on angiographic findings, integrated with assessment of cardiac function and hemodynamics.

According to the ISHLT 35th Adult Heart Transplant Report(1), 8% of HTx recipients develop CAV within the first year post-transplant, and 47% within the first 10 years. Unfortunately, the Registry does not report on CAV severity. In fact, long-term outcome data of HTx recipients with detailed information on angiographic severity are scarce(13-17).

The aim of this study was to describe the prevalence, risk factors and long-term outcome of CAV, graded according to the recommended nomenclature, in a large single-center cohort.

Methods

Study population

We studied all consecutive adult HTx recipients transplanted at the University Hospitals Leuven, Belgium, between January 1991 and December 2016. Patients who died or were retransplanted within the first postoperative year, and patients without angiographic follow-up at our center, were excluded. Patients receiving more than one transplant in the study period were considered as separate subjects. The study was approved by the local institutional board of the University Hospitals Leuven (S61635).

All patients received induction therapy with polyclonal anti-thymocyte globulin (ATG). Most were maintained on a triple immunosuppressive regimen including a calcineurin inhibitor (CNI), an antimetabolite drug and corticosteroids. Around 2000, the immunosuppressive protocol was changed from cyclosporine to tacrolimus and from azathioprine to mycophenolate mofetil (MMF). Patients without rejection episodes were weaned off steroids over 6 to 12 months. Statins were started in all patients without contra-indication from around 2000. Aspirin was started when clinically indicated.

Data collection

All data were collected during routine clinical follow-up. Follow-up ended on December 31st, 2018. Baseline immune suppression, statin and antihypertensive drug use were recorded at 3 months after transplantation. Post-transplant smoking was defined as persistent cigarette smoking within the first year after HTx. Recipient pretransplant hemodynamic instability was defined as the use of inotropic drugs or mechanical circulatory support other than long-term left ventricular assist device (LVAD). Data on DSA were available from 2004: until 2008 as determined by ELISA (GTI), and thereafter by Luminex (Lifecodes, Immucor), with a cut-off for positivity of MFI > 2000. Protocol coronary angiograms were performed at year 1 after transplantation, then every 3 years during the first 10

years, and every 5 years thereafter. Additional angiograms were performed when clinically indicated. CAV was classified as not significant (CAV 0), mild (CAV 1), moderate (CAV 2) or severe (CAV 3), according to the ISHLT grading scale(12). Accordingly, patients with angiographic scores CAV 1 or CAV 2 with allograft dysfunction (defined as left ventricular ejection fraction < 45%) or restrictive physiology (based on right atrial pressure > 12 mmHg, pulmonary capillary wedge pressure > 25 mmHg or cardiac index < 2 L/min/m²) were classified as CAV 3.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), categorical variables were presented as numbers and percentages. Risk factors for development of CAV were analyzed using the Cox proportional hazard method, with landmarking at 1 year post-transplantation(18). To determine the prognostic impact of CAV, the outcome was a composite of all-cause mortality and retransplantation. CAV grades were analyzed as a time-dependent variable, using the Cox proportional hazard method, stratifying each patient's follow-up into "bins". The first bin represented the time interval between transplantation and the first angiogram; consecutive bins represented the time intervals between angiograms; and the last bin represented the time interval between the last angiogram and time of event or last follow-up. The first bin was assumed to represent CAV grade 0. Both the model for CAV risk factors and the one for CAV impact on prognosis were corrected for covariates that were significant at the 0.2 level in univariate analysis. Time-to-event data were visualized using the Kaplan-Meier method and differences between groups were assessed with the log-rank test. Statistical tests were 2-tailed, and p-values of < 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC, USA).

Results

Patients' characteristics

In this study, 501 HTx in 490 individual patients were included, with mean follow-up of 11.9 ± 6.4 years. **Figure 1** is a flow diagram illustrating the selection of the study population and the comprehensiveness of angiographic follow-up. Amongst surviving patients, 89% underwent coronary angiography up to 10 years post-transplant and 74% up to 20 years. In total, 2141 angiograms were performed (on average 4.3 per patient): 1565 angiograms on protocol time points and 576 additional angiograms.

Baseline characteristics are summarized in **Table 1**. Mean donor and recipient age were 36.7 ± 12.8 and 51.4 ± 12.1 years, respectively. The majority of donors (69%) and recipients (79%) were male. The most frequent indication for HTx was ischemic cardiomyopathy (42%). Five percent were re-transplantations. Statin use at baseline was 72%. Mean LDL-cholesterol was 103.3 ± 39.7 mg/dL: 95.3 ± 36.7 mg/dL in patients on statin treatment and 125.9 ± 39.4 mg/dL in patients not on statin treatment.

At baseline, all patients were treated with a CNI (tacrolimus in 61% and cyclosporine in 39%) and 95% percent of patients were treated with an antimetabolite (MMF in 63% and azathioprine in 32%). During follow-up, maintenance immunosuppression was switched to a CNI plus everolimus in 20 patients with severe CAV, at a median of 7.1 years (range, 1.0 – 16.1) post-HTx. In addition, 39 patients without severe CAV received everolimus: because of renal insufficiency in 18 (most in a CNI-free regimen as part of a clinical study(19)), intolerance for MMF in 10, skin cancer in 6 and miscellaneous reasons in 5. By the end of the first postoperative year, 12% of patients had experienced at least one episode of treated acute rejection (acute cellular rejection in 57 patients and antibody-mediated rejection in 5 patients). Of the 246 patients with available data, 9% had preformed DSA.

CAV prevalence over time

Figure 2 shows the distribution of CAV among survivors at 1, 4, 7, 10, 15 and 20 years. CAV prevalence increased over time after transplantation, reaching 10% at 1 year, 22% at 4 years, 35% at 7 years, 44% at 10 years, 56% at 15 years and 59% at 20 years. One out of eight patients had moderate to severe vasculopathy (CAV 2-3) at 10 years and one out of four at 20 years post-transplant.

Risk factors for CAV

Univariate and multivariable analysis of risk factors for CAV are shown in **Figure 3**. Older donor age (hazard ratio (HR) 1.38 per 10 years, 1.20 – 1.59, $p < 0.001$), male donor gender (HR 1.86, 1.31 – 2.64, $p < 0.001$), stroke as donor cause of death (HR 1.47, 1.04 – 2.09, $p = 0.03$), recipient pretransplant hemodynamic instability (HR 1.79, 1.15 – 2.77, $p = 0.01$), post-transplant smoking (HR 1.59, 1.06 – 2.39, $p = 0.03$) and one or more treated rejection episodes during the first year (HR 1.49, 1.01 – 2.20, $p = 0.046$) were independent risk factors for CAV. Baseline antimetabolite drug use, either MMF or azathioprine, in addition to CNIs plus steroids (HR 0.57, 0.34 – 0.95, $p = 0.03$) and more recent transplant date (HR 0.78 per 10 years, 0.62 – 0.99, $p = 0.04$) were independently associated with lower risk of CAV. There was a trend towards less CAV in patients who received statin therapy at baseline (HR 0.74, 0.55 – 1.01, $p = 0.06$) and more CAV in the patients with preformed DSA (HR 1.59, 0.71 – 3.57, $p = 0.26$). However, data on DSA were only available in 246 patients and therefore not included in the multivariable model.

Association between CAV and outcome

Figure 4 shows the Kaplan-Meier estimates of retransplant-free survival, starting from 1, 4, 7 and 10 years post-transplant, in function of ISHLT CAV grade. Patients with CAV 2-3 had the worst prognosis. This was most evident early after transplantation, with median retransplant-free survival of only 5.3 years at 4 years post-HTx (Figure 4B). This observation was in part explained the retransplantation of 3 of the 14 patients who had developed severe vasculopathy by year 4.

In the multivariable Cox proportional hazards model, CAV grades were assessed as a time-dependent variable and adjusted for date of transplantation, recipient age and gender, pre-transplant ischemic cardiomyopathy, baseline hypertension and estimated glomerular filtration rate. The adjusted hazard ratio for death or retransplantation was 1.22 (0.85 – 1.76, $p = 0.28$) for CAV 1, 1.86 (1.08 – 3.22, $p = 0.03$) for CAV 2 and 5.71 (3.64 – 8.94, $p < 0.001$) for CAV 3, compared to patients without CAV. In the subgroup of patients who were transplanted after 2000, the adjusted hazard ratios were 1.13 (0.58 – 2.20, $p = 0.73$), 1.91 (0.78 – 4.71, $p = 0.16$) and 4.60 (1.92 – 11.03, $p < 0.001$) for CAV 1, 2 and 3, respectively.

During follow-up, 83 patients developed CAV 2-3. Forty-four of them (53%) underwent revascularization: 65 percutaneous coronary interventions (PCI) and 6 coronary artery bypass grafting (CABG) procedures were performed. Compared to patients with CAV 0-1, patients with CAV 2-3 had worse survival (68% versus 46%, $p < 0.001$), were retransplanted more often (0.5% versus 12%, $p < 0.001$) and were more likely to die from a cardiac cause (5% versus 22%, $p < 0.001$). **Table 2** shows all endpoints, stratified by the highest CAV grade during follow-up. The predominant cause of death of patients with CAV 2-3 was sudden cardiac death (10 deaths in 83 patients, 12%).

Discussion

The current single-center European cohort study provides an overview of CAV prevalence, risk factors and long-term outcome. CAV prevalence at 1 and 10 years post-transplant was comparable to the reported prevalence in the ISHLT Registry(1). What this study adds, is the relative distribution of CAV severity, up to 20 years post-transplant, and its impact on survival.

CAV pathophysiology is a complex interplay between donor and recipient risk factors and allo-immunity. Known donor risk factors are older age(20-24), male gender(13) and stroke(20). We confirm these associations, which are likely attributed to transmission of pre-existing donor coronary lesions that are more prevalent in older, male donors. The date of transplantation had no clear effect in univariate analysis, but was associated with reduced CAV incidence after correction for confounders, such as older donor age in patients who were transplanted at a more recent date. Most known recipient risk factors for CAV are also risk factors for native coronary artery disease(25, 26). The high number of HTx recipients who continued or restarted smoking after HTx and its deleterious effect on CAV is reason for concern. Hypertension and diabetes were not identified as risk factors in the current study, possibly because of adequate treatment. The well-established protective effect of statin therapy on CAV(8) did not reach statistical significance. The changing implementation of statin therapy over time - in the first decade in selected patients only, and later on in all patients - could be a possible explanation. This has inevitably led to confounding by indication and crossover bias.

Allo-immunity is another main driver of CAV. Consistent with previous reports(6, 23, 27), we show that treated rejection episodes during the first post-transplant year are a risk factor for CAV.

Additionally, patients who were on standard triple immunosuppression at baseline, developed less CAV than patients who did not tolerate an antimetabolite drug. The association with preformed DSA(7) was not statistically significant. However, these data were only available in a subgroup of patients.

The gradual effect of CAV grades 1 to 3 on survival underscores the importance of the 2010 ISHLT classification. Most evidence supporting this classification dates from the 1990s(28, 29). Some recent papers(15, 16) have suggested that CAV carries nowadays a less deleterious prognosis than 3 decades ago. In contrast, we show a strong negative impact of higher CAV grades, also in patients who were transplanted more recently.

The poor prognosis of CAV 2-3 remains a difficult challenge. While early conversion to mTOR inhibitor-based immunosuppression can have a protective effect on CAV progression(9, 10), late conversion appears to be ineffective(30, 31). Revascularization is limited by the diffuse nature of CAV, high mortality with surgical intervention and high restenosis rates with percutaneous coronary intervention(32, 33). In highly selected patients with CAV 3 and allograft dysfunction, retransplantation is the ultimate therapy(34). The high proportion of sudden cardiac death in patients with CAV is noteworthy(35). Although the absolute number of sudden cardiac deaths was higher in patients *without* significant CAV, representing the larger patient group, the relative risk was threefold higher in patients with CAV 2-3 (12 vs. 4%). Future studies should assess whether prophylactic ICD implantation could reduce deaths in selected HTx recipients with CAV.

Our study has some limitations. First, it is an observational, single-center study. Generalizability of our findings was not evaluated. Notable baseline characteristics in our cohort were universal ATG induction and a low use of mTOR inhibitors(36). Second, we could provide DSA status only in the subgroup of patients transplanted after 2004. Similarly, we chose to report only treated acute rejection, because data on subclinical rejection, especially AMR, were not available for all patients. Third, subclinical coronary events between protocol angiography time points cannot be excluded. In addition, CAV severity was evaluated solely by angiography, which is less sensitive to early stages of CAV than intravascular ultrasound or optical coherence tomography. Finally, we could not assess the impact of therapeutic interventions on outcome after detection of CAV, due to the observational nature of the study and the inherent risk for bias by indication.

The major strength of this cohort study is the low rate of loss to follow-up, with availability of coronary angiography data in nearly 90% of surviving patients up to 10 years post-transplantation and nearly 75% up to 20 years. To the best of our knowledge, this is the most comprehensive study to assess long-term outcomes of HTx recipients with CAV.

To conclude, CAV prevalence remains high. Given the preponderance of non-modifiable risk factors such as donor age, CAV is likely to remain a challenge in the future. Continued efforts are needed to tackle well-established cardiovascular risk factors and motivate patients to stop smoking. Recognition of allo-immunity as an important player in CAV pathophysiology could provide a potential target for CAV prevention. Once established, CAV continues to carry a poor prognosis. Higher ISHLT CAV grades are independently associated with worse graft survival. Poor prognosis in patients with CAV is mainly driven by an excess of cardiac events. The high number of sudden cardiac deaths in patients with CAV should be explored in further studies.

Disclosure statement

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Legends

Figure 1. Flowchart

Selection of the study population and comprehensiveness of angiographic follow-up, at 1 year post-transplant (baseline) and at 4, 7, 10, 15 and 20 years post-transplant (follow-up). n patients, number of patients alive at these timepoints; n patients with angiogram, number of patients that had an angiogram at these timepoints; % angiogram, proportion of patients that had an angiogram at these timepoints.

Figure 2. Prevalence of CAV over time

Prevalence of ISHLT CAV grades 0, 1, 2 and 3, at 1, 4, 7, 10, 15 and 20 years post-transplant.

Figure 3. Risk factors for CAV

Hazard ratios of risk factors for development of CAV. The unadjusted hazard ratios (univariate analysis) are represented above, in blue; the adjusted hazard ratios (multivariable analysis) are represented below, in red. HR, hazard ratio; 95% CI, 95% confidence interval; MMF, mycophenolate mofetil; AZA, azathioprine; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Figure 4. Kaplan-Meier estimates of retransplant-free survival, by CAV grade

Kaplan-Meier estimates of retransplant-free survival, by ISHLT CAV grade at year 1 (A), year 4 (B), year 7 (C) and year 10 post-transplant (D).

Figure 1

Figure 2

Figure 3

Risk factors for development of CAV

Figure 4

Table 1

Baseline characteristics of the study population (n=501)		
Donor		
Date of transplantation - no. (%)		
1991-1999		172 (34.3%)
2000-2009		182 (36.3%)
2010-2016		147 (29.3%)
Organ of transplantation - no. (%)		
Heart		478 (95.4%)
Heart-Kidney		21 (4.2%)
Heart-Liver		2 (0.4%)
Male sex - no. (%)		345 (68.9%)
Age - years		36.7 ± 12.8
BMI - kg/m ²		24.3 ± 3.5
Donor cause of death - no. (%)		
Head trauma		278 (55.5%)
Stroke		163 (32.5%)
Other		60 (12.0%)
CMV mismatch (D+R-) - no. (%)		100 (20.0%)
Cold ischemia time - hours		2.8 ± 0.7
Recipient		
Male sex - no. (%)		394 (78.6%)
Age - years		51.4 ± 12.1
BMI - kg/m ²		24.6 ± 3.8
Diagnosis - no. (%)		
Retransplant		25 (5.0%)
Ischemic cardiomyopathy		211 (42.1%)
Dilated cardiomyopathy		178 (35.5%)
Hypertrophic cardiomyopathy		17 (3.4%)
Restrictive cardiomyopathy		9 (1.8%)
Congenital heart disease		22 (4.4%)
Valvular cardiomyopathy		24 (4.8%)
Other		15 (3.0%)
Pretransplant circulatory support - no. (%)		
None		350 (69.9%)
Left ventricular assist device		103 (20.6%)
Inotropic drugs		24 (4.8%)
Intra-aortic balloon pump		4 (0.8%)
Extracorporeal membrane oxygenation		2 (0.4%)
Biventricular assist device		18 (3.6%)
eGFR - mL/min/1.73m ²		47.2 ± 17.0
Pretransplant diabetes - no. (%)		48 (9.6%)
Baseline antihypertensive use - no. (%)		260 (51.9%)
Baseline statin use - no. (%)		358 (71.5%)
LDL-cholesterol - mg/dL *		103.3 ± 39.7
Post-transplant smoking - no. (%)		55 (11.0%)

Immune

Baseline calcineurin inhibitor - no. (%)	
Tacrolimus	306 (61.1%)
Cyclosporine	195 (38.9%)
Baseline antimetabolite drug - no. (%)	
Mycophenolate mofetil	315 (62.9%)
Azathioprine	160 (31.9%)
None	26 (5.2%)
Human leukocyte antigen A/B/DR mismatches - no. (%)	
0-2	21 (4.2%)
3-4	167 (33.3%)
5-6	313 (62.5%)
Preformed donor-specific antibodies - no. (%) **	21 (8.5%)
Treated rejection episodes during 1st year - no. (%)	
none	439 (87.6%)
1 episode	55 (11.0%)
≥ 2 episodes	7 (1.4%)

* LDL-cholesterol available in 478 patients

** Donor-specific antibody status available in 246 patients

Table 2

Events, by CAV grade at last follow-up			
	CAV 0-1 (n=418)	CAV 2-3 (n=83)	p-value
Alive	285 (68.2%)	38 (45.8%)	< 0.001
Retransplantation	2 (0.5%)	10 (12.0%)	< 0.001
Acute cellular rejection	2 (0.5%)	1 (1.2%)	
Cardiac allograft vasculopathy		6 (7.2%)	
Nonspecific chronic graft failure		3 (3.6%)	
Death	131 (31.3%)	35 (42.2%)	< 0.001
Cardiac death	19 (4.6%)	18 (21.7%)	< 0.001
Sudden cardiac death	16 (3.8%)	10 (12.0%)	
Heart failure	2 (0.5%)	5 (6.0%)	
Myocardial infarction		3 (3.6%)	
Rejection	1 (0.2%)		
Cancer	60 (14.4%)	7 (8.4%)	
Infection	21 (5.0%)	3 (3.6%)	
Other causes	31 (7.4%)	7 (8.4%)	