ORIGINAL RESEARCH

Cardiac Allograft Vasculopathy in Redo-Transplants: Is it More or Less the Same the Second Time Around?

Lauren McCreath, BA,[1] Michael J. Bonios, MD, PhD,[1,3] Antigone Koliopoulou, MD,[1] Omar Wever-Pinzon, MD,[1] Spencer Wright, BS, MBA/MHA,[1] Rami Alharethi, MD,[1] Stephen H. McKellar, MD,[1] Greg Snow, PhD,[1] Bruce B. Reid, MD,[1] Katerina Skedros, BA,[1] Anya Ragnhildstveit, HS,[1] Stamatis N. Adamopoulos, MD, PhD,[3] Jose Nativi, MD,[1] Abdallah G. Kfoury, MD,[1] Stavros G. Drakos, MD, PhD[1,2]

[1] Utah Transplantation Affiliated Hospitals (UTAH) Cardiac Transplant Program (University of Utah Healthcare and School of Medicine, Intermountain Medical Center, Salt Lake cVeterans Affairs Medical Center), Salt Lake City, Utah

[2] Third Department of Cardiology, National & Kapodistrian University of Athens Medical School, Athens, Greece

[3] Onassis Cardiac Surgery Center, Athens, Greece

Conflicts of Interest: None

Running Title: Cardiac Allograft Vasculopathy in Redo-Transplants

Address for correspondence: Division of Cardiovascular Medicine, University of Utah School of Medicine & 3rd Department of Cardiology, National Kapodestrian University of Athens School of Medicine. Address: 30 North 1900 East, Room 4A150, Salt Lake City, Utah, United States; Tel: 801-5852340, Fax: 801-5850701, Email: stavros.drakos@hsc.utah.edu

Abstract

Purpose: Cardiac allograft vasculopathy (CAV) continues to hinder the long-term success of heart transplant recipients. Redo-transplantation is currently the only definitive treatment for advanced CAV. We examined whether these patients are at similar CAV-risk with the second transplant

Methods: Heart recipients from 1985 to 2011 at the UTAH program were included in the study and those with CAV as an indication for redo-transplantation were identified. CAV diagnosis was made by coronary angiography and based on the 2010 ISHLT standardized nomenclature for CAV. Patient demographics, rejection history, and CAV incidence were analyzed.

Results: Of the 1,169 eligible patients, 135 (11.5%) developed CAV post their first transplant; 78 cases within 10 years and 54 beyond 10 years. The mean time to CAV was 6.58 years. Of the 135 patients who developed CAV, only 21 (15.5%) ended up requiring a redo-transplant. Of the 21 retransplanted patients, 4 (19.0%) developed CAV again; 2 patients within 10 years and 2 patients beyond 10 years indicating a similar risk for CAV occurrence for first and redo-transplant.

Conclusions: Our results indicate that CAV is as likely to develop in redo-transplants despite recent advances in immunosuppression and the standardized use of lipid-lowering agents. Although outcomes in redo-transplantation for the indication of CAV are favorable, efforts to better understand and minimize CAV are needed, especially in the face of scarce donor organs. ***Rhythmos 2018;13(1):9-12***.

Key Words: cardiac allograft vasculopathy; redo-transplantation

List of Abbreviations: CAV = cardiac allograft vasculopathy; ISHLT = International Society for Heart and Lung Transplantation

Introduction

Cardiac transplantation is the gold standard of treatment for patients with end-stage heart failure. Analysis of International Society for Heart and Lung Transplantation (ISHLT) registry data show improvements of survival in patient's 1-year post-transplant.[1] However, long term success of heart transplantation continues to be hindered by the development of cardiac allograft vasculopathy (CAV). CAV is an accelerated form of coronary artery disease in transplanted hearts. Despite advances in immunosuppression and the standardized use of lipid-lowering agents, the incidence of CAV has seen little reduction in the past decade.[1] Today, the standard method of surveillance of CAV is invasive coronary angiography because of its greater availability in most hospitals, cost effectiveness, and its applicability at any time in the post-transplant setting.[2] In 2010, ISHLT developed a consensus document to standardize the nomenclature CAV (**Fig.** 1) that advocates the usage of coronary angiography.[3] Once CAV is established in the allograft, treatment options are limited and outcomes are poor. Currently, the only definitive treatment for patients with advanced CAV is retransplantation. Whether these patients are at similar CAV-risk with the second transplant remains unknown and the topic of this study. Efforts to better understand and minimize CAV are needed, especially with chronic disparities between donor supply and the heart transplant waiting list. This study sought to identify the risk of CAV development in heart recipients undergoing a second transplant because of advanced CAV.

Methods

We retrospectively analyzed all patients who received an orthotropic heart transplant (HT) from the UTAH Cardiac Transplant Program (University of Utah Health, Intermountain Healthcare, and Salt Lake City Veterans Affairs Medical Center) from 1985 to 2011. An Institutional Review Board approved this project. Heart recipients who did not have CAV as an indication for redo-

transplantation were excluded. CAV was defined as coronary artery narrowing in the proximal or distal branches diagnosed by coronary angiogram or necropsy report. Severity of CAV was based on the 2010 ISHLT standardized nomenclature for CAV.[3] Classification was categorized as not significant (CAV0), mild (CAV1), moderate (CAV2), or severe (CAV3). CAV incidence was compared between primary and secondary allografts.

We further gathered variables related to patient demographics, rejection history, donor and recipient cardiovascular risk factors, types of immunosuppression administered, medical therapy, and clinical examinations for primary and secondary allograft. Patient clinical follow ups were conducted at any UTAH Cardiac Transplant affiliated hospital in accordance with post-HT management standards.

Data are expressed as mean ± SEM. Paired-samples Student *t* tests were used for comparisons between primary and secondary allograft. Independent-samples *t* tests were used for comparisons between donor characteristics. Significance was considered at a value of $p < 0.05$.

Recommended Nomenclature For Cardiac Allograft Vasculopathy
ISHLT CAV0 (Not significant): No detectable angiographic lesion
ISHLT CAV1 (Mild): Angiographic left main <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
ISHLT CAV2 (Moderate): Angiographic left main <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction
ISHLT CAV3 (Severe): Angiographic left main ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific; see text for definitions)
Definitions
a). A "Primary Vessel" denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.
b). A "Secondary Branch Vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant right coronary artery.
c). Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12mmHg, Pulmonary Capillary Wedge Pressure >25 mmHg, Cardiac Index <2 l/min/m2)

CAV, cardiac allograft vasculopathy; ISHLT, International Society of Heart and Lung Transplantation; LVEF, left ventricular ejection fraction

Figure 1. Nomenclature for cardiac allograft vasculopathy (CAV)

Results

A total of 1,169 eligible patients received a heart transplant between 1985 and 2011. **Figure** 2 depicts their flow through the study. Of the 1,169 transplanted patients, 135 patients developed CAV in their first allograft. 78 cases developed CAV within 10 years and 54 beyond 10 years. The mean time to CAV was 6.58 years. Of the 135 patients who developed CAV, only 21 (15.5%) ended up requiring a redo-transplant. From the 21 patients retransplanted, 4 (19%) developed CAV again with 2 patients within 10 years and 2 patients beyond 10 years. Of the 4 patients who redeveloped CAV, two patients developed CAV 3, one patient developed CAV 2, and one developed CAV 1. Patient with CAV 1 continues to be managed by UTAH clinicians with the remaining three patients passing away due to CAV recurrence. Of the 17 patients who did not develop CAV in their secondary allograft, 4 of those patients died due to early mortality. Causes of death were acute rejection, pneumocytosis, cardiac and respiratory arrest, and one patient had no data.

The incidence of CAV was statistically similar between primary and secondary allograft.

Patients' baseline characteristics along with etiologies of heart disease are included in **Table** 1**.** The average age was 31.2 ± 3.9 years for the first transplant and 35.6 ± 4.1 (p= not significant [NS]) years for the redo-transplant. 76% of the cohort was male and 24% female (p=NS). The leading cause of heart disease was non-ischemic cardiomyopathy (81%). BMI was 22.3 ± 1.2 and 24.8 ± 1.4 (p=0.04) and hypertension prevalence was 44% and 86% (p=0.003) in the primary and redo-transplant, respectively. Post-transplant clinical parameters are listed in **Table** 2**.** Leading treatment for developing CAV was stents with medical therapy (57%) (data not shown).

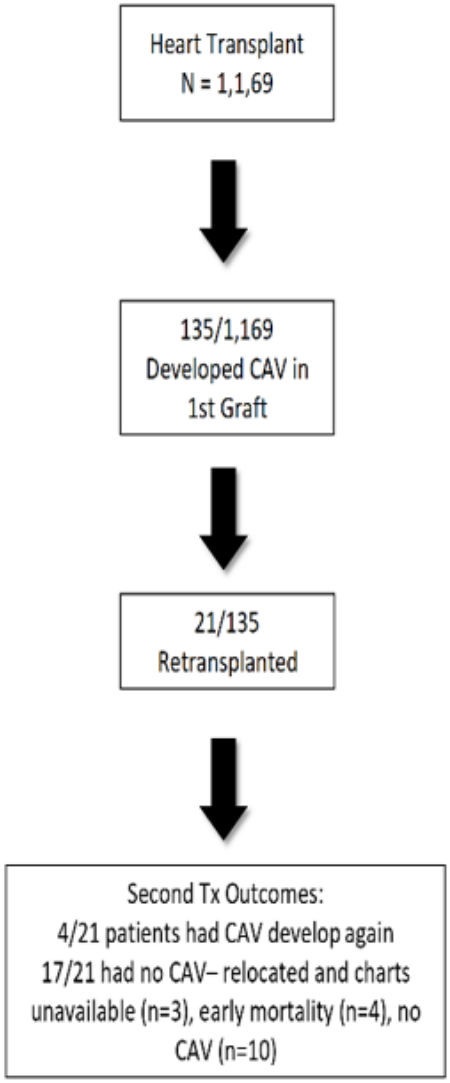

Figure 2. Patient flow chart. CAV = cardiac allograft vasculopathy

Donor baseline characteristics along with donor cause of death are listed in **Table** 3. The average age was 26.6 ± 2.7 years for the first transplant and 24.4 ± 2.9 (p=NS) years for the redo-transplant. 71% of the donors were male and 29% female (p=NS) for the primary transplant and 76% were male and 24% (p=NS) female for secondary transplant. Total ischemic times were 174.8 ± 19.9 minutes and 192.2 ± 13.4 (p=NS) minutes for the first and redo-transplant, respectively.

Table 1. Patient Characteristics

	1st Tx	2nd Tx	Significance *p*-value
Recipient Baseline Characteristics			
Age	31.2 ± 3.9	35.6 ± 4.1	NS
Male	16 (76%)	N/A	NS
DM	2 (10%)	4 (19%)	NS
HTN	9 (44%)	18 (86%)	0.003
CKD	8 (38%)	10 (48%)	NS
HLD	8 (38%)	14 (67%)	NS
Smoked	4 (19%)	N/A	NS
BMI	22.3 ± 1.2	24.8 ± 1.4	0.04
Cause of HF–no.(%)			
Ischemic	4 (19%)	N/A	NS
Non-Ischemic	17 (81%)	N/A	NS

All values are expressed as frequency with (%) or mean ± SEM. DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; HLD, hyperlipidemia; BMI, body mass index; NS, not significant.

Table 2. Post-Transplant Clinical Parameters

	1st Tx	2nd Tx	Significance *p*-value
Rejection History in 1st Year Post Tx			
2R or Greater	0.9 ± 0.2	0.5 ± 0.2	NS
1R	5.1 ± 0.9	4.1 ± 0.8	NS
Transplant Characteristics (yrs)			
Time from Tx to CAV	6.6 ± 0.8	9.7 ± 0.3 (n=4)	NS
Time from Diagnosis to 2nd Tx	1.3 ± 0.6	N/A	NS
Maintenance Immunosuppression			
CSA + AZA + PRED	12 (57%)	8 (38%)	NS
TAC + MMF + PRED	7 (33%)	8 (38%)	NS
CSA + MMF + PRED	1 (5%)	3 (14%)	NS
TAC + AZA + PRED	1 (5%)	2 (10%)	NS
Pharmacological Therapy			
Statins	16 (76%)	20 (95%)	NS
BB	7 (33%)	2 (10%)	NS
Diuretics	13 (62%)	13 (62%)	NS
ACE-I	15 (71%)	17 (81%)	NS
Inotropic Support	3 (14%)	3 (14%)	NS

All values are expressed as frequency with (%) or mean ± SEM. CSA, Cyclosporine; TAC, Tacrolimus; AZA, Azathioprine; MMF, Mycophenolate Mofetil; PRED, Prednisone; BB, beta-blocker; ACE-I, angiotensin-converting enzyme inhibitor; NS, not significant.

Table 3. Donor Characteristics

	1st Tx	2nd Tx	Significance *p*-value
Donor Characteristics			
Age	26.6 ± 2.7	24.4 ± 2.9	NS
Male	15 (71%)	16 (76%)	NS
Weight (kg)	63.3 ± 5.0	69.8 ± 4.2	NS
Total Ischemia Time (min)	174.8 ± 19.9	192.2 ± 13.4	NS
Cause of Death			
CVA	7 (33%)	5 (23%)	NS
MVA	2 (10%)	5 (24%)	NS
Other	12 (57%)	11 (52%)	NS

All values are expressed as frequency with (%) or mean ± SEM. CVA, cerebrovascular accident; MVA, motor vehicle accident; NS, not significant.

Discussion

CAV is a leading cause of death in HT patients after first year post-transplant period, and it represents the leading cause of need for retransplantation worldwide.[3,4] A recent registry analysis reported comparable 9-year survival among patients with CAV retransplanted (n=65) or medically managed (n=4,530): 55% versus 51%.[5] During both transplants, data were collected on patients who had infectious disease, particularly diseases which are associated with atherosclerosis in transplanted patients. No patients were found to have developed an infectious disease, such as herpes simplex virus or cytomegalovirus. Subgroup analysis suggested a survival benefit for retransplantation with associated allograft systolic dysfunction. The results from our retrospective study indicate that CAV is as likely to develop in redo-transplants despite recent advances. Identification of risk factors associated with CAV development could reduce its incidence.[2] Risk factors for CAV such as hypertension, hyperlipidemia, and diabetes can promote the development of CAV.[6,7] In our study, the aforementioned risk factors were similar between the primary allograft and the secondary with the exception of hypertension being significantly higher during the secondary allograft. Hypertension often develops in HT patients because of necessary immunosuppressive regimens and may be an unavoidable risk factor.[8]

Studies have showed that early recurrent rejection episodes correlate with progression of CAV.[9,10,11] We did not find any significant differences in the incidences of allograft rejection between the first and second transplantation. Additionally, patients received similar post-transplant immunosuppression at both time points.

Older donor age as a risk factor for CAV development was first noted by Gao and colleagues.[12] In our study, the effect of older donor age was apparent in the second

allograft with donors over the age of 40 years old, although the number of older donors was limited. Older donor age is an important issue due to increased tendency for atherosclerotic changes in the older donor .[13]

The pathogenesis of CAV is complex and prevention strategies must be initiated early with annual surveillance for detection of early disease.[14,15,16] The usage of statin therapies, treatment of cardiovascular risk factors, prevention of acute rejection, and the introduction of everolimus and sirolimus have been important in the prevention and treatment of CAV.[14]

Limitations. This study has several limitations. It was conducted at a single center which did not offer us a large sample size. Second, incidence of CAV in the primary allograft is low which could be due to failure of our database to identify everyone who developed CAV. Nomenclature of CAV was not standardized until 2010 so variability of CAV diagnosis was present in older patient charts. Finally, multivariable analysis was not adjusted for systolic dysfunction after CAV diagnosis due to the number of missing data points. Also potential late factors associated with mortality risk following the CAV diagnosis, such as new development of systolic dysfunction, rejection or additional comorbidities are not included.

Conclusions

CAV remains a leading cause of death after heart transplantation. Although outcomes in redo-transplantation for the indication of CAV are favorable, efforts to better understand and minimize CAV are needed, especially in the face of scarce donor organs.

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