Effect of Pretransplant Continuous-Flow Left Ventricular Assist Devices on Cellular and Antibody-Mediated Rejection and Subsequent Allograft Outcomes

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The aim of this study was to evaluate the impact of continuous-flow left ventricular assist devices (CF-LVAD) on subsequent rejection after heart transplantation (HT) by using cellular rejection score and antibody-mediated rejection score (AMRS) and correlating with subsequent allograft outcomes. We retrospectively analyzed 108 consecutive patients who underwent HT without (n = 67) or with (n = 41) previous CF-LVAD in 2008 to 2014. The 24 months cumulative effect of rejection was calculated by using cellular rejection scores and AMRS, based on the total number of rejections divided by valid biopsy samples. Vasculopathy was assessed both by routine coronary angiogram and intravascular ultrasound. Patients who underwent pretransplant CF-LVAD demonstrated a significant increase in the number of cellular rejection episodes as compared with the nonbridged patients, for 1 and 2 years of follow-up (p = 0.026 and p = 0.016), respectively. There were no differences in AMRS (p >0.05) and allograft outcomes, such as vasculopathy and overall survival (p >0.05) over the period of follow-up. Implantation of a CF-LVAD before HT impacts cellular rejection during the post-transplant period. Despite these findings, CF-LVAD does not translate to differences in allograft outcomes after transplant, such as vasculopathy and overall survival over the period of the study. In conclusion, whether this affects longer term outcomes than studied remains to be determined. **(Am J Cardiol 2016;■:■−■)**

Due to the limited availability of donor hearts, left ventricular assist devices (LVAD) are often used to support patients with advanced heart failure awaiting heart transplantation (HT) or as destination therapy. Many reports have suggested a correlation between LVAD as a risk factor for allosensitization and the development of anti-human leukocyte antigens (HLA) antibodies, leading to increased rates of rejection with or without negative impact at other allograft outcomes.[1−12] Most of these reported data are based on an earlier generation of pulsatile flow LVAD. The newer generation of LVAD, continuous-flow left ventricular assist devices (CF-LVAD), has helped to reduce mortality in patients awaiting transplant, and have become the standard of care as a bridge to transplantation.[13] There have been conflicting results regarding the impact of CF-LVAD on allosensitization, rejection, and allograft outcomes after HT.[14−19] This could be explained by the different criteria used to define rejection across previously published studies. The aim of this study was to evaluate incidence of cellular rejection (CR) and antibody-mediated rejection (AMR) and subsequent allograft outcomes (survival and vasculopathy) in patients who underwent HT with or without previous CF-LVAD. The incidence of rejection was evaluated using cellular rejection score (CRS) and antibody-mediated rejection score (AMRS) that were developed based on heart biopsy findings.

Methods

This is a retrospective single-center cohort study of 108 consecutive patients who underwent HT without (Group HT, n = 67) or with (Group CF-LVAD + HT, n = 41) CF-LVAD at Mayo Clinic, Rochester, between January 1, 2008, and May 31, 2014. The median follow-up was 30 (37) months. All donor organs accepted for transplantation were carefully assessed by the surgical team and were deemed to be of good quality and appropriate for transplantation. Donor organs were rejected if biventricular function, hemodynamics, and coronary angiography data were not optimal. There were no significant HLA mismatches and retrospective flow cross-match was within acceptable parameters for all patients. Routine immunosuppression protocols were used after transplant. All patients (100%) underwent perioperative induction therapy with antithymocyte globulin. The maintenance immunosuppression included calcineurin inhibitors (CNIs) (tacrolimus or cyclos-porine),

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See page 4 for disclosure information.

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0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.10.020

Table 1
Baseline clinical characteristics of patients who underwent heart transplantation with or without previous Continuous Flow Left Ventricular Assist Device

Variable	HT (n = 67)	CF-LVAD + HT (n = 41)	p Value
Age at transplant (years)	49.6±14.1	52.4±11.2	0.287
Male	41 (61%)	32 (78%)	0.069
Reason for heart transplant			
Ischemic cardiomyopathy	17 (25%)	17 (42%)	
Dilated cardiomyopathy	13 (19%)	13 (32%)	0.016
Other	37 (55%)	11 (27%)	
Time from CF-LVAD to transplant (months)	-	10 (13.8)	-
Heart Mate II - CF-LVAD		38 (93%)	
Months of follow-up	31 (37)	26 (38)	0.674
Replaced calcineurin inhibitor with Sirolimus at 1st year	25 (38%)	15 (40%)	0.872
% Panel reactive antibody Class I at the time of transplant	5 (22)	8 (21)	0.180
% Panel reactive antibody Class II at the time of transplant	21 (45)	21 (49)	0.980

Table 2
Distribution of endomyocardial biopsies over time in heart transplant patients with or without previous Continuous Flow Left Ventricular Assist Device

Variable	Months		
	0 − 6	7 − 12	13 − 24
Biopsies, No. HT/CF-LVAD + HT	589/386	166/122	168/107
Biopsies per patient, No.HT/CF-LVAD +HT	9/9	3/3	4/3

mycophenolate mofetil (MMF) or azathioprine, and prednisone. MMF was the initial choice for secondary agent and replaced with azathioprine in patients who were intolerant of MMF. Maintenance levels of immunosuppressives were kept in the 8- to 12-ng/ml range for tacrolimus and 100 to 200 ng/ml for cyclosporine. MMF levels were not routinely measured. CNIs were replaced with sirolimus in 40 and 33 patients by the end of the first and third post-transplant year, respectively. Prednisone was tapered within 1 month after transplantation, and discontinued in 9 and 26 patients by the end of the first and third post-transplant year, respectively. The CF-LVAD + HT group comprised patients with CF-LVAD before HT. The HeartMate II (Thoratec Corp, Pleasanton, California) was implanted in 38 patients (93%), and Heartware (HeartWare Ltd, Framingham, Massachusetts) in 3 patients (7%). In addition, the antibodies against HLA class I or II antigens were determined by the panel reactive antibody (PRA) assay performed by Luminex flow cytometry in both groups of patients waiting for HT. For the purposes of this analysis the PRA class I and II findings at the time of HT are presented.

First routine endomyocardial biopsies (EMB) were performed 2 weeks after the HT, then weekly for the first 4 weeks, every 2 weeks until 2 months after transplant, monthly from 3 to 6 months, every 3 months until the end of the second year, and yearly afterward. The frequency of biopsies varied based on clinical symptoms and heart biopsy findings. Specifically rebiopsies were indicated for CR 2R or higher and at least AMR grade 1. As per protocol, 5 myocardial specimens were obtained during each EMB. We investigated both CR and AMR, assessed by the 2004 and 2011 International Society for Heart and Lung Transplantation (ISHLT) grading system. All biopsies obtained before the institution of the 2004 and 2011 ISHLT grading system were reclassified according to the new system. The incidence of rejection was evaluated by a rejection score that was developed based on heart biopsy histopathology and immunopathology findings.

The following rejection scores were calculated for each patient at 6, 12, and 24 months.

CRS was calculated as 0R = 0, 1R = 1, 2R = 2, and 3R = 3, based on 2004 ISHLT R grading, and represented the total number of rejections divided by the total number of valid biopsies performed during the study period. AMRS was calculated as pAMR 0 = 0, pAMR 1 = 1, pAMR 2 = 2, and p AMR 3 = 3, based on 2011 ISHLT AMR grading, and represented the total number of rejections divided by the total number of valid biopsies performed during the study period. The purpose of using a rejection score was to take into account both low-grade and higher grade rejection, normalized for the total number of valid biopsy samples taken over the time course of the study. A minimum of 3 myocardial specimens were considered valid biopsy findings. Besides the rejection based on the rejection score, subsequent allograft outcomes (overall survival and vasculopathy) were also evaluated by the last available patient's follow-up.

The development of cardiac allograft vasculopathy (CAV) after transplant was based on both coronary angiogram and intravascular ultrasound (IVUS) of the left anterior descending artery (LAD) at 2 months after HT and then annually in all patients. The definition of CAV angiographically was based on the 2010 ISHLT CAV grading scale.[20] IVUS was performed during routine coronary angiography after intracoronary administration of 100 to 200 μg nitroglycerin. Mechanical pullback (0.5 mm/s) was performed from the mid to distal LAD to the left main coronary artery with a 20-MHz, 2.9Fr, monorail, electronic Eagle Eye Gold IVUS imaging catheter (Volcano Therapeutics Inc., Rancho Cordova, California) and a dedicated IVUS scanner (Volcano Therapeutics). The presence of CAV was based on visual assessment of an experienced intervention cardiologist. CAV classification using IVUS was: 0 = normal (without visible intimal thickening); 1 = mild atherosclerosis (any visible intimal thickening <20% occlusive); 2 = moderate atherosclerosis (any visible intimal thickening <50% occlusive); 3 = severe atherosclerosis (any visible intimal thickening >50% occlusive). Vasculopathy outcomes included moderate and severe CAV. The association between future CAV and CRS in patients with CF-LVAD + HT was analyzed as follows: because the rejection score at 6 months can only be used as a risk factor for CAV beyond 6 months, patients with CAV at