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Myocardial Structural and Functional Response After Long-Term Mechanical Unloading With Continuous Flow Left Ventricular Assist Device

Axial Versus Centrifugal Flow

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ABSTRACT

OBJECTIVES The aim of this study was to assess the impact of continuous-flow left ventricular assist device (LVAD) type—axial flow (AX) versus centrifugal flow (CR)—on myocardial structural and functional response following mechanical unloading.

BACKGROUND The use of continuous-flow LVADs is increasing steadily as a therapeutic option for patients with end-stage heart failure who are not responsive to medical therapy. Whether the type of mechanical unloading influences the myocardial response is yet to be determined.

METHODS A total of 133 consecutive patients with end-stage heart failure implanted with continuous-flow LVADs (AX, n = 107 [HeartMate II Thoratec Corporation, Pleasanton, California]; CR, n = 26 [HeartWare, HeartWare International, Framingham, Massachusetts]) were prospectively studied. Echocardiograms were obtained pre-LVAD implantation and then serially at 1, 2, 3, 4, 6, 9, and 12 months post-implantation.

RESULTS The 2 pump types led to similar degrees of mechanical unloading as assessed by invasive hemodynamic status and frequency of aortic valve opening. Myocardial structural and functional parameters showed significant improvement post-LVAD in both AX and CR groups. Left ventricular ejection fraction increased significantly from a mean of 18% to 28% and 26% post-LVAD in the AX and CR groups, respectively. Left ventricular end-systolic volume index and left ventricular end-diastolic volume index decreased significantly as early as 30 days post-implantation in the 2 groups. The degree of myocardial structural or functional response between patients in the AX or CR groups appeared to be comparable.

CONCLUSIONS Long-term mechanical unloading induced by AX and CR LVADs, while operating within their routine clinical range, seems to exert comparable effects on myocardial structural and functional parameters.
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Left ventricular assist devices (LVADs) are increasingly used as a bridge to heart transplantation or destination therapy. Their use has demonstrated significant improvements in quality of life, exercise capacity, and survival in patients with end-stage heart failure (HF) (1–3). Additionally, long-term LVAD unloading has been shown to lead to significant improvement in the structural and functional parameters of the failing human heart (4,5).

Historically, pulsatile-flow (PF) LVADs were the first mechanical pumps used successfully to unload the heart and led to improvements in myocardial and

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end-organ function, exercise capacity, quality of life, and survival in patients with end-stage HF (6–8). However, PF LVADs were eventually replaced by smaller, quieter, and more durable second- and third-generation continuous-flow (CF) LVADs, which have been shown to offer enhanced survival with less morbidity compared with PF LVADs (9). CF LVADs deliver blood with reduced pulse pressures to peripheral organs and are classified according to the direction of blood flow inside the pump: parallel to the impeller axis in second-generation axial-flow (AX) LVADs or perpendicular to the rotor in third-generation centrifugal-flow (CR) LVADs (10).

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Attempts to evaluate clinical outcomes between AX and CR rotary-flow LVADs have yielded mixed results. In general, studies have shown similar survival between the axial HeartMate II (Thoratec Corporation, Pleasanton, California) and centrifugal HeartWare (HeartWare International, Framingham, Massachusetts) (2,11–13). Basic engineering differences between the 2 types of CF LVADs, including bearing design, hemodynamic performance, pre-load and afterload sensitivity, and flow pulsatility, are summarized in a review by Moazami et al. (14). It is hypothesized that differences in pump design are likely to influence hemodynamic performance or clinical outcomes (15). However, it remains unknown to what extent these differences affect myocardial structure and function.

METHODS

STUDY POPULATION. We prospectively studied 167 consecutive patients with end-stage HF who required circulatory support with CF LVADs as bridge to transplantation or destination therapy between 2008 and 2014. We prospectively excluded patients with acute HF etiologies (n = 13) and patients who were implanted with CF LVADs other than the HeartMate II or HeartWare (n = 21). The remaining 133 patients formed our study cohort. One hundred seven patients received the AX LVAD HeartMate II and 26 received the CR LVAD HeartWare. The selection of the pump was left to the discretion of the treating HF clinical team. Patients were enrolled at the institutions constituting the Utah Transplantation Affiliated Hospitals Cardiac Transplant Program (University of Utah Health Science Center, Intermountain Medical Center, and the Veterans Administration Salt Lake City Health Care System, all in Salt Lake City, Utah). Informed consent was obtained from all patients, and the study was approved by the Institutional Review Boards of the participating institutions.

CLINICAL DATA. Clinically relevant data, including demographics, medications, comorbidities, and invasive hemodynamic data, were collected prior to LVAD implantation.

LVAD MANAGEMENT. Before patients were discharged home, the effect of LVAD unloading on cardiac size, shape, and function was assessed by echocardiography. Device speed was adjusted to achieve adequate flows and optimal LV and right ventricular (RV) decompression with positioning of the interventricular and interatrial septa in the midline plus minimal mitral valve regurgitation. Aortic valve opening was desirable but considered of lower priority compared with the conditions outlined earlier. Subsequent adjustments to speed were made as indicated by patients' symptoms or clinical events. Clinical care for LVAD patients at our institutions was provided by a multidisciplinary team including HF cardiologists, cardiac surgeons, and LVAD nurses and coordinators.

ABBREVIATIONS AND ACRONYMS

AX = axial-flow
CF = continuous-flow
CR = centrifugal-flow
HF = heart failure
LV = left ventricular
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
PF = pulsatile-flow
RV = right ventricular

ASSESSMENT OF MECHANICAL UNLOADING FOLLOWING LVAD IMPLANTATION. The degree of mechanical unloading in both AX and CR groups was assessed by both invasive hemodynamic data from right heart catheterization performed 6 to 8 weeks post-LVAD implantation and by frequency of aortic valve opening as assessed with echocardiography at 1 to 2 months post-LVAD implantation. Invasive hemodynamic data included systolic blood pressure, diastolic blood pressure, mean blood pressure, right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac index. Aortic valve opening during 3 LV systoles was graded as consistent opening, intermittent opening (1 to 2 openings in 3 LV systoles), or as consistently closed.

ECHOCARDIOGRAPHIC DATA. Surveillance for functional recovery was undertaken using a protocol developed and tested at the University of Utah (16). We performed transthoracic echocardiography within 2 weeks preceding LVAD implantation and then at months 1, 2, 3, 4, 6, 9, and 12 after implantation. Of note, echocardiograms obtained in patients during pump thrombosis episodes or pump thrombosis-related hospitalizations or outpatient clinic visits were not included in this study. Echocardiographic evaluation was done during 2 LV loading conditions. The first set of echocardiographic images was obtained while the LVAD was providing full support. Subsequently, the speed of the LVAD was gradually reduced to the lowest setting recommended by the manufacturer (i.e., 8,000 rpm for the HeartMate II and 1,800 rpm for the HeartWare), and a second set of echocardiographic images was obtained approximately 30 min later ("turn-down study"). This maneuver results in a marked reduction of flow through the LVAD and an increase in pressure and volume loading of the heart. The effectiveness of LV reloading was assessed by aortic valve opening during cardiac systole. During regular full LVAD support, the aortic valve opened rarely, whereas during the LVAD turn-down studies, the aortic valve opened with every beat in both types of pumps (ratio 1:1). In preparation for a turn-down study patients had to be on therapeutic anticoagulation (international normalized ratio: 2 to 3). Turn-down echocardiographic studies were not performed in patients with histories of stroke or transient ischemic attack, LVAD thrombosis, hemolysis, or difficulty achieving optimal anticoagulation or when a subtherapeutic international normalized ratio was present. Of the patients who performed full-speed echocardiographic studies, 52% performed turn-down studies at 1 month post-LVAD, 50% at 2 months, 47% at 3 months, 47% at 4 months, 46% at 6 months, 46% at 9 months, and 41% at 12 months.

Echocardiographic studies included complete 2-dimensional, M-mode, and Doppler (color, spectral, and tissue) examinations. LV wall thickness, internal dimensions, and their derivatives LV mass and fractional shortening were obtained from 2-dimensional echocardiographic images using techniques in accordance with current American Society of Echocardiography guidelines (15). Assessment of LV volumes and left ventricular ejection fraction (LVEF) was performed using the apical 4- and 2-chamber views. RV size was evaluated by means of RV dimensions obtained at end-diastole from a RV-focused apical 4-chamber view (basal RV end-diastolic dimension) and from a parasternal long-axis views (RV outflow tract). Similarly, left atrial dimensions and volumes were measured.

Doppler evaluation included the assessment of mitral inflow velocities and tissue mitral annular velocities obtained from an apical 4-chamber view and using pulsed-wave Doppler. Mitral inflow parameters evaluated included early mitral inflow velocity (E-wave), late or atrial mitral inflow velocity (a-wave), and E-wave deceleration time. Tissue Doppler mitral annular velocities included early diastolic annular velocity (E′) and late diastolic annular velocity (a′). These measurements were performed in accordance with current American Society of Echocardiography guidelines (17,18).

STATISTICAL ANALYSIS. Standard summary descriptors were used, such as frequencies, percentages, and means. Measures of variation are presented in the form of the standard deviation and standard error of the mean. Comparisons of categorical variables were performed using chi-square tests. Ordinal variables were compared using nonparametric tests (e.g., the Wilcoxon signed rank test and the Kruskal-Wallis test). Comparisons between continuous variables were performed using 1-sample paired and 2-group Student *t* tests. Comparison of results between axial and centrifugal pumps for continuous echocardiographic variables was performed using linear mixed modeling with repeated measures for the 8 measurement time points, with multivariate adjustment performed for age, sex, and HF etiology. A p value <0.05 was considered to indicate statistical significance, with further correction for multiple comparisons made using Bonferroni correction for analyses of the primary echocardiographic variables ($p < 0.005$ [0.05/10 tests of hypothesis]). Analyses were performed using Stata version 13 (StataCorp LP, College Station, Texas) and IBM SPSS version 23.0 (IBM, Inc., Chicago, Illinois).

RESULTS

PATIENT CHARACTERISTICS PRE–LVAD IMPLANTATION. Baseline characteristics of the study group are summarized in Table 1. The mean age was 57 years (56 years in the AX group vs. 61 years in the CR group), and 80% of patients were male (78% in the AX group vs. 88% in the CR group). Approximately one-half of the patients had ischemic cardiomyopathy (38% in the AX group vs. 50% in the CR group). Bridge to transplantation was the indication for implantation in the majority of patients for both groups (64% in the AX group vs. 58% in the CR group). Patients in the AX group tended to have higher values of body mass index compared with those in the CR group (29 kg/m^2 vs. 26 kg/m^2, $p = 0.05$). The remaining baseline characteristics were similar between the 2 groups. Patients in the 2 groups had comparable end-organ function pre-LVAD implantation, and baseline biochemical data demonstrating this are shown in Table 2.

UNLOADING EFFECT OF CF LVAD TYPE: INVASIVE HEMODYNAMIC STATUS AND AORTIC VALVE OPENING. The degree of unloading, as assessed by invasive hemodynamic status and frequency of aortic valve opening, was found to be comparable between the 2 types of CF-LVAD. Specifically, the left- and right-sided filling pressures were significantly decreased after 6 to 8 weeks of LVAD support in both groups (Table 3). In the AX group, diastolic and mean blood pressure values increased significantly from 62 to 84 mm Hg and from 81 to 90 mm Hg, respectively. In the CR group, however, the increase in diastolic

TABLE 1 Baseline Characteristics of Patients Before Left Ventricular Assist Device Implantation

	Axial (n = 107)	Centrifugal (n = 26)	p Value
Age at LVAD implantation, yrs	56 ± 15	61 ± 16	NS
Male	83 (78)	23 (88)	NS
BMI, kg/m^2	28.5 ± 5.5	26.3 ± 4.3	0.05
Diabetes	36 (34)	7 (27)	NS
Hypertension	46 (43)	10 (38)	NS
Atrial fibrillation	46 (43)	11 (42)	NS
Etiology of HF			NS
Ischemic	41 (38)	13 (50)	
Nonischemic	66 (62)	13 (50)	
Duration of HF symptoms, yrs	6.7 ± 6.5	5.9 ± 5.0	NS
LVEF, %	18.2 ± 7.4	18.1 ± 6.3	NS
LVEDD, cm	6.8 ± 1.0	6.6 ± 0.6	NS
Moderate or severe MR	21 (21)	3 (13)	NS
NYHA functional class			NS
III	32 (31)	6 (23)	
IV	75 (69)	20 (77)	
Inotrope therapy	72 (67)	19 (73)	NS
IABP or MCS	7 (7)	2 (8)	NS
INTERMACS profile			NS
1	8 (7)	2 (8)	
2	21 (20)	3 (11)	
3	46 (43)	14 (54)	
4	26 (24)	4 (15)	
5	5 (5)	1 (4)	
6	1 (1)	1 (4)	
7	0 (0)	1 (4)	
LVAD indication			NS
BTT	69 (64)	15 (58)	
DT	38 (36)	11 (42)	
Duration of unloading, d	566 ± 472	562 ± 429	NS

Values are mean ± SD or n (%).

BMI = body mass index; BTT = bridge to transplantation; DT = destination therapy; HF = heart failure; IABP = intra-aortic balloon pump; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MR = mitral regurgitation; NYHA = New York Heart Association.

TABLE 2 Biochemical Profile of Subjects Before Left Ventricular Assist Device Implantation

	Axial (n = 107)	Centrifugal (n = 26)	p Value
Serum sodium, mEq/l (135–145)	135 ± 5	137 ± 4	NS
Serum BUN, mg/dl (5–25)	33 ± 20	30 ± 14	NS
Serum creatinine, mg/dl (0.66–1.25)	1.4 ± 0.5	1.3 ± 0.4	NS
AST, U/l (0–55)	53 ± 48	39 ± 26	NS
ALT, U/l (0–70)	73 ± 142	39 ± 41	NS
Total bilirubin, mg/dl (0.2–1.3)	1.7 ± 1.4	1.2 ± 0.5	NS
Serum albumin, g/dl	3.7 ± 0.6	3.8 ± 0.4	NS
Serum hemoglobin, g/dl (11.7–15.7)	12 ± 2	12 ± 12	NS
Platelet count, ×10^9/l (150–450)	199 ± 80	217 ± 85	NS
WBC count, ×10^9/l (4.0–11.0)	8.2 ± 3.7	8.6 ± 3.4	NS
LDH, U/l (325–750)	574 ± 426	501 ± 192	NS

Values are mean ± SD. Values in parentheses are the normal range for each variable.

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; WBC = white blood cells.

and mean blood pressure values did not reach statistical significance. To further assess the degree of induced unloading with each type of pump, we recorded the frequency of aortic valve opening (**Figure 1**). Again, no significant difference in the frequency of aortic valve opening between the AX and CR groups was noted, suggesting that the left ventricle was unloaded to comparable degrees in the 2 groups.

MYOCARDIAL STRUCTURAL AND FUNCTIONAL RESPONSE TO MECHANICAL UNLOADING. Baseline and serial follow-up echocardiographic parameters are shown in **Figure 2**. Peak LVEF was achieved at 9 and 4 months in the AX and CR groups, respectively (**Figure 2A**). Twenty-two percent of patients in the AX group achieved peak LVEFs of 40% or more, while 18% of patients in the CR group achieved peak LVEFs of 40% or more. After using a repeated-measures linear mixed model adjusting for age, sex, and HF etiology, LVEF showed a trend toward more significant improvement in the AX group over time than the CR group (p = 0.003). LV end-systolic volume index and LV end-diastolic volume index decreased significantly as early as 30 days post-implantation in the 2 groups (**Figures 2B and 2C**). LV mass index also decreased significantly at 30 days post-implantation (**Figure 2D**). LV mass index, however, remained within the normal reference range. After using a repeated-measures linear mixed model adjusting for age, sex, and HF etiology, LV end-systolic volume index, LV end-diastolic volume index, and LV mass index showed no differences between the groups (p = 0.57, p = 0.60, and p = 0.05, respectively). Of note, we compared the LVAD turn-down echocardiographic results with those obtained at regular LVAD speed and found no differences between the 2 pump types (data not shown).

LV diastolic functional parameters improved significantly post-LVAD implantation in both AX and CR groups (**Figure 3**, Online Table 1) and again, the change in diastolic parameters was comparable between the 2 groups at each time point.

DISCUSSION

Little is known about the impact of pump type (AX or CR) as it relates to myocardial structural and functional response following long-term mechanical unloading. We found that long-term mechanical unloading with both AX and CR LVADs led to

TABLE 3 Invasive Hemodynamic Status Pre- and 6 to 8 Weeks Post-Left Ventricular Assist Device Implantation

	Axial (n = 107)	Centrifugal (n = 26)	p Value
Pre-implantation			
RAP, mm Hg	12.7 ± 6.5	12.1 ± 5.3	NS
PAM, mm Hg	37.7 ± 10.2	37.5 ± 9.2	NS
PCWP, mm Hg	24.8 ± 8.3	27.9 ± 9.5	NS
CI, l/min/m^2	1.6 ± 0.5	1.9 ± 0.4	NS
PVR, Wood units	4.6 ± 3.3	3.2 ± 1.7	NS
SBP, mm Hg	104 ± 14	98 ± 18	NS
DBP, mm Hg	62 ± 12	66 ± 10	NS
MBP, mm Hg	81 ± 11	77 ± 12	NS
Post-implantation			
RAP, mm Hg	8.3 ± 3.5*	9.1 ± 5.2*	NS
PAM, mm Hg	22.5 ± 7.1*	23.0 ± 10.4*	NS
PCWP, mm Hg	11.7 ± 5.7*	12.8 ± 6.8*	NS
CI, l/min/m^2	2.4 ± 0.6*	2.3 ± 0.5*	NS
PVR, Wood unit	2.3 ± 1.3*	2.9 ± 1.8*	NS
SBP, mm Hg	104 ± 12	99 ± 12	NS
DBP, mm Hg	84 ± 14*	71 ± 15	0.008
MBP, mm Hg	90 ± 11*	81 ± 13	0.03

Values are mean ± SD. *$p < 0.05$, pre- versus post-LVAD implantation.

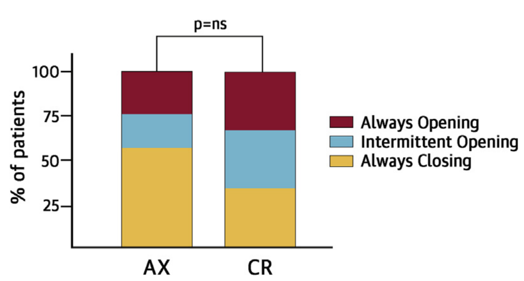
CI = cardiac index; DBP = diastolic blood pressure; LVAD = left ventricular assist device; MBP = mean blood pressure; PAM = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SBP = systolic blood pressure.

comparable improvements in several myocardial structural and functional parameters.

STRUCTURAL AND FUNCTIONAL MYOCARDIAL RESPONSE. Studies comparing PF and CF LVADs showed similar pressure unloading between the 2 pump types, while PF LVADs provide more pronounced LV volume unloading (7,8,19). It has been speculated that AX LVADs may provide better LV volume unloading than CR LVADs (20,21). However, a recent study by Giridharan et al. (10) using mock flow loop and chronic HF bovine models found no significant differences in hemodynamic status and echocardiographic findings between models of AX and CR LVADs. In our study, patients in the AX group showed more rapid improvement in structural and functional myocardial response post-LVAD implantation. At subsequent time points, however, patients in both groups showed comparable improvement in structural and functional myocardial response, suggesting that long-term mechanical unloading with AX and CR LVADs, while operating within their normal clinical range, provide similar improvement in structural and functional parameters of the failing human heart.

Our previous experience with CF LVADs showed that functional parameters peak at 6 months post-implantation, while structural parameters significantly improve as early as 30 days post-implantation (16). This is consistent with our results, in which structural parameters significantly improved at 30 days post-implantation in the AX and CR groups, while systolic function peaked at 9 and 4 months in the AX and CR LVADs, respectively. Finally, we show that although LV mass decreased in patients unloaded with both AX and CR LVADs, it remained within the normal reference range during the follow-up period. These findings are consistent with our prior findings, in which we demonstrated no histological, molecular, or metabolic evidence of induced atrophy in a heterogeneous LVAD population (22).

FIGURE 1 Frequency of Aortic Valve Opening at 1 to 2 Months Post-Left Ventricular Assist Device Implantation

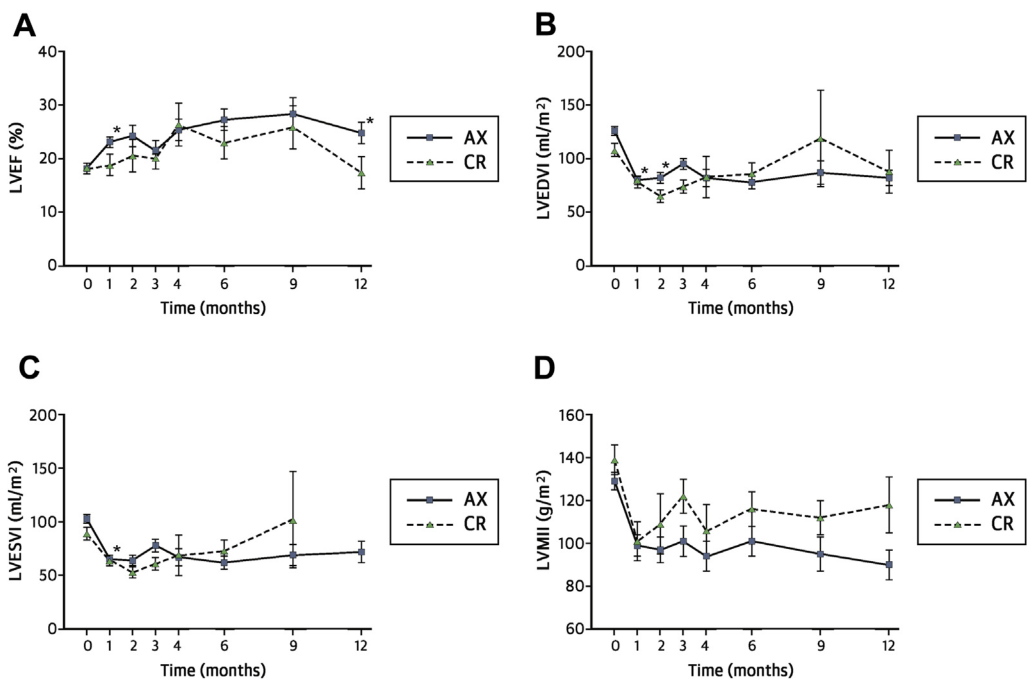


Aortic valve opening was graded as: 1) always opening; 2) intermittent opening (1 to 2 openings in 3 LV systoles); or 3) always closing during 3 LV systoles. AX = axial flow; CR = centrifugal flow.

HEMODYNAMIC PERFORMANCE POST-LVAD. It has been shown that LVAD unloading leads to improvement in hemodynamic status compared with pre-LVAD time points (23). This is consistent with our results, in which pulmonary hemodynamic status significantly improved post-LVAD implantation in patients implanted with the 2 types of LVADs. Furthermore, our results show that although systolic blood pressure did not significantly change post-LVAD in the 2 groups, diastolic and hence mean blood pressures increased in the AX group. The fact that diastolic blood pressure increased without a simultaneous increase in systolic blood pressure indicates that the augmented cardiac output occurred principally during diastole.

In our study, the reduction in pulse pressure values post-LVAD implantation was more prominent in AX than in CR pumps. This is because CR LVADs, when exposed to physiological conditions of varying preload and afterload, provide greater pulsatility than AX LVADs (10,14,24). The lower pulse pressure values in the AX group might explain the lower frequency of aortic valve opening (albeit not statistically

FIGURE 2 Serial Echocardiographic Changes

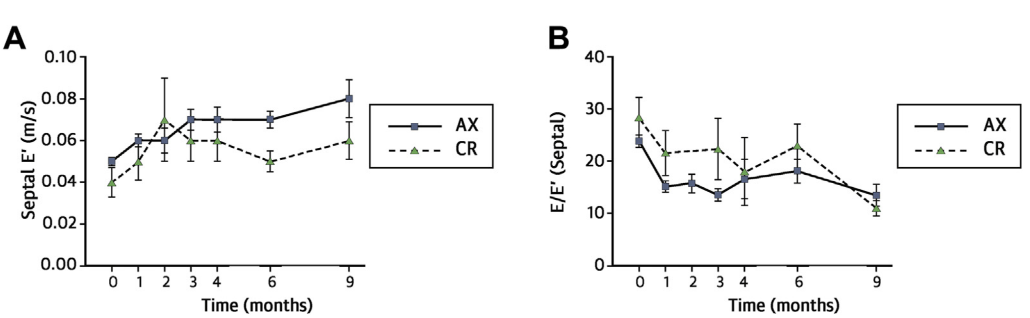


Data are presented as mean ± SEM. *$p < 0.05$, axial flow (AX) versus centrifugal flow (CR). LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVESVI = left ventricular end-systolic volume index.

significant) observed in the AX group compared with the CR group (25).

STUDY LIMITATIONS. Our study had limitations, including the uneven number of patients in each group. This is mainly because the HeartMate II was approved for use before the HeartWare. Additionally, the 2 groups were nonrandomized, and although most of the baseline characteristics were similar between the 2 groups, some factors that were not part of the analyses might have affected our results. Also, despite similar blood pressure medical management in the 2 groups, the fact that the mean blood pressure values were different might have affected our results. In addition, our study group was followed for 12 months post-LVAD implantation, and whether our results are applicable to longer periods of support will need further evaluation.

FIGURE 3 Serial Changes in Diastolic Function Echocardiographic Parameters



Data are presented as mean ± SEM. E = mitral valve inflow early velocity; E′ = early diastolic motion of the mitral annulus. Other abbreviations as in Figure 2.

CONCLUSIONS

Although patients showed improvements in structural and functional myocardial parameters post-implantation with CF LVADs, no difference was shown in myocardial response between patients supported with AX versus CR pumps.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Mechanical unloading with CF LVADs may lead to significant improvements in myocardial structural and functional parameters, with no significant advantage for one pump type over the other.

TRANSLATIONAL OUTLOOK: Further studies should look into the characteristics of patients showing the most significant restoration of myocardial function after unloading with different types of pumps.

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KEY WORDS axial versus centrifugal, continuous flow, left ventricular assist device, mechanical unloading, myocardial function, myocardial structure

APPENDIX For a supplemental table, please see the online version of this paper.