Aortic Insufficiency in Patients With Sustained Left Ventricular Systolic Dysfunction After Axial Flow Assist Device Implantation

Teruhiko Imamura, MD, PhD; Koichiro Kinugawa, MD, PhD; Takeo Fujino, MD, PhD;
Toshiro Inaba, MD, PhD; Hisataka Maki, MD, PhD; Masaru Hatano, MD; Osamu Kinoshita, MD, PhD;
Kan Nawata, MD, PhD; Shunei Kyo, MD, PhD; Minoru Ono, MD, PhD

Background: Predicting the occurrence of aortic insufficiency (AI) during left ventricular assist device (LVAD) support has remained unsolved.

Methods and Results: We enrolled 52 patients who had received continuous flow LVAD (14 axial and 38 centrifugal pumps) and who been followed for ≥ 6 months between Jun 2006 and Dec 2013. Native aortic valve (AV) opening was observed in 18 patients (35%) with improved LV systolic function, and none of them had AI. On multivariate logistic regression analysis preoperative shorter heart failure duration was the only independent predictor of postoperative native AV opening ($P=0.042$; odds ratio [OR], 0.999). Of the remaining 34 patients (65%) with closed AV, 11 had AI with enlargement of the aortic root and narrow pulse pressure. Among those with closed AV, axial pump use ($n=13$) was the only significant predictor of the development of AI ($P=0.042$; OR, 4.950). Patients with AI had lower exercise capacity and a higher readmission rate than those without AI during 2-year LVAD support (55% vs. 8%; $P<0.001$).

Conclusions: Native AV opening during LVAD support is profoundly associated with reversal of LV systolic function, especially in patients with preoperative shorter heart failure duration. Among those in whom the native AV remains closed, low pulsatility of axial flow pump may facilitate aortic root remodeling and post-LVAD AI development that results in worse clinical outcome. (*Circ J* 2015; **79**: 104–111)

Key Words: Centrifugal; EVAHEART; HeartMate II; Ventricular assist device

Although the outcome of left ventricular assist device (LVAD) treatment has been improving thanks to the development of the continuous flow (CF) pump, patient selection, and perioperative management,^{1–5} aortic insufficiency (AI) remains an unsolved problem during LVAD support.⁶ AI leads to reduced forward cardiac output and end-organ hypoperfusion,⁷ which eventually results in poor outcome.^{8,9}

AI is a multifactorial phenomenon, but continuous closure of native AV would be a key for the development of AI.¹⁰ Although several studies proposed higher age, usage of CF pump, or preoperative lower left ventricular ejection fraction (LVEF) as risk factors for AI,^{9,11–13} the precise mechanism has remained unknown. Therefore, the aim of the present study was to identify the perioperative factors affecting AI during CF LVAD support.

Editorial p43

There have been no established treatments for AI thus far. Although some authors recently reported successful replacement or plasty of aortic valve (AV) for progressed AI, such procedures are invasive and still have various fatal complications.¹⁰ Preoperative risk stratification and successful prevention of AI is an inevitable concern for successful long-term LVAD treatment.

Methods

Patients

We retrospectively enrolled 52 patients with stage D heart failure (HF) who had received CF LVAD (14 axial pumps: HeartMate II, $n=11$; Jarvik 2000, $n=3$; 38 centrifugal pumps: EVAHEART, $n=24$; DuraHeart, $n=14$) as a bridge to heart transplantation and who had been followed at the University

Received August 24, 2014; revised manuscript received October 1, 2014; accepted October 5, 2014; released online November 7, 2014
Time for primary review: 29 days

Department of Therapeutic Strategy for Heart Failure (T. Imamura, K.K., S.K.), Department of Cardiovascular Medicine (T.F., T. Inaba, H.M., M.H.), Department of Thoracic Surgery (O.K., K.N., M.O.), Graduate School of Medicine, University of Tokyo, Tokyo, Japan
Mailing address: Koichiro Kinugawa, MD, PhD, Department of Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: kinugawa-ky@umin.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-14-0944

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

of Tokyo Hospital for at least 6 months between 2006 and 2013. Those with concomitant AV replacement were excluded. No patients had received concomitant right VAD implantation.

All patients were treated preoperatively with guideline-directed medical therapy consisting of β -blocker, angiotensin-converting enzyme inhibitor, and aldosterone antagonist unless contraindicated and doses of these drugs were titrated considering patient hemodynamics.

The rotation speed of LVAD was optimized as low as possible considering patient hemodynamics and interventricular septum shift observed in regular echocardiography. Written informed consent was obtained before LVAD implantation from all patients. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, University of Tokyo [application number 779 (1)].

Preoperative Variables

Preoperative baseline data including patient demographics and laboratory parameters were obtained within 24h before surgery. Hemodynamic and echocardiographic parameters were obtained within 1 week before operation or before initiation of intra-aortic balloon pump. LVEF was calculated using the biplane Simpson method. Valvular regurgitation was classified into 5 grades: 0, none; 1, trace; 2, mild; 3, moderate; 4, severe. Valsalva sinus and aortic root diameters were measured in all patients on long axis view. HF duration was defined as the time between HF diagnosis and LVAD implantation.

Postoperative Variables

Hemodynamic examination was carried out in all patients at 5 weeks after operation. VAD flow was estimated using algorithms of each device. Transthoracic echocardiography was performed regularly, and AI was defined as aortic regurgitation $\geq$ grade 2 at 6 months. To determine the frequency of the native AV opening, we counted the number of native AV openings per native heart rate over at least 1 min. We defined native AV opening for $<30\%$ of the native heart rate as “remaining closed”. Computed tomography was done in all patients, and the height from native AV to the VAD outflow graft anastomosed at the ascending aorta was measured. Peak oxygen consumption during cardiopulmonary exercise test and 6-min walk distance were measured at 6 months after operation. Readmission due to cardiovascular events was counted during 2 years after the first discharge.

Statistical Analysis

All statistical analysis was done using PASW Statistics 18 (SPSS, Chicago, IL, USA). All hypothesis tests were 2-tailed, and used $P<0.05$ as significant. All data are expressed as mean $\pm$ SD unless otherwise specified. Continuous variables were compared using unpaired t-test or Mann-Whitney U-test as appropriate. Categorical variables were compared using chi-squared test or Fisher’s exact test as appropriate. Logistic regression analysis was used to calculate significant predictors for AI or native AV opening. Kaplan-Meier analysis was performed to compare readmission-free rate among those with/without AI. Variables significant on univariate analysis at $P<0.05$ were used in multivariate analysis.

Results

AI and Native AV Opening During LVAD Support

All 18 patients (35%) who had achieved native AV opening, did not have AI (group X; [Table 1](#)). Among those with continuous AV closure, 23 patients (44%) had no AI (group Y), whereas

Table 1. AV Opening vs. AI

	AV opening (+)	AV opening (–)
AI (+)	0 (0)	11 (21) (Z)
AI (–)	18 (35) (X)	23 (44) (Y)

Data given as n (%). * $P<0.02$ (chi-squared test). AI, aortic insufficiency; AV, aortic valve; X, native AV opening; Y, no AI during continuous AV closure; Z, AI during continuous AV closure.

11 (21%) did have AI (group Z).

Preoperative Predictors for Postoperative Native AV Opening

The mean age was 41 ± 13 years, and 43 patients (83%) were male ([Table 2](#)). All patients were dependent on continuous inotrope infusion and received elective LVAD implantation. No patients had AI preoperatively. On multivariate logistic regression preoperative shorter HF duration was the only significant predictor for native AV opening ([Table 2](#)).

Postoperative Characterization of Native AV Opening

Compared with those whose native AV remained closed, wider pulse pressure and higher systolic blood pressure were observed in patients with native AV opening ([Table 3](#)). Improved LVEF with smaller Valsalva sinus or aortic root was also associated with native AV opening ([Table 3](#)). Postoperative medical treatment was similar among all patients.

Predictors for Development of AI in Continuous AV Closure

In patients with continuous AV closure ($n=34$), univariate logistic regression analyses indicated that use of axial pump was the only significant predictor for AI ($P=0.042$; odds ratio, 4.950; [Table 4](#)). There were no significant statistical differences in patient background except for gender and Valsalva sinus diameter between the axial and centrifugal pumps ([Table S1](#)). Notably, larger Valsalva sinus diameter was observed in patients with centrifugal pump.

Postoperative Characterization of AI

Among postoperative variables, narrow pulse pressure along with enlargement of Valsalva sinus and aortic root were associated with the development of AI during LVAD support ($P<0.05$ in all; [Table 5](#)).

Patients with centrifugal LVAD had significantly wider pulse pressure than those with axial LVAD ([Table S2](#)). There were no significant differences in estimated VAD flow between axial and centrifugal pumps. Patients with axial pump experienced more enlargement in Valsalva sinus and aortic root during LVAD support ([Table S2](#)).

Clinical Course vs. Presence of AI

Patients with AI had lower peak oxygen consumption during cardiopulmonary exercise test compared to those without AI ([Figure A](#); 11.0 ± 3.3 vs. 14.4 ± 3.5 ml $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$, $P=0.004$) and shorter 6-min walk distance ([Figure B](#); 328 ± 84 vs. 407 ± 66 m, $P=0.001$) at 6 months after LVAD implantation. Patients with AI had a higher readmission rate due to cardiovascular events than those without AI during the 2-year LVAD support period ([Figure C](#); 55% vs. 8%, $P<0.001$). There was no difference in 2-year survival under LVAD support regardless of AI ([Figure D](#); $P=0.856$). The prevalence of AI was 6% at 1 month (3/52), 13% at 3 months (7/52), 21% at 6 months (11/52), and 18% at 1 year (7/40). No significant AI newly developed after the first 6 months. LVAD was explanted in 2 patients (4%), and 7 pa-

Table 2. Preoperative Predictors for Postoperative Native AV Opening

Preoperative parameters	Total (n=52)	AV opening (+) (n=18)	AV opening (–) (n=34)	Univariate analysis			Multivariate analysis		
		Group X	Group Y+Z	P-value	OR	95% CI	P-value	OR	95% CI
Demographic parameters									
Age (years)	41±13	40±11	42±13	0.584	0.987	0.941–1.035			
Male	43 (83)	17 (94)	26 (76)	0.068	0.128	0.048–1.020			
Ischemic etiology	5 (10)	4 (22)	1 (3)	0.054	9.429	0.966–92.06			
Body surface area (m²)	1.7±0.2	1.72±0.11	1.65±0.17	0.141	20.13	0.370–1094			
HF duration (days)	2,138±1,721	1,122±1,650	2,677±1,522	0.024*	0.999	0.999–1.000	0.042*	0.999	0.999–1.000
Device selection and valve plasty									
Axial pump	14 (27)	1 (6)	13 (38)	0.030*	0.095	0.011–1.010	0.154	0.098	0.014–1.176
Centrifugal pump	38 (73)	17 (94)	21 (62)	–	–	–	–	–	–
Mitral valve plasty	20 (38)	7 (39)	13 (38)	0.963	0.973	0.301–3.144			
Tricuspid annuloplasty	22 (42)	10 (56)	12 (4)	0.163	0.436	0.136–1.400			
Hemodynamic parameters									
SBP (mmHg)	85±13	86±12	85±14	0.885	1.003	0.961–1.048			
DBP (mmHg)	56±12	54±12	57±11	0.382	0.977	0.927–1.030			
Heart rate (beats/min)	87±15	85±14	89±14	0.264	1.025	0.981–1.072			
mPAP (mmHg)	32±8	35±10	31±10	0.140	1.046	0.985–1.111			
PCWP (mmHg)	23±8	26±6	22±9	0.181	1.055	0.975–1.142			
Cardiac index (L·min ^{–1} ·m ^{–2})	2.0±0.4	2.0±0.5	2.0±0.4	0.655	0.738	0.187–2.917			
mRAP (mmHg)	10±5	12±4	8±5	0.014*	1.192	1.037–1.372	0.274	1.045	0.956–1.654
RVSWI (g/m²)	7.2±3.4	6.8±3.3	7.4±3.6	0.538	0.946	0.795–1.127			
Echocardiographic parameters									
LVDd (mm)	75±15	75±16	75±14	0.984	1.000	0.962–1.040			
LVEF (%)	19±8	22±6	19±9	0.259	1.042	0.970–1.118			
AR (grade)	0.4±0.6	0.2±0.4	0.5±0.7	0.058	0.269	0.072–1.010			
MR (grade)	2.3±1.0	2.2±1.0	2.4±1.1	0.669	0.888	0.515–1.532			
TR (grade)	1.5±0.7	1.6±0.6	1.5±0.8	0.686	1.177	0.534–2.592			
Valsalva sinus diameter (mm)	29±3	30±4	29±3	0.136	1.145	0.958–1.368			
AV ring diameter (mm)	20±2	20±1	19±2	0.088	1.365	0.955–1.951			
Laboratory parameters									
Hemoglobin (g/dl)	11.5±2.0	11.4±1.5	11.6±2.3	0.682	0.940	0.699–1.264			
Platelets (×10 ³ /μl)	21.1±7.1	20.6±8.5	20.3±6.8	0.898	1.005	0.928–1.088			
Serum albumin (g/dl)	3.5±0.6	3.4±0.5	3.6±0.7	0.178	0.530	0.201–1.346			
Serum sodium (mEq/L)	134±5	132±7	134±4	0.234	0.937	0.842–1.043			
Serum creatinine (mg/dl)	1.1±0.5	1.0±0.3	1.2±0.6	0.249	0.451	0.116–1.746			
Serum total bilirubin (mg/dl)	1.6±1.3	2.1±1.6	1.4±1.0	0.065	1.611	0.971–2.673			
Plasma BNP (pg/ml)	877±667	872±630	880±695	0.968	1.000	0.999–1.001			

Data given as mean±SD or n (%). *P<0.05 (logistic regression). ACEI, angiotensin-converting enzyme inhibitor; AR, aortic valve regurgitation; AV, aortic valve; BNP, B-type natriuretic peptide; CI, confidence interval; DBP, diastolic blood pressure; HF, heart failure; LVDd, left ventricular (LV) diastolic diameter; LVEF, LV ejection fraction; mPAP, mean pulmonary artery pressure; MR, mitral valve regurgitation; mRAP, mean right atrial pressure; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; TR, tricuspid valve regurgitation.

Table 3. Postoperative Characterization of Native AV Opening During LVAD Support

Parameters	AV opening (+) (n=18)	AV opening (-) (n=34)	P-value
	Group X	Group Y+Z	
Postoperative hemodynamics			
Heart rate (beats/min)	84±9	82±10	0.587
mPAP (mmHg)	18±7	16±5	0.364
PCWP (mmHg)	9±6	8±4	0.695
Cardiac index (L · min ⁻¹ · m ⁻²)	2.5±0.6	2.6±0.6	0.694
mRAP (mmHg)	9±6	7±4	0.458
RVSWI (g/m ²)	4.1±2.1	3.9±1.9	0.738
Pulse pressure (mmHg)	24±8	15±7	0.003*
SBP (mmHg)	93±6	89±6	0.042*
DBP (mmHg)	69±7	73±9	0.078
Estimated VAD flow (L/min)	4.1±1.3	3.5±0.8	0.097
Height of outflow cannula (cm)	2.2±0.3	2.3±0.3	0.395
Carvedilol at 6 months (mg/day)	14.2±5.5	15.6±13.7	0.600
Enalapril at 6 months (mg/day)	2.1±2.0	1.6±1.8	0.323
Postoperative echocardiography			
LVDd (mm)	67±13	63±16	0.378
%change in LVDd (%)	-11±12	-15±17	0.303
LVEF (%)	28±14	17±7	0.012*
%change in LVEF (%)	34±83	2±47	0.139
MR (grade)	0.6±0.7	0.6±0.9	0.984
TR (grade)	0.6±0.6	1.1±0.9	0.067
Valsalva sinus diameter (mm)	29±3	31±4	0.253
%change in Valsalva sinus diameter (%)	-1±3	8±7	0.001*
AV ring diameter (mm)	20±2	21±2	0.225
%change in AV ring diameter (%)	-2±5	6±9	0.002*

Data given as mean ± SD. *P<0.05 (unpaired t-test or Mann-Whitney test). LVAD, LV assist device; VAD, ventricular assist device. Other abbreviations as in Table 2.

tients (13%) underwent heart transplant during the study period.

AV condition and clinical course during the study period among the 4 devices (EVAHEART, DuraHeart, HeartMate II, and Jarvik 2000) are summarized in [Table 6](#).

Discussion

All patients who achieved native AV opening were free from AI development during 6 months of CF LVAD support. On logistic regression analysis preoperative shorter HF duration was associated with AV opening accompanied by improved LVEF during LVAD support. Among those with continuous AV closure, more patients with axial LVAD had AI along with less pulsatility, and aortic root remodeling. Patients with AI had worse clinical course than those without AI.

Definition of AI During LVAD Support

We considered that AI ≥grade 2 was hemodynamically significant, because AI after LVAD implantation was typically continuous throughout the cardiac cycle and the regurgitant fraction was approximately twice as much as that in the patients without VAD support.¹² Patients with preoperative AI ≥grade 2 received concomitant AV replacement at the time of LVAD implantation, and such patients were excluded from this study. As a result, all AI during LVAD support were de novo. Considering that all AI accompanied continuous AV closure in the present study ([Table 1](#)), AI was analyzed in a stepwise manner, that is, continuous AV closure at first, and

then the development of AI.

We evaluated AI at 6 months after LVAD implantation, which was relatively earlier than the observation periods used in other studies.^{8,11,12,14} We chose 6 months for evaluation of endpoints because death or explantation of LVAD occurred in some patients soon after 6 months. Moreover, no significant AI was newly developed after the first 6 months of LVAD implantation in the present study. Although AI is a progressive phenomenon, its onset may be determined within the first 6 months after LVAD implantation with closed native AV.

Prevalence of AI and Optimization of Rotation Speed

Although the prevalence of AI varied in each report, probably because of variation in definition, timing of evaluation, device type, patient background, or perioperative management, most authors reported an AI prevalence of 20–50% within the first year.^{8,9,11,12,14} Jorde et al argued that optimization of rotation speed as low as possible so as to accomplish native AV opening eventually repressed development of AI.⁸ We here defined native AV opening at <30% of the native heart rate as “remaining closed”, because Slaughter et al noted that AV opening at least once per 3 native heart beats may be sufficient to avoid development of AI.¹⁵ We carried out such optimization in all patients during scheduled hemodynamic examination and serial transthoracic echocardiography, but still observed a prevalence of AI of 33% within 6 months. Lowering rotation speed down to the level of native AV opening sometimes limited maintenance of sufficient cardiac output. Because there has

Table 4. Predictors for Development of AI in Continuous AV Closure

Preoperative parameters	Continuous AV closure (n=34)				
	AI (+) (n=11) Group Y	AI (−) (n=23) Group Z	P-value	OR	95% CI
Demographic parameters					
Age (years)	42±10	42±14	0.933	1.002	0.947–1.062
Male	7 (63)	18 (78)	0.370	0.486	0.100–2.356
Etiology of ischemia	1 (9)	0 (0)	–	–	–
Body surface area (m ²)	1.6±0.2	1.7±0.2	0.601	0.318	0.004–23.27
HF duration (days)	2,986±1,512	2,530±1,537	0.412	1.000	1.000–1.001
Medications					
Cumulative dose of β -blocker (g)	31±27	19±19	0.184	1.026	0.984–1.060
Cumulative dose of ACEI (g)	13±23	9±13	0.413	1.018	0.976–1.063
Device selection and valve plasty					
Axial pump	7 (63)	6 (26)	0.042*	4.950	1.062–23.26
Centrifugal pump	4 (36)	17 (74)	–	–	–
Mitral valve plasty	3 (27)	8 (35)	0.417	0.375	0.035–3.999
Tricuspid annuloplasty	3 (27)	7 (30)	0.699	0.643	0.068–6.056
Hemodynamic parameters					
SBP (mmHg)	90±9	83±16	0.209	1.035	0.981–1.093
DBP (mmHg)	58±7	57±14	0.863	1.06	0.944–1.072
Heart rate (beats/min)	86±11	85±15	0.929	1.002	0.949–1.059
mPAP (mmHg)	45±17	43±15	0.906	1.004	0.935–1.079
PCWP (mmHg)	21±7	24±9	0.478	0.969	0.887–1.058
Cardiac index (L·min ^{−1} ·m ^{−2})	2.0±0.4	2.1±0.4	0.504	0.515	0.074–3.606
mRAP (mmHg)	7±4	8±5	0.403	0.929	0.782–1.104
RVSWI (g/m ²)	7.7±3.5	7.7±3.6	0.951	1.007	0.817–1.241
Echocardiographic parameters					
LVDd (mm)	78±12	75±14	0.445	1.022	0.966–1.081
LVEF (%)	16±6	20±10	0.124	0.916	0.818–1.025
AR (grade)	0.6±0.7	0.4±0.7	0.404	1.589	0.535–4.717
MR (grade)	2.4±1.0	2.3±1.2	0.849	1.067	0.548–2.075
TR (grade)	1.8±0.8	1.4±0.7	0.068	2.948	0.991–8.752
Valsalva sinus diameter (mm)	29±3	28±3	0.608	1.066	0.836–1.358
AV ring diameter (mm)	20±2	19±2	0.210	1.297	0.864–1.947
Laboratory parameters					
Hemoglobin (g/dl)	12.5±2.5	11.2±2.0	0.121	1.313	0.930–1.854
Platelets (×10 ³ /μl)	19±7	21±7	0.454	0.957	0.854–1.073
Serum albumin (g/dl)	3.6±0.8	3.7±0.6	0.815	0.878	0.294–2.624
Serum sodium (mEq/L)	136±3	134±5	0.239	1.126	0.924–1.372
Serum creatinine (mg/dl)	1.1±0.5	1.2±0.6	0.294	0.440	0.095–2.039
Serum total bilirubin (mg/dl)	1.3±0.6	1.5±1.2	0.569	0.784	0.39–1.813
Plasma BNP (pg/ml)	839±673	899±718	0.812	1.000	0.999–1.001

Data given as mean ± SD or n (%). *P<0.05 (logistic regression). Abbreviations as in Tables 1,2.

been no comprehensive solution for AI, optimal patient/device selection is required in order to prevent AI.

Continuous AV Closure as a Premise for AI

On early histological examination, continuous AV closure was associated with commissural fusion of native AV,¹⁶ which resulted in the development of AI.¹⁷ AI developed consistently only in patients with continuous AV closure (groups Y+Z; [Table 1](#)). Therefore, the first step to prevent AI would be to open native AV during LVAD support.

Opening of native AV is determined by the pressure gradient between the LV and aortic root during the systolic phase.¹⁸ Elevated pressure in the aortic root due to VAD outflow causes

the native AV to remain closed, especially under decreased LV systolic function. Therefore, recovery of LV systolic function is essential for the opening of native AV, especially under already optimized VAD flow with lower rotation speed. After LVAD implantation, those with native AV opening had higher pulse pressure. Such a pressure gradient would be largely dependent on improved LVEF due to the aforementioned LV reverse remodeling under LVAD support.

Considering the early studies, patients with non-ischemic etiology, less fibrosis in myocardium, less dilated LV cavity with shorter HF duration indicating less remodeling, can expect LV reverse remodeling under LVAD support.^{19–21} Preoperative shorter HF duration was consistently a significant predic-

Table 5. Postoperative Characterization of AI During LVAD Support

Parameters	Continuous AV closure (n=34)		P-value
	AI (+) (n=11)	AI (-) (n=23)	
	Group Y	Group Z	
Postoperative hemodynamics			
Heart rate (beats/min)	82±10	82±10	0.934
mPAP (mmHg)	18±4	16±6	0.419
PCWP (mmHg)	9±4	8±4	0.317
Cardiac index (L · min ⁻¹ · m ⁻²)	2.5±0.7	2.7±0.6	0.382
mRAP (mmHg)	8±5	7±4	0.714
RVSWI (g/m ²)	4.0±1.6	3.9±2.1	0.924
Pulse pressure (mmHg)	10±7	18±7	0.042*
SBP (mmHg)	87±6	89±6	0.389
DBP (mmHg)	76±8	73±9	0.314
Estimated VAD flow (L/min)	3.3±0.6	3.6±0.9	0.271
Carvedilol at 6 months (mg/day)	16.4±14.3	15.2±13.8	0.824
Enalapril at 6 months (mg/day)	1.2±1.5	1.6±1.6	0.157
Postoperative echocardiography			
LV and valve			
LVDd (mm)	64±15	62±16	0.724
%change in LVDd (%)	-17±16	-15±17	0.763
LVEF (%)	15±6	18±8	0.335
%change in LVEF (%)	9±47	-2±48	0.515
MR (grade)	0.5±1.0	0.6±0.8	0.628
TR (grade)	1.2±1.0	1.0±0.6	0.076
Aorta and AV			
Valsalva sinus diameter (mm)	32±3	30±4	0.096
%change in Valsalva sinus diameter (%)	13±9	6±5	0.021*
AV ring diameter (mm)	21±2	20±2	0.087
%change in AV ring diameter (%)	9±8	5±7	0.048*
Height of outflow cannula (cm)	22±3	23±3	0.297

Data given as mean±SD. *P<0.05 (unpaired t-test or Mann-Whitney test). Abbreviations as in Tables 1,2.

tor of native AV opening during LVAD support in this study. Shorter HF duration may be associated with less remodeled LV as well as less preoperative exposure to medical therapy, especially to β -blockers.²² Therefore, those with shorter HF duration may have a greater likelihood of achieving LV reverse remodeling accompanied by native AV opening due to increased LVEF under hemodynamic unloading on LVAD support and postoperative sufficient medical therapy. Other preoperative predictors of LV reverse remodeling may be found in future studies.

AI During Continuous AV Closure

In patients with continuous AV closure, AI developed in 33% (group Y), whereas the remaining 67% did not have AI (group Z). AI occurred more frequently during axial LVAD support than centrifugal support.

Pulsatility was more reduced during axial LVAD support than during centrifugal support, as noted in other studies.^{23–25} Turbulence, which increases wall shear stress and the retrograde pressure in the aortic root, develops during LVAD support.^{7,26} Degenerative remodeling of aortic root accompanied by thinning of aortic wall emerges, especially under reduced pulsatility due to apoptosis of smooth muscle cells and fragmentation of elastic fibers.²⁷ Remodeling of aortic root appears to be associated with higher prevalence of AI as well as degeneration of native AV.¹⁴ We consistently observed that pa-

tients on axial LVAD support had more enlarged aortic root than those with centrifugal support. There were no differences in postoperative LVEF between patients with axial pump and those with centrifugal pump (Table S2). Among those with continuous AV closure, lower pulse pressure might be largely attributable to the use of axial pump.

In other words, pulsatility was relatively preserved during centrifugal LVAD support than axial support. Preserved pulsatility may not only prevent remodeling of aortic root but also reduce diastolic systemic pressure, as shown in the present study, which may reduce diastolic phase retrograde regurgitation through native AV.¹³ An early study in which a lower prevalence of AI was observed during pulsatile LVAD support than CF support, also supported the hypothesis.¹²

Poor Prognosis in Patients With AI

Toda et al noted worse survival in patients with AI during mainly extracorporeal LVAD support.⁹ AI may contribute to poor survival during extracorporeal VAD support, because AI impairs systemic perfusion and worsens congestion, probably due to the low flow nature of extracorporeal VAD. In contrast, in early studies using mainly CF LVAD,^{11,28} there were no differences in 2-year survival regardless of AI, as observed in the present study. Systemic perfusion may not be decreased even if AI occurs in CF LVAD support. Consistently, we did not observe any differences in hemodynamic parameters be-

Figure. (A) Peak oxygen consumption ($\dot{V}O_2$) and (B) 6-min walk distance (6MWD) at 6 months after left ventricular assist device (LVAD) implantation, and (C) readmission-free rate and (D) survival during 2-year LVAD support among those with/without aortic insufficiency (AI). * $P < 0.05$ (unpaired t-test).

Table 6. AV Condition and Clinical Course vs. Device Type

	Centrifugal pump (n=38)		Axial pump (n=14)	
	EVAHEART (n=24)	DuraHeart (n=14)	HeartMate II (n=11)	Jarvik 2000 (n=3)
Aortic valve				
AV opening	11 (46)	6 (43)	1 (9)	0 (0)
AI	3 (13)	3 (21)	5 (45)	2 (67)
Clinical course				
$\dot{V}O_2$ ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)	14.3 $\pm$ 3.6	13.1 $\pm$ 3.0	13.0 $\pm$ 4.6	9.9 $\pm$ 2.0
6MWD (m)	404 $\pm$ 78	388 $\pm$ 46	361 $\pm$ 104	314 $\pm$ 44
Re-admission rate (%)	4 (17)	1 (7)	4 (36)	2 (67)

Data given as mean $\pm$ SD or n (%). $\dot{V}O_2$, peak oxygen consumption; 6MWD, 6-min walk distance. Other abbreviations as in Table 1.

tween patients with and without AI (Table 5).

Patients with AI, however, had decreased exercise capacity compared to those without AI. Although hemodynamics were not different with regard to AI at rest condition, AI may be worsened during exercise with increased afterload. Patients with AI had higher readmission rate due to cardiovascular events such as cerebral thrombosis, ventricular tachyarrhythmia, or congestive HF. Turbulence in ascending aorta due to AI along with continuous AV closure may increase unstable thrombus formation. Increased workload on the LV due to trans-aortic regurgitation may trigger ventricular tachyarrhythmia.

Study Limitations

First, data were analyzed in a retrospective manner at a single center, and the sample size was small. The present results should be tested in a prospective manner by randomizing device type in a larger subject group. Second, LVAD were selected by the attending physicians, and selection bias existed. There was no statistical differences, however, in patient background between axial and centrifugal LVAD except for gender and Valsalva sinus diameter. Third, optimization of rotation speed and pre/postoperative sufficient titration of β -blocker treatment were carried out in all patients. The present results would not apply

in situations in which these procedures were not carried out. And fourth, we did not perform AV plasty or replacement to manage developed AI after LVAD implantation. Whether such procedures improve prognosis is a subject for future study.

Conclusions

Native AV opening during LVAD support is profoundly associated with reversal of LV systolic function, especially in patients with preoperative shorter HF duration. Among those in whom the native AV remains closed, the low pulsatility nature of axial flow pump may facilitate aortic root remodeling and post-LVAD AI development, resulting in poor quality of life.

Acknowledgments

Grant-in-Aid from Secom Science and Technology Foundation to K.K. K.K. has conflicts of interest as follows. Employment: Daiichi-Sankyo, Otsuka, Terumo, Hitachi-Aloka, CSL Behring, Medix Japan, KCI, Nishimura Kikai, GlaxoSmithKline, Century Medical, Nippon Shinyaku, Edwards, Bayer, Senko Medical Instrument; Research grant: Terumo, Otsuka, ONO, Novartis, Sun Medical; Honoraria: Daiichi-Sankyo, ONO, Otsuka.

References

- Imamura T, Kinugawa K, Shiga T, Endo M, Kato N, Inaba T, et al. Preoperative levels of bilirubin or creatinine adjusted by age can predict their reversibility after implantation of left ventricular assist device. *Circ J* 2013; **77**: 96–104.
- Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Sixth INTERMACS annual report: A 10,000-patient database. *J Heart Lung Transplant* 2014; **33**: 555–564.
- Imamura T, Kinugawa K, Hatano M, Fujino T, Inaba T, Maki H, et al. Low cardiac output stimulates vasopressin release in patients with stage D heart failure. *Circ J* 2014; **78**: 2259–2267.
- Imamura T, Kinugawa K, Shiga T, Endo M, Kato N, Inaba T, et al. Novel risk scoring system with preoperative objective parameters gives a good prediction of 1-year mortality in patients with a left ventricular assist device. *Circ J* 2012; **76**: 1895–1903.
- Shiga T, Kinugawa K, Imamura T, Kato N, Endo M, Inaba T, et al. Combination evaluation of preoperative risk indices predicts requirement of biventricular assist device. *Circ J* 2012; **76**: 2785–2791.
- Deo SV, Sharma V, Cho YH, Shah IK, Park SJ. De novo aortic insufficiency during long-term support on a left ventricular assist device: A systematic review and meta-analysis. *ASAIO J* 2014; **60**: 183–188.
- Karmonik C, Partovi S, Loebe M, Schmack B, Weymann A, Lumsden AB, et al. Computational fluid dynamics in patients with continuous-flow left ventricular assist device support show hemodynamic alterations in the ascending aorta. *J Thorac Cardiovasc Surg* 2014; **147**: 1326–1333.
- Jorde UP, Uriel N, Nahumi N, Bejar D, Gonzalez-Costello J, Thomas SS, et al. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. *Circ Heart Fail* 2014; **7**: 310–319.
- Toda K, Fujita T, Domae K, Shimahara Y, Kobayashi J, Nakatani T. Late aortic insufficiency related to poor prognosis during left ventricular assist device support. *Ann Thorac Surg* 2011; **92**: 929–934.
- Holtz J, Teuteberg J. Management of aortic insufficiency in the continuous flow left ventricular assist device population. *Curr Heart Fail Rep* 2014; **11**: 103–110.
- Aggarwal A, Raghuvir R, Eryazici P, Macaluso G, Sharma P, Blair C, et al. The development of aortic insufficiency in continuous-flow left ventricular assist device-supported patients. *Ann Thorac Surg* 2013; **95**: 493–498.
- Hatano M, Kinugawa K, Shiga T, Kato N, Endo M, Hisagi M, et al. Less frequent opening of the aortic valve and a continuous flow pump are risk factors for postoperative onset of aortic insufficiency in patients with a left ventricular assist device. *Circ J* 2011; **75**: 1147–1155.
- Gregory SD, Stevens MC, Wu E, Fraser JF, Timms D. In vitro evaluation of aortic insufficiency with a rotary left ventricular assist device. *Artif Organs* 2013; **37**: 802–809.
- Pak SW, Uriel N, Takayama H, Cappleman S, Song R, Colombo PC, et al. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. *J Heart Lung Transplant* 2010; **29**: 1172–1176.
- Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010; **29**(Suppl): S1–S39.
- Connelly JH, Abrams J, Klima T, Vaughn WK, Frazier OH. Acquired commissural fusion of aortic valves in patients with left ventricular assist devices. *J Heart Lung Transplant* 2003; **22**: 1291–1295.
- Martina JR, Schipper ME, de Jonge N, Ramjankhan F, de Weger RA, Lahpor JR, et al. Analysis of aortic valve commissural fusion after support with continuous-flow left ventricular assist device. *Interact Cardiovasc Thorac Surg* 2013; **17**: 616–624.
- John R, Mantz K, Eckman P, Rose A, May-Newman K. Aortic valve pathophysiology during left ventricular assist device support. *J Heart Lung Transplant* 2010; **29**: 1321–1329.
- Simon MA, Primack BA, Teuteberg J, Kormos RL, Bermudez C, Toyoda Y, et al. Left ventricular remodeling and myocardial recovery on mechanical circulatory support. *J Card Fail* 2010; **16**: 99–105.
- Simon MA, Kormos RL, Murali S, Nair P, Heffernan M, Gorcsan J, et al. Myocardial recovery using ventricular assist devices: Prevalence, clinical characteristics, and outcomes. *Circulation* 2005; **112**(Suppl): I32–I36.
- Matsumiya G, Monta O, Fukushima N, Sawa Y, Funatsu T, Toda K, et al. Who would be a candidate for bridge to recovery during prolonged mechanical left ventricular support in idiopathic dilated cardiomyopathy? *J Thorac Cardiovasc Surg* 2005; **130**: 699–704.
- Imamura T, Kinugawa K, Hatano M, Fujino T, Muraoka H, Inaba T, et al. Preoperative beta-blocker treatment is a key for deciding left ventricular assist device implantation strategy as a bridge to recovery. *J Artif Organs* 2014; **17**: 23–32.
- Stanfield JR, Selzman CH. In vitro pulsatility analysis of axial-flow and centrifugal-flow left ventricular assist devices. *J Biomech Eng* 2013; **135**: 34505.
- Soucy KG, Koenig SC, Giridharan GA, Sobieski MA, Slaughter MS. Defining pulsatility during continuous-flow ventricular assist device support. *J Heart Lung Transplant* 2013; **32**: 581–587.
- Moazami N, Fukamachi K, Kobayashi M, Smedira NG, Hoercher KJ, Massiello A, et al. Axial and centrifugal continuous-flow rotary pumps: A translation from pump mechanics to clinical practice. *J Heart Lung Transplant* 2013; **32**: 1–11.
- Hata H, Fujita T, Ishibashi-Ueda H, Nakatani T, Kobayashi J. Pathological analysis of the aortic valve after long-term left ventricular assist device support. *Eur J Cardiothorac Surg* 2014; **46**: 193–197.
- Westaby S, Bertoni GB, Clelland C, Nishinaka T, Frazier OH. Circulatory support with attenuated pulse pressure alters human aortic wall morphology. *J Thorac Cardiovasc Surg* 2007; **133**: 575–576.
- Rajagopal K, Daneshmand MA, Patel CB, Ganapathi AM, Schechter MA, Rogers JG, et al. Natural history and clinical effect of aortic valve regurgitation after left ventricular assist device implantation. *J Thorac Cardiovasc Surg* 2013; **145**: 1373–1379.

Supplementary Files

Supplementary File 1

Table S1. Preoperative parameters vs. device type

Table S2. Postoperative hemodynamics and echocardiographic parameters vs. device type

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-14-0944>