lating inflammatory cytokines in HF has been reported.[21] On the other hand, it is possible that low cholesterol is a marker only for cachexia, a state associated with poor HF mortality, and has no pathophysiologic role. However, in our study low cholesterol was a predictor of early VAD necessity, independent of body mass index or serum albumin, which are also variables associated with poor nutritional condition (data not shown). Therefore, cardiac cachexia may not only be the cause of low serum total cholesterol in our study.

Anemia is common in patients with HF, and patients with both HF and anemia have a lower functional capacity, worse quality of life, and higher rates of hospitalization and death than those without anemia.[22,23] There are several potential causes of anemia in HF: malnutrition; hemodilution; renal dysfunction and impaired erythropoietin production; usage of ACEIs/ARB; elevated levels of proinflammatory cytokines; and others.[24] We found that anemia in the early-VAD group was normocytic and none had undergone blood transfusion prior to referral (data not shown). Renal function was comparable between the early-VAD and late/no-VAD groups (**Table 2**). We did not have enough data about iron metabolism. Right atrial pressure and pulmonary capillary wedge pressure by cardiac catheterization were significantly higher in the early-VAD group (**Table S1**). We speculate that hemodilution because of systemic congestion at least partially caused the anemia in the early-VAD group.

Pitfalls of Previous Risk Scores

This study revealed that the INTERMACS profile 3 or greater on admission was another good predictor of early VAD necessity, and the results were consistent with previous recommendations for VAD implantation.[3,4] However, stratification by these profiles is largely dependent on the physician's decision. In fact, we often suggest that physicians in non-VAD institutes start inotropes before transfer of their patients in order to avoid end-organ dysfunction. Two patients in our study became 'profile 3' just before transfer because of this suggestion. We consider that a scoring system composed of factors that are independent of the decision or intervention by physicians is preferable. In this regard, the scoring system that we newly created is valuable because we selected objective parameters that can be obtained noninvasively.

Is the Current Referral Timing Appropriate?

In Japan, implantable LVADs are available only as a bridge to transplantation, so being listed for heart transplantation is required before implantable LVAD therapy can be performed. Evaluation of eligibility for heart transplant usually takes more than 1 month, and we consider that the current timing of referral is still too late for implantable LVAD therapy. The delay in referral, at least in part, caused the need for life-saving paracorporeal VAD in 7 patients as well as 1 death during evaluation. Although all-cause mortality was not significantly different between the groups stratified by the new scoring system or by INTERMACS profile (data not shown), it is not true that patients are best referred after they have accumulated a high score. We have not yet established the best timing of referral to VAD implant centers, but we would like to emphasize that the referral timing of the patients in early-VAD group was not soon enough for implantable LVAD therapy.

Study Limitations

We acknowledge that our study has several limitations. First, this study was conducted in a single center, and consequently included a limited number of patients. The timing of the decision for VAD implantation may be different in different institutes. Second, we cannot yet propose appropriate timing of referral for implantable VAD therapy, including preoperative listing for transplant. Because the timing of referral is always a matter of debate, especially for physicians in non-VAD institutes, further investigations such as prospective studies or large-scale surveys are anticipated to establish the best timing of referral. Finally, in this study advanced HF with an ischemic etiology was found in only 4 patients (8.7%), which is a remarkable feature specific to the Japanese population requiring VAD for advanced HF. Other factors may be found in other populations.

Conclusions

Low BP, low serum total cholesterol level and anemia on admission were factors that predicted the early necessity for VAD in advanced HF patients referred from non-VAD institutes. Such patients should be promptly referred for VAD implantation.

Disclosures

Grants: None. We have no conflict of interest to disclosure.

References

1. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001; **345:** 1435–1443.
2. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; **361:** 2241–2251.
3. Kinugawa K. How to treat stage D heart failure?: When to implant left ventricular assist devices in the era of continuous flow pumps? *Circ J* 2011; **75:** 2038–2045.
4. 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.
5. Kato N, Kinugawa K, Imamura T, Muraoka H, Minatsuki S, Inaba T, et al. Trend of clinical outcome and surrogate markers during titration of β-blocker in heart failure patients with reduced ejection fraction: Relevance of achieved heart rate and β-blocker dose. *Circ J* 2013; **77:** 1001–1008.
6. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: Prediction of survival in heart failure. *Circulation* 2006; **113:** 1424–1433.
7. Levy WC, Mozaffarian D, Linker DT, Farrar DJ, Miller LW. Can the Seattle Heart Failure Model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? *J Heart Lung Transplant* 2009; **28:** 231–236.
8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **128:** e240–e327, doi:10.1161/CIR.0b013e31829e8776.
9. Kirklin JK, Naftel DC, Stevenson LW, Kormos RL, Pagani FD, Miller MA, et al. INTERMACS database for durable devices for circulatory support: First annual report. *J Heart Lung Transplant* 2008; **27:** 1065–1072.
10. Rao V, Oz MC, Flannery MA, Catanese KA, Argenziano M, Naka Y. Revised screening scale to predict survival after insertion of a left ventricular assist device. *J Thorac Cardiovasc Surg* 2003; **125:** 855–862.
11. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-rematch era: Implications for patient selection. *Circulation* 2007; **116:** 497–505.
12. 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.
13. Imamura T, Kinugawa K, Hatano M, Fujino T, Inaba T, Maki H, et al. Status 2 patients had poor prognosis without mechanical circulatory support. *Circ J* 2014; **78:** 1396–1404.
14. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart fail-

ure. *JAMA* 2006; **296:** 2217–2226.
15. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subacius H, Konstam MA, et al. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: Insights from the efficacy of vasopressin antagonism in heart failure: Outcome study with tolvaptan (EVEREST) trial. *Am Heart J* 2013; **165:** 216–225.
16. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: Insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003; **107:** 223–225.
17. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients: A systematic review and meta-analysis. *J Am Coll Cardiol* 2008; **52:** 818–827.
18. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002; **8:** 216–224.
19. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J* 2006; **152:** 1077–1083.
20. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, et al. Acute heart failure syndromes: Current state and framework for future research. *Circulation* 2005; **112:** 3958–3968.
21. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet* 2000; **356:** 930–933.
22. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013; **368:** 1210–1219.
23. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. Anemia in patients with heart failure: Prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005; **11:** 91–98.
24. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. *Eur J Heart Fail* 2002; **4:** 681–686.

Supplementary Files

Supplementary File 1

Table S1. Hemodynamic parameters of the 46 enrolled patients with advanced heart failure

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0749

Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

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.

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]

Editorial p????

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.

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.

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-tky@umin.ac.jp

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

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.

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 24 h 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 ≥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±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 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) Group X	AV opening (−) (n=34) Group Y+Z	Univariate analysis P-value	OR	95% CI	Multivariate analysis 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 (m^2)	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 ($L \cdot min^{-1} \cdot m^{-2}$)	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/m^2)	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 ($\times 10^3/\mu l$)	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) Group X	AV opening (–) (n=34) Group Y+Z	P-value
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 ($L \cdot min^{-1} \cdot m^{-2}$)	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)	AI (–) (n=23)	Univariate analyses		
	Group Y	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 ($L \cdot min^{-1} \cdot m^{-2}$)	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 ($\times 10^3/\mu l$)	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) Group Y	AI (–) (n=23) 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 ($L \cdot min^{-1} \cdot m^{-2}$)	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 patients 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-

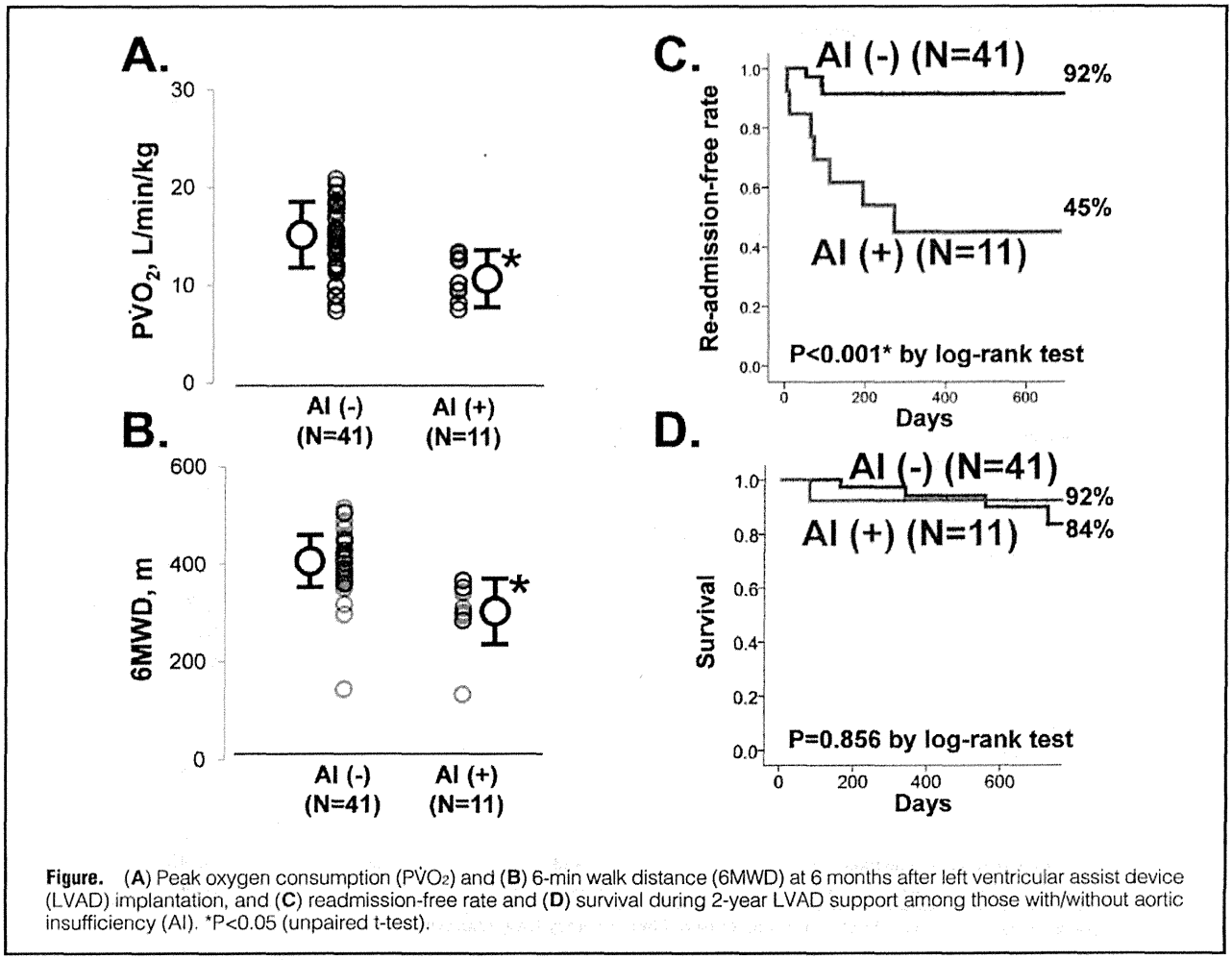

Figure. (**A**) Peak oxygen consumption ($P\dot{V}O_2$) and (**B**) 6-min walk distance (6MWD) at 6 months after left ventricular assist device (LVAD) implantation, and (**C**) readmission-free rate and (**D**) survival during 2-year LVAD support among those with/without aortic insufficiency (AI). *P<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				
$P\dot{V}O_2$ (ml·min^{-1}·kg^{-1})	14.3±3.6	13.1±3.0	13.0±4.6	9.9±2.0
6MWD (m)	404±78	388±46	361±104	314±44
Re-admission rate (%)	4 (17)	1 (7)	4 (36)	2 (67)

Data given as mean±SD or n (%). $P\dot{V}O_2$, 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 transaortic 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. Stanfield JR, Selzman CH. In vitro pulsatility analysis of axial-flow and centrifugal-flow left ventricular assist devices. *J Biomech Eng* 2013; **135:** 34505.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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

J Artif Organs
DOI 10.1007/s10047-014-0800-2

ORIGINAL ARTICLE

Artificial Heart (Clinical)

Lower rotation speed stimulates sympathetic activation during continuous-flow left ventricular assist device treatment

Teruhiko Imamura · Koichiro Kinugawa · Daisuke Nitta · Takeo Fujino · Toshiro Inaba · Hisataka Maki · Masaru Hatano · Osamu Kinoshita · Kan Nawata · Shunei Kyo · Minoru Ono

Received: 21 August 2014 / Accepted: 13 October 2014

Abstract Although the suppression of sympathetic activity is an essential mission for the current heart failure treatment strategy, little is known about the relationship between the rotation speed setting and autonomic nervous activity during continuous-flow left ventricular assist device (LVAD) treatment. We evaluated 23 adult patients with sinus rhythm (36 ± 13 years) who had received continuous-flow LVAD and been followed at our institute between March 2013 and August 2014. Heart rate variability measurement was executed along with hemodynamic study at 3 rotation speeds (low, middle, and high) at 5 weeks after LVAD implantation. Lower rotation speed was associated with higher ratio of low-frequency over high-frequency spectral level (LF/HF), representing enhanced sympathetic activation ($p < 0.05$ by repeated analyses of variance). Among hemodynamic parameters, cardiac index was exclusively associated with LF_{NU} = LF/(LF + HF), representing relative sympathetic activity over parasympathetic one ($p < 0.05$). After 6 months LVAD support at middle rotation speed, 19 patients with higher LF_{NU} eventually had higher plasma levels of B-type natriuretic peptide and achieved less LV reverse remodeling. A logistic regression analysis demonstrated that lower LF_{NU} was significantly associated with improvement of LV reverse remodeling ($p = 0.021$, odds ratio 0.903) with a cut-off level of 55 % calculated by the ROC analysis (AUC 0.869). In conclusion, autonomic activity can vary in various rotation speeds. Patients with higher LF_{NU} may better be controlled at higher rotation speed with the view point to suppress sympathetic activity and achieve LV reverse remodeling.

Keywords Heart failure · Autonomic nerve · Heart rate variability · Reverse remodeling

T. Imamura (✉) · K. Kinugawa (✉) · S. Kyo
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: te.imamu@gmail.com

K. Kinugawa
e-mail: kinugawa-tky@umin.ac.jp

D. Nitta · T. Fujino · T. Inaba · H. Maki · M. Hatano
Department of Cardiovascular Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

O. Kinoshita · K. Nawata · M. Ono
Department of Cardiac Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Introduction

Sympathetic activation is one of the major neurohormonal changes seen in patients with heart failure (HF), and inappropriately elevated sympathetic stimulation has a primary role in the deterioration of failing heart through multiple mechanisms: transduction abnormalities of the β-adrenergic signal, induction of tachyarrhythmias, activation of renin–angiotensin–aldosterone system, facilitation of myocardial remodeling, and acceleration of myocardial cell death [1, 2]. Considering the above mechanisms, β-blockers have been established as an essential tool for the standard regimen for the treatment of HF or even the prevention of HF development owing to its sympatholytic effect [3, 4].

Ventricular assist device (VAD) is a powerful therapeutic tool in patients with stage D HF by unloading left ventricle and ameliorating end-organ hypoperfusion, and has also been demonstrated to improve cardiac autonomic innervation [5]. Although adjustment of rotation speed in

Published online: 22 October 2014

consideration of various clinical aspects is essential for patients' management during VAD support [6], the relationship between rotation speed and sympathetic nerve activity remains unknown. Therefore, we here tried to clarify the effect of rotation speed for sympathetic nerve system and discussed how to find the optimal rotation speed especially on the view point of autonomic nerve activity.

Methods

Patients selection

We retrospectively enrolled 23 adult patients with stage D HF who had received continuous-flow LVADs (EVAHEART, 5; DuraHeart, 5; Jarvik 2000, 2; HeartMate II, 10; HeartWare, 1) and been followed at the University of Tokyo Hospital between Mar 2013 and Aug 2014. All patients gave written informed consent and were listed for heart transplantation before LVAD implantation. All patients had sinus rhythm. No patient received concomitant right VAD implantation. No complications such as systemic/device infection, retention of pleural effusion, stroke, or significant electrolyte imbalance occurred. Rotation speed was adjusted considering patients' hemodynamics and transthoracic echocardiographic information such as interventricular shift and opening of aortic valve. Doses of β-blocker, angiotensin converting enzyme inhibitor (ACEI), and aldosterone antagonist were titrated considering patients' hemodynamics before and after the operation. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, the University of Tokyo [application number 779 (1)].

Evaluated baseline characteristics

Patients' demographic, laboratory, and echocardiographic data were obtained at 5 weeks after LVAD implantation as baseline characteristics. LV ejection fraction (LVEF) was calculated by the biplane Simpson methods on transthoracic echocardiography. The doses of anti-HF medications were evaluated as following: to compare different types of β-blocker, the dose of bisoprolol was normalized to approximately equivalent dose of carvedilol [7]. In the same manner, the doses of ACEI were normalized to approximately equivalent dose of enalapril [8].

Hemodynamic study at 5 weeks after LVAD implantation

All patients underwent hemodynamic study along with transthoracic echocardiography at 5 weeks after LVAD implantation, and 3 rotation speeds (low, middle, and high rotation speeds) were tested. Considering patients' hemodynamics and echocardiographic parameters, "low rotation speed" was defined by decreasing rotation speed as low as possible. "High rotation speed" was defined by increasing rotation speed as high as possible in the same manner. "Middle rotation speed" was defined as median value between low and high rotation speed. Of them, plasma catecholamine levels were measured at each rotation speed after 5-min rest without any stimulation in 11 patients.

Heart rate variability (HRV) spectral analysis at 5 weeks after LVAD implantation

HRV parameters were measured at each rotation speed just before the above-described hemodynamic study. All HRV parameters were measured for 2 min at 9:00–12:00 AM after 15-min rest at the supine position under fixed 0.25 Hz of respiratory rate along with fasting condition [9]. All patients had sinus rhythm without any mechanical pacing support. Electrocardiographic signals from bipolar leads attached at patients' precordium were transformed to digital ones to calculate the R–R intervals at a sampling rate of 512 Hz. Power spectral analysis of HRV was performed by the MemCalc power spectral density method (MemCalc/Win, Suwa Trust) that used the maximum entropy method for spectral analysis and the nonlinear least-squares method for fitting analysis [10]. The low-frequency (LF) component was defined as 0.04–0.15 Hz, and the high-frequency (HF) component was defined as 0.15–0.40 Hz. The HF power denotes the parasympathetic activity, whereas the ratio of LF over HF component (LF/HF) represents sympathetic activity [9]. To evaluate proportional sympathetic activity over parasympathetic one, normalized unit (NU) was calculated by the following formula: $LF_{NU} = LF/(LF + HF)$ [11].

Variables evaluated at 6 months after LVAD implantation as midterm outcome

Of all, 19 patients were followed ≥6 months after LVAD implantation. Echocardiography was executed along with measurement of plasma B-type natriuretic peptide (P-BNP) concentration at 6 months after the operation, and the midterm endpoint was defined as meeting all 3 following variables: (1) any decreases in P-BNP; (2) any decreases in LV diastolic diameter (LVDd); and (3) any increases in LV ejection fraction (LVEF) compared with those of baseline. The equivalent doses of anti-HF medications were also evaluated as described above. Rotation speed was maintained at the middle rotation speed during the study period considering hemodynamic and echocardiographic results.

Table 1 Baseline characteristics at 5 weeks after LVAD implantation

	$N = 23$
Demographic parameters	
Age, years	36 ± 13
Male, *n* (%)	19 (83)
Body height, cm	167 ± 10
BMI	20.7 ± 3.4
Heart rate, bpm	75 ± 15
sBP, mmHg	94 ± 8
Medications	
β-blocker, mg	16 ± 7
ACEI, mg	1.0 ± 1.6
Aldosterone antagonist, mg	33 ± 18
Laboratory parameters	
Hemoglobin, g/dL	10.6 ± 1.5
Platelets, $\times 10^3/\mu L$	27.9 ± 8.5
Serum albumin, mg/dL	3.5 ± 0.5
Serum sodium, mEq/L	141 ± 2
Serum potassium, mEq/L	4.2 ± 0.6
Serum BUN, mg/dL	12 ± 4
Serum creatinine, mg/dL	0.8 ± 0.3
Serum total bilirubin, mg/dL	0.8 ± 0.4
Plasma BNP, pg/mL	268 ± 202
Echocardiographic parameters	
LVDd, mm	61 ± 10
LVEF, %	16 ± 9

BMI body mass index, *sBP* systolic blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *BUN* blood urea nitrogen, *BNP* B-type natriuretic peptide, *LVDd* left ventricular diastolic diameter, *LVEF* left ventricular ejection fraction

Statistical analysis

All statistical analyses were performed by using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). We showed categorical variables as frequencies and percentages, and compared using Chi-square test or Fisher's exact test as appropriate. We also represented continuous variables as mean ± standard deviation unless otherwise specified, and compared using unpaired *t* test or Mann–Whitney *U* test as appropriate. Each HRV parameter was compared with that of low rotation speed by ad hoc Dunnett's test when repeated analysis of variance was approved significance. We adopted the Pearson's product-moment correlation coefficients to analyze the relationship between LF_{NU} and hemodynamic parameters or LF_{NU} and midterm clinical parameters. A logistic regression analysis and a receiver operating curve analysis were performed to analyze the relationship between LF_{NU} and improvement of parameters indicating LV reverse remodeling. Time courses of 3 parameters associated with LV reverse remodeling were stratified by LF_{NU} and compared between 5 weeks and 6 months by paired *t* test. All hypothesis tests reported were two-tailed, and used a p value <0.05 as significant.

Results

Patients background (Table 1)

In the present study, 23 adult patients (36 ± 13 years and 83 % male) were enrolled. There were no patients with end-organ dysfunction or severe valve disease during the study period.

Hemodynamic and HRV parameters at each rotation speed (Fig. 1)

Systolic blood pressure and mean right atrial pressure remained unchanged regardless of any rotation speeds. Lower cardiac index (CI) and higher pulmonary capillary wedge pressure were associated with lower rotation speed (Fig. 1a–d). Lower HF levels were observed at lower rotation speed. LF/HF ratio and LF_{NU}, both representing sympathetic nerve activity, were higher at lower rotation speed (Fig. 1e–h).

Serum catecholamine levels at each rotation speed (Fig. 2)

All 3 plasma catecholamine (noradrenaline, adrenaline, and dopamine) levels were significantly increased at lower rotation speed in 11 patients ($p < 0.05$) (Table 2).

HRV and hemodynamic parameters (Table 3)

Among hemodynamic parameters at all 3 rotation speed ($N = 69$), only CI was significantly associated with LF_{NU} ($p = 0.001$ and $r = -0.381$).

HRV and midterm clinical parameters (6 months observation)

Of all 23 patients, 19 were treated with LVAD at fixed middle rotation speed adjusted considering hemodynamic and echocardiographic results for ≥6 months. The midterm endpoint, i.e., improvement of all 3 parameters associated with LV reverse remodeling, were eventually achieved in 6 recipients during the study period. A logistic regression analysis demonstrated that lower LF_{NU} level was significantly associated with achievement of improved LV reverse remodeling ($p = 0.021$, odds ratio 0.903). A receiver operating characteristic analysis showed the cut-off point of LF_{NU} was 55 % for achievement of the

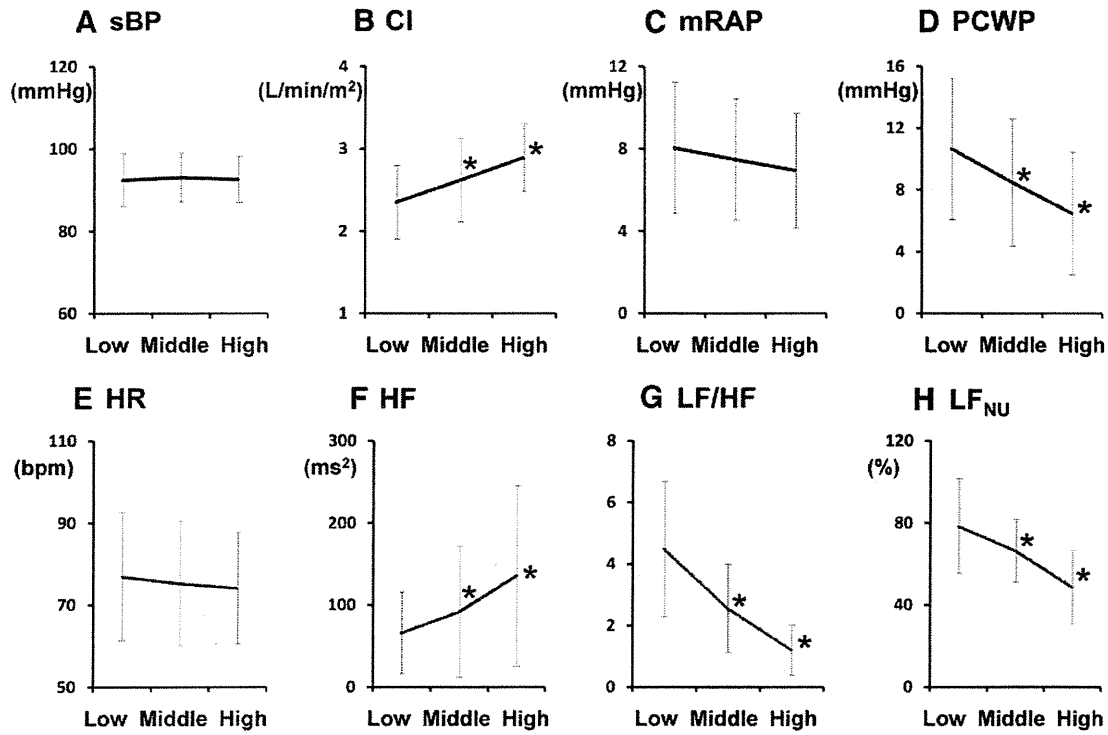

Fig. 1 Hemodynamic (**a**–**d**) and HRV parameters (**e**–**h**) at each rotation speed. *sBP* systolic blood pressure, *CI* cardiac index, *mRAP* mean right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *HR* heart rate, *HF* high frequency, *LF/HF* ratio of low-frequency over high-frequency power, LF_{NU}, normalized unit of LF calculated by the formula: LF/(LF + HF). *$p < 0.05$ by Dunnett's test compared with that of low rotation speed when repeated analyses of variance approved significance

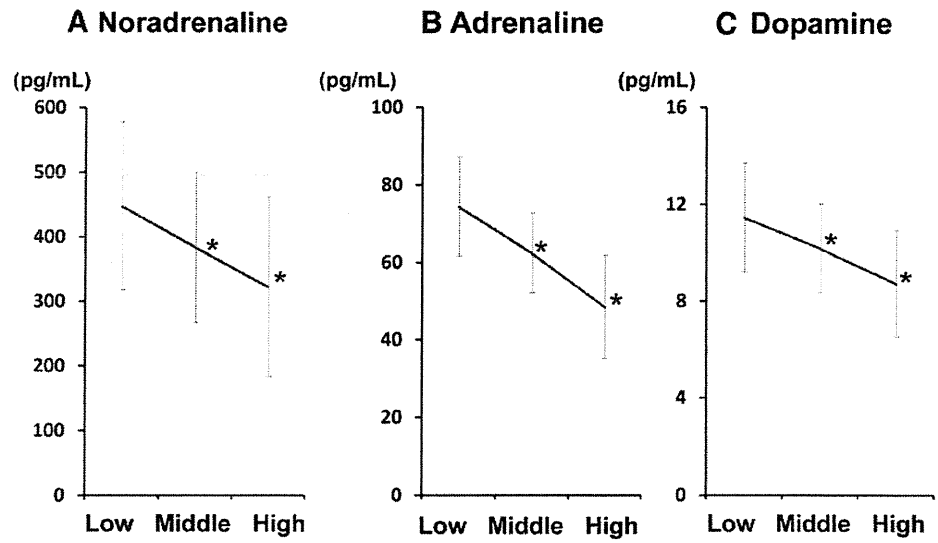

Fig. 2 Plasma catecholamine levels at each rotation speed. *$p < 0.05$ by Dunnett's test compared with that of low rotation speed when repeated analyses of variance approved significance

midterm endpoint (area under the curve, 0.869; sensitivity, 0.714; specificity, 0.917). The cut-off level significantly stratified time course of 3 parameters indicating improvement of LV reverse remodeling during the study period ($p < 0.05$ for all) (Fig. 3). Patients' background stratified by LF_{NU} 55 % was shown in Table 4. Higher HR, P-BNP, and lower LVEF were observed in patients with LF_{NU} >55 %, i.e., higher sympathetic activity group, although not statistically significant. There were no differences between doses of anti-HF agents regardless of LF_{NU} levels.

Table 2 Rotation speeds in each devices

	Rotation speed (rpm)		
	Low	Middle	High
Devices			
EVAHEART ($N = 5$)	1590 ± 55	1830 ± 45	2040 ± 55
DuraHeart ($N = 5$)	1410 ± 55	1750 ± 50	1980 ± 84
HeartMate II ($N = 10$)	8020 ± 92	8620 ± 92	9110 ± 74
Jarvik 2000 ($N = 2$)	8000	9000	10000
HeartWare ($N = 1$)	1800	2000	2300

Table 3 Correlation between LF_{NU} and hemodynamic parameters at 5 weeks after LVAD implantation

vs. LF_{NU}	$N = 69$	p value	R value
sBP, mmHg	94 ± 8	0.867	0.037
CI, L/min/m^2	2.7 ± 0.5	0.001*	−0.381
mRAP, mmHg	8 ± 3	0.856	0.028
mPAP, mmHg	18 ± 5	0.796	0.040
PCWP, mmHg	9 ± 6	0.084	0.271

CI cardiac index, *mRAP* mean right atrial pressure, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure

* $p < 0.05$ by the Pearson's product-moment correlation coefficients

Discussion

By using HRV spectral analyses, we demonstrated here that autonomic nerve activity was varied at each rotation speed during LVAD support, and higher LF/HF and LF_{NU} levels, indicating sympathetic nerve activation were associated with lower rotation speed accompanied by lower CI. Sympathetic activation was also validated by elevated catecholamine concentration at lower rotation speed. Patients with LF_{NU} >55 % had higher P-BNP level and achieved less LV reverse remodeling during midterm LVAD support.

Lower rotation speed and sympathetic activation

Although there have been no studies discussing the relationship between rotation speed and autonomic activity during LVAD support, we demonstrated for the first time that lower rotation speed was significantly associated with sympathetic nerve activation. Sympathetic activation was defined as higher LF/HF level or LF_{NU} calculated by the HRV analyses [12]. We use the power spectral analyses of HRV, which is an established non-invasive method to assess autonomic cardiac modulation and provides information on both sympathetic and parasympathetic activity of the sinus node [9]. The activated sympathetic tone was validated by the elevated plasma catecholamine concentration at lower rotation speed (Fig. 2) [13].

The lower rotation speed was associated with lower CI due to decreased LVAD flow (Fig. 1b), and lower CI was significantly associated with higher LF_{NU} level among hemodynamic parameters (Table 3). Neither congestion nor elevated cardiac pressure seemed to be a trigger for sympathetic activation. The results were consistent with the previous authors' reports: significantly decreased cardiac output stimulates baroreceptor and activates sympathetic tone, which results in venous constriction to increase venous return, increased cardiac contractility and heart rate, arterial constriction to elevate vascular resistance, and activation of renin–angiotensin–aldosterone system or arginine–vasopressin system [14–16].

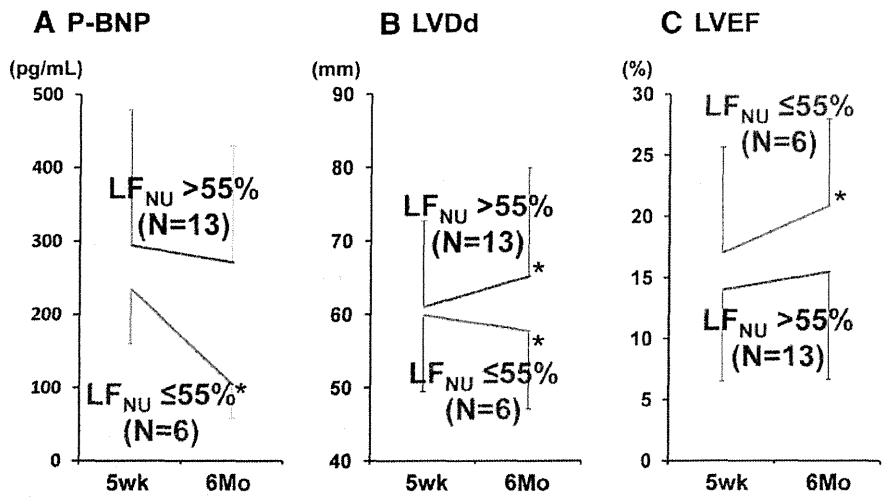

Fig. 3 Time course of three parameters indicating LV reverse remodeling stratified by the cut-off level of LF_{NU} during the study period. *$p < 0.05$ by the paired t test

Table 4 Baseline parameters stratified by the cut-off level of LFNU

	LF_{NU} ≤55 % ($N = 6$)	LF_{NU} >55 % ($N = 13$)	*p* value
Demographic parameters			
Body height, cm	165 ± 9	167 ± 10	0.534
BMI	19.4 ± 2.9	20.7 ± 3.4	0.287
Heart rate, bpm	73 ± 13	77 ± 15	0.094
sBP, mmHg	95 ± 7	93 ± 6	0.534
Medications			
β-blocker, mg	15 ± 6	17 ± 7	0.708
ACEI, mg	1.0 ± 1.4	1.0 ± 1.3	0.660
Aldosterone antagonist, mg	32 ± 15	34 ± 17	0.834
Laboratory parameters			
Hemoglobin, g/dL	10.5 ± 1.5	11.0 ± 1.3	0.484
Platelets, $\times 10^3/\mu L$	28 ± 8	28 ± 7	0.935
Serum sodium, mEq/L	140 ± 3	140 ± 2	0.817
Serum potassium, mEq/L	4.2 ± 0.3	4.1 ± 0.5	0.906
Serum BUN, mg/dL	10 ± 3	11 ± 3	0.272
Serum creatinine, mg/dL	0.7 ± 0.1	0.8 ± 0.4	0.518
Serum total bilirubin, mg/dL	1.0 ± 0.5	0.8 ± 0.2	0.324
Plasma BNP, pg/mL	234 ± 74	294 ± 185	0.087
Hemodynamic parameters			
CI, L/min/m^2	2.7 ± 0.7	2.6 ± 0.4	0.738
mRAP, mmHg	8 ± 3	7 ± 3	0.384
mPAP, mmHg	17 ± 5	16 ± 5	0.814
PCWP, mmHg	8 ± 3	9 ± 5	0.569
Echocardiographic parameters			
LVDd, mm	60 ± 10	62 ± 11	0.729
LVEF, %	18 ± 9	12 ± 7	0.068

BMI body mass index, *sBP* systolic blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *BUN* blood urea nitrogen, *BNP* B-type natriuretic peptide, *LVDd* left ventricular diastolic diameter, *LVEF* left ventricular ejection fraction

Sympathetic activation and adverse clinical course during LVAD support

This mechanism has emerged in the course of human evolution to maintain hemodynamic homeostasis, but is often affected adversely by inappropriately activated sympathetic tone in patients with HF especially during chronic phase [2]. In patients with chronic HF, inappropriate sympathetic activation induces transduction abnormalities of the β-adrenergic signal that results in reduced maximal functional capacity and myocardial protection from adrenergic stimulation [17], permits LV remodeling and accelerated myocardium death [18], encourages fatal ventricular tachyarrhythmias [19]. These mechanisms again stimulate sympathetic activity, and then the vicious cycle emerges in patients with chronic HF. Considering the above etiology, there is now a well-established evidence, derived from many large-scale clinical randomized control studies [3, 4], that long-term β-blocker treatment in patients with HF substantially improves their LV function, clinical condition, and prognosis by suppressing the vicious cycle.

Doses of β-blocker were well titrated in all patients during LVAD support. Although there was no correlation between LF_{NU} level and dose of β-blockers, higher LF_{NU} level (≥55 %) at the maintenance rotation speed was significantly associated with midterm adverse outcome on the view point of LV reverse remodeling: higher P-BNP level, less decreases in LVDd, and less increases in LVEF compared with those of baseline (Fig. 3). Residual inappropriate sympathetic activity due to accordingly lower rotation speed might have progressed HF regardless of sufficient β-blocker treatment during LVAD support.

Optimal rotation speed setting considering autonomic activity

How should we optimize the rotation speed during LVAD support? Generally, lower rotation speed is recommended because ventricular tachyarrhythmia or aortic insufficiency sometimes develops at higher rotation speed [6]. To achieve optimal rotation speed, routine hemodynamic and echocardiographic studies are strongly recommended as we already did in all patients [6, 20]. We decided the maintenance rotation speed at the median value between lowest and highest rotation speed tested during the hemodynamic study.

However, we demonstrated that patients with LF_{NU} >55 % at the maintenance rotation speed, i.e., middle rotation speed, could not achieve improvement of LV reverse remodeling. Relative activation of sympathetic tone appeared to be associated with worse clinical course during LVAD support. Since we adjusted rotation speed at the middle one in consideration of hemodynamics, the hemodynamic parameters at the maintenance speed were comparable between patients with higher LF_{NU} and those with lower LF_{NU} (Table 4). Higher rotation speed may be recommended in such patients with higher LF_{NU} to achieve optimal LV unloading. Therefore, HRV analyses may be an additional novel tool to optimize rotation speed especially in the view point of autonomic activation during LVAD treatment.

Limitations

1. Since the present study was performed at a single center among a small size sample in a retrospective manner, statistical power may not be strong. Prospective study discussing the long-term result under

optimized rotation speed considering the results of HRV analyses would be a future concern.
2. We analyzed the relationship between rotation speed and autonomic nerve activity only at rest condition. Analyses during exercise may approach daily condition.
3. We evaluated short-term HRV parameters at each rotation speed. Whether the observed trend of HRV parameters remains for longer period would be a future concern.
4. We evaluated only patients with sinus rhythm. HRV analyses cannot be adopted in patients with atrial fibrillation or pacing rhythm in general.

Conclusion

Autonomic activation can vary at various rotation speeds during LVAD support. HRV analyses may be an additional novel tool to optimize rotation speed considering autonomic nerve activity.

Conflict of interest None.

Reference

1. Floras JS. Sympathetic activation in human heart failure: diverse mechanisms, therapeutic opportunities. Acta Physiol Scand. 2003;177:391–8.
2. Metra M, Nodari S, D'Aloia A, Bontempi L, Boldi E, Cas LD. A rationale for the use of beta-blockers as standard treatment for heart failure. Am Heart J. 2000;139:511–21.
3. The Cardiac Insufficiency Bisoprolol Study II. (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.
4. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334:1349–55.
5. George RS, Birks EJ, Cheetham A, Webb C, Smolenski RT, Khaghani A, Yacoub MH, Kelion A. The effect of long-term left ventricular assist device support on myocardial sympathetic activity in patients with non-ischaemic dilated cardiomyopathy. Eur J Heart Fail. 2013;15:1035–43.
6. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, Starling RC, Chen L, Boyle AJ, Chillcott S, Adamson RM, Blood MS, Camacho MT, Idrissi KA, Petty M, Sobieski M, Wright S, Myers TJ, Farrar DJ. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29:S1–39.
7. Hori M, Nagai R, Izumi T, Matsuzaki M. Efficacy and safety of bisoprolol fumarate compared with carvedilol in Japanese patients with chronic heart failure: results of the randomized, controlled, double-blind, Multistep Administration of bisoprolol IN Chronic Heart Failure II (MAIN-CHF II) study. Heart Vessel. 2014;29:238–47.
8. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation. 1999;100:1056–64.
9. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17:354–81.
10. Sawada Y, Ohtomo N, Tanaka Y, Tanaka G, Yamakoshi K, Terachi S, Shimamoto K, Nakagawa M, Satoh S, Kuroda S, Iimura O. New technique for time series analysis combining the maximum entropy method and non-linear least squares method: its value in heart rate variability analysis. Med Biol Eng Comput. 1997;35:318–22.
11. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res. 1986;59:178–93.
12. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213:220–2.
13. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311:819–23.
14. Skorecki KL, Brenner BM. Body fluid homeostasis in man. A contemporary overview. Am J Med. 1981;70:77–88.
15. Frye RL, Braunwald E. Studies on Starling's law of the heart. I. The circulatory response to acute hypervolemia and its modification by ganglionic blockade. J Clin Invest. 1960;39:1043–50.
16. Imamura T, Kinugawa K, Hatano M, Fujino T, Inaba T, Maki H, Kinoshita O, Nawata K, Kyo S, Ono M, Komuro I. Low cardiac output stimulates vasopressin release in patients with stage d heart failure. Circ J. 2014;78:2259–67.
17. Bristow MR. Mechanism of action of beta-blocking agents in heart failure. Am J Cardiol. 1997;80:26L–40L.
18. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart. A new era in the treatment of heart failure. Circulation. 1996;94:2285–96.
19. Lown B, Verrier RL. Neural activity and ventricular fibrillation. N Engl J Med. 1976;294:1165–70.
20. Imamura T, Kinugawa K, Kato N, Muraoka H, Fujino T, Inaba T, Maki H, Kinoshita O, Hatano M, Kyo S, Ono M. Late-onset right ventricular failure in patients with preoperative small left ventricle after implantation of continuous flow left ventricular assist device. Circ J. 2014;78:625–33.

Recipients With Shorter Cardiopulmonary Bypass Time Achieve Improvement of Parasympathetic Reinnervation Within 6 Months After Heart Transplantation

Teruhiko IMAMURA,[1] MD, Koichiro KINUGAWA,[2] MD, Takeo FUJINO,[1] MD, Toshiro INABA,[1] MD, Hisataka MAKI,[1] MD, Masaru HATANO,[1] MD, Osamu KINOSHITA,[3] MD, Kan NAWATA,[3] MD, Shunei KYO,[2] MD, *and* Minoru ONO,[3] MD

SUMMARY

Although cross-sectional late-phase reinnervation in heart transplantation (HTx) recipients has been demonstrated by several earlier studies, early-phase successive analyses especially for parasympathetic reinnervation remain unknown. Successive heart rate variability (HRV) data calculated by the MemCalc power spectral density method were obtained from 16 non-rejection recipients 1-24 weeks after HTx. High frequency (HF) level representing parasympathetic magnitude increased significantly at 6 months after HTx (from 0.9 ± 0.7 to 4.1 ± 2.8 ms^{2*}). Only intraoperative shorter cardiopulmonary bypass time (181 ± 59 minutes) correlated with a higher level of HF at post-HTx 6 months among all baseline variables (r = -0.530*). Higher level of HF was associated with recovery of tachycardia at post-HTx 6 months (r = -0.514*). In conclusion, parasympathetic reinnervation emerges along with recovery of tachycardia < 6 months after HTx, which is accelerated by shorter intraoperative cardiopulmonary bypass time (*$P < 0.05$ for all). (Int Heart J 2014; 55: 440-444)

Key words: Sympathetic, Heart rate variability, Memcalc, Donor

Heart transplantation (HTx) is the ultimate treatment for patients with stage D heart failure because the deteriorated heart of the recipient is completely replaced with a healthy donor heart. However, complete allograft denervation occurs during the operation,[1] which results in adverse clinical effects including higher heart rates (HR) at rest, slow acceleration of HR during exercise, decreased exercise tolerability, and absence of angina at coronary ischemia.[2-6] Recent clinical and experimental studies have provided evidence of progressive partial sympathetic reinnervation during several years after HTx through HR variability (HRV) analyses, positron emission tomography imaging with the catecholamine analogue C-11 hydroxyephedrine, or hormonal measurement.[3,7-12]

However, most studies were executed by cross-sectional observation at several years after HTx, while fewer studies were conducted successively within postoperative 1 year. Moreover, little has been investigated about parasympathetic reinnervation. We here analyzed successive HRV parameters 1-24 weeks after HTx to investigate postoperative early-stage parasympathetic reinnervation.

METHODS

Patients selection: Sixteen recipients who had received HTx and been followed > 6 months without acute rejection or heart failure at the University of Tokyo Hospital between April 2013 and March 2014 were retrospectively enrolled in the present study (early-stage group). All recipients had been treated with a ventricular assist device (VAD) before HTx, and had undergone a standard HTx procedure with a modified bicaval anastomosis technique.[13] Rejection was monitored by serial endomyocardial biopsy and hemodynamic studies every 1 week until 1 month, every 2 weeks until 3 months, and then every month until 6 months. All candidates had sinus rhythm during the study period. Written informed consent was obtained before the study enrollment from the patients and/or their family members in all cases. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, the University of Tokyo [application number 779 (1)].

Immunosuppressant protocol: All recipients were treated with standard triple immunosuppressant therapy including carcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mophetil, and low dose prednisolone as we previously described.[14-16] The target trough concentration of cyclosporine was 300-400 ng/mL during the first 3 months, and then re-

From the Departments of [1] Cardiovascular Medicine, [2] Therapeutic Strategy for Heart Failure, and [3] Cardiac Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

Address for correspondence: Koichiro Kinugawa, MD, 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-tky@umin.ac.jp

Received for publication April 10, 2014. Revised and accepted April 28, 2014.

Released in advance online on J-STAGE August 11, 2014.

duced to 250-300 ng/mL until 6 months. The trough level of tacrolimus was maintained at 10-15 ng/mL during the first 3 months, and about 10 ng/mL thereafter. Mycophenolate mophetil was initiated within the first 3 days and maintained at a dose of 1500-2000 mg/day. Prednisolone was administered at 1 mg/kg initially, and then tapered off gradually until the first year if possible.

Variables evaluated: Demographic data before HTx such as VAD selection or duration of VAD therapy were obtained. Perioperative and donor data such as ischemic time of donor heart and donor age were also obtained. Laboratory, echocardiographic, and hemodynamic data at 1 week (baseline) and 6 months after HTx were obtained.

HRV spectral analysis: Mean HR and HRV were measured for 5 minutes at 9:00-12:00 AM after 15 minutes of rest in the supine position under fixed 0.25 Hz of respiratory rate along with fasting every 1 week until 1 month, every 2 weeks until 3 months, and every month until 6 months after HTx. Electrocardiographic signals from bipolar leads were transformed to digital signals to calculate the R-R intervals at a sampling rate of 512 Hz. Power spectral analysis of HRV was performed by the MemCalc power spectral density method using a commercial software package (MemCalc/Win, Suwa Trust) that used the maximum entropy method for spectral analysis and the nonlinear least-squares method for fitting analysis.[17] Low frequency (LF) was defined as 0.04 to 0.15 Hz, and high frequency (HF) as 0.15 to 0.40 Hz. The HF power denotes solely the parasympathetic activity, whereas the LF/HF power represents sympathetic activity.

Statistical analysis: All statistical analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). Categorical variables were summarized as frequencies and percentages, and compared using the Chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as the mean ± standard deviation unless otherwise specified, and compared using the unpaired *t*-test or Mann-Whitney test as appropriate. Pearson's product-moment correlation coefficients were calculated to assess the relationship between HF values at 24 weeks and background parameters. Each HRV parameter was compared with that of baseline by the ad-hoc Dunnett test when repeated analysis of variance was proved to be significant. All hypothesis tests reported were two-tailed, and used a P value < 0.05 as significant.

RESULTS

Baseline characteristics (Table I): All patients were treated by VAD treatment for > 1 year (average, 904 ± 233 days, median, 919 days) before HTx due to dilated cardiomyopathy (14 patients), ischemic cardiomyopathy (1 patient), and dilated phase of hypertrophic cardiomyopathy (1 patient). Mean donor age was 38 ± 14 years (range, 17-60 years-old) and there were 5 males (31%). Mean duration of allograft ischemia was 253 ± 33 minutes (range, 201-298 minutes), and mean cardiopulmonary bypass time was 181 minutes (range, 119-360 minutes). HTx procedures were executed without any complications in all recipients.

Mean recipient age was 36 ± 14 years-old (range, 21-61 years-old) and 9 patients (56%) were male. Six patients (38%) received cyclosporine, and tacrolimus was prescribed for 10

Table I. Baseline Parameters in HTx Recipients

Variables	
Donor parameters	
Age, years	38 ± 14
Male, *n* (%)	5 (31)
Transplant Surgery	
Duration of allograft ischemia, min	253 ± 33
Cardiopulmonary bypass time, min	181 ± 59
Aortic cross-clamp time, min	104 ± 14
Recipients' pre-HTx parameters	
PF LVAD, *n* (%)	8 (50)
CF LVAD, *n* (%)	8 (50)
Duration of VAD treatment, days	904 ± 233
Etiology of ischemia, *n* (%)	1 (6)
Recipients' demographic parameters	
Age, years	36 ± 14
Male, *n* (%)	9 (56)
Body mass index	19.9 ± 2.8
Systolic blood pressure, mmHg	124 ± 24
Diastolic blood pressure, mmHg	68 ± 12
HbA_{1c} (NGSP), %	5.2 ± 0.5
Recipients' medications	
Beta-blocker, *n* (%)	12 (75)
ACEI or ARB, *n* (%)	11 (69)
Statin, *n* (%)	12 (75)
Cyclosporine, *n* (%)	6 (38)
Tacrolimus, *n* (%)	10 (63)
Recipients' laboratory parameters	
White blood cells, × $10^3/\mu L$	13.4 ± 3.2
Hemoglobin, g/dL	11.4 ± 1.5
Platelets, × $10^3/\mu L$	24.4 ± 11.3
Serum sodium, mEq/L	134 ± 4
Serum potassium, mEq/L	4.7 ± 0.4
Serum BUN, mg/dL	31 ± 21
Serum creatinine, mg/dL	1.1 ± 0.7
Serum albumin, g/dL	3.1 ± 0.3
Serum total bilirubin, mg/dL	1.4 ± 1.1
Serum CRP, mg/dL	2.4 ± 1.2
Plasma BNP, pg/mL	358 ± 319
Recipients' echocardiographic parameters	
LVDd, mm	41 ± 6
LVDs, mm	26 ± 4
LVEF, %	67 ± 6
AR, grade	0.1 ± 0.3
MR, grade	0.1 ± 0.3
TR, grade	0.3 ± 0.5
E/e'	12.5 ± 3.5
Recipients' hemodynamic parameters	
mRAP, mmHg	7 ± 4
mPAP, mmHg	19 ± 6
PCWP, mmHg	13 ± 4
CI, L/min/m^2	2.8 ± 0.4

HF indicates high frequency; HTx, heart transplantation; PF, pulsatile flow; CF, continuous flow; LVAD, left ventricular assist device; NGSP, national glycohemoglobin standardization program; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; CRP, C-reactive protein; BNP, B-type natriuretic peptide; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; E/e', ratio of early diastolic transmitral flow velocity to mitral annular velocity at the lateral wall; mRAP, mean right atrial pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and CI, cardiac index.

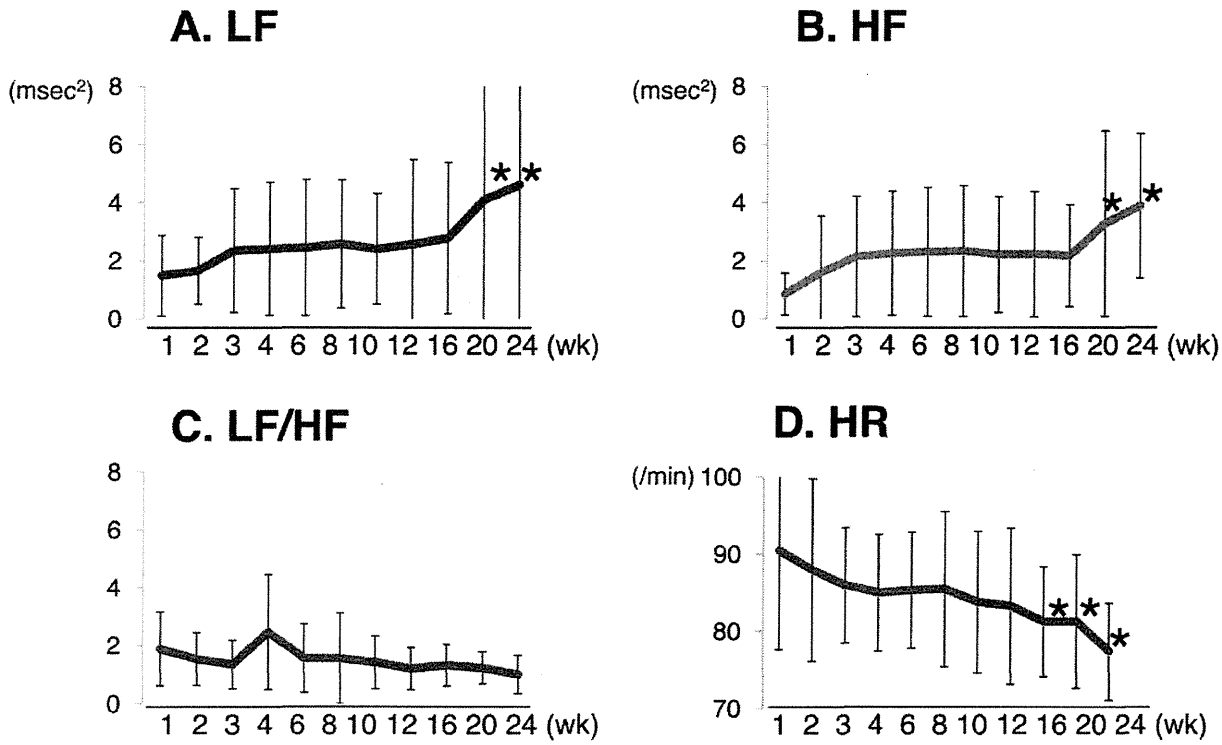

Figure. Time courses of HRV parameters from 1 week to 24 weeks after HTx, ie, LF (**A**), HF (**B**), LF/HF (**C**), HR (**D**). *$P < 0.05$ by Dunnett's test compared with those of 1 week post-HTx when repeated analysis of variance proved significance.

patients (63%). Left ventricle contractility was well preserved without any significant valvular diseases, and hemodynamics were stable.

Time courses of HRV parameters during the study period (Early-stage : 1-24 weeks): LF and HF increased gradually and reached significantly higher levels after postoperative 20 weeks (Figure A and B). LF/HF, which represents sympathetic activity, remained unchanged during the study period (Figure C). HR was 91 ± 10 beats per minute (bpm) at baseline and decreased gradually down to 80 ± 10 bpm (Figure D).

Relationship between achieved HF and baseline parameters (Table II): Among baseline parameters including donor, transplant surgery, and recipient data, only a shorter cardiopulmonary bypass time was significantly associated with higher HF levels at 6 months after HTx ($P = 0.035$, $r = -0.530$).

Relationship between achieved HF and clinical parameters at 6 months after HTx: Clinical parameters at 6 months after HTx are shown in Table III. HF levels correlated with HR levels and %changes in HR levels among post-HTx recipient clinical parameters at 6 months including laboratory, echocardiographic, and hemodynamic parameters (Table IV).

Discussion

We demonstrated here that parasympathetic reinnervation gradually occurs < 6 months after HTx by HRV analyses. Shorter cardiopulmonary bypass time correlated with improvement of parasympathetic reinnervation among the recipient baseline parameters, and improved parasympathetic reinnervation was associated with recovery of tachycardia at 6 months after HTx.

Time courses of reinnervation: Earlier studies demonstrated that sympathetic reinnervation occurs approximately > 1 year after HTx mainly using positron emission tomography imaging or measurement of transcardiac norepinephrine release induced by intravenous tyramine.[3,7,8,11,18] However, these modalities cannot analyze parasympathetic nerve activity.

Power spectral analyses of HRV is a noninvasive method to assess autonomic cardiac modulation and provides information on not only sympathetic but also parasympathetic activity of the sinus node.[19] A few investigators demonstrated parasympathetic reinnervation at several years after HTx using cross-sectional or paired-time data.[10,20,21] Our successive analyses of HRV data demonstrated for the first time that parasympathetic reinnervation occurred earlier than 1 year after HTx. Our result that no significant sympathetic reinnervation occurred < 6 months after HTx was consistent with the findings of the previous studies discussed above. Six months may be too short for sympathetic reinnervation.

Factors that influence reinnervation: Autonomic reinnervation does not occur in the same manner in each recipient.[10,11] What affects autonomic reinnervation after HTx? Bengel, *et al* showed that the regenerational capacity of the cardiac sympathetic nervous system was reduced if the recipient had diabetes mellitus, because impaired glucose handling adversely affected autonomic nerve activity and regeneration.[22] They also demonstrated in another paper that sympathetic reinnervation was more likely with a younger donor/recipient and a fast and uncomplicated HTx procedure.[12] Neuronal regeneration is de-