Advantage of Pulsatility in Left Ventricular Reverse Remodeling and Aortic Insufficiency Prevention During Left Ventricular Assist Device Treatment

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Background: A continuous flow (CF) left ventricular assist device (LVAD) has various advantages over a pulsatile flow (PF) LVAD, but the extent of preventing aortic insufficiency (AI) by each type of LVAD remains controversial.

Methods and Results: Of 86 patients with non-ischemic cardiomyopathy who underwent LVAD implantation between 2006 and 2015, 20 propensity score-matched patients with PF LVADs and 20 with CF LVADs were enrolled in this study. There were no significant differences in the baseline variables of both groups. During the 6-month LVAD treatment, the LV ejection fraction of the PF group was significantly higher than that of the CF group; the PF group also had a wider pulse pressure and less enlargement of the aortic root (P<0.05 for all). Patients in the PF group experienced more frequent opening of the native aortic valve and less AI than those in the CF group (P<0.05 for both). The PF LVAD was explanted in 5 patients (25%), and a CF LVAD was explanted in 1 patient (5%).

Conclusions: Compared with CF LVADs, PF LVADs seem to have an advantage in improving LV reverse remodeling and preventing AI. It may be best to incorporate pulsatility into current CF LVADs while retaining their existing benefits.

Key Words: Heart failure; INTERMACS; Pulsatile flow; Ventricular assist devices

A continuous-flow left ventricular assist device (CF LVAD) is currently the most widely used mechanical circulatory support device as a bridge-to-transplant or destination therapy for patients with stage D heart failure (HF). The use of CF LVADs has resulted in better prognosis compared with pulsatile-flow (PF) LVADs, because of their smaller size, less frequent complications, including thromboembolism and device-related infection, and longer durability. However, the effects of preserved pulsatility during LVAD treatment on LV reverse remodeling (LVRR) or aortic insufficiency (AI) remain controversial.

In this study, we selected 2 sets of background-matched patients (ie, the PF group and the CF group), by performing the recently developed propensity score-matching analyses, and compared the clinical outcomes, including LVRR and AI, between the groups.

Methods

Patient Selection

Between 2006 and 2015, a total of 151 patients underwent LVAD implantation (93 extracorporeal PF LVADs, 58 implantable CF LVADs) and were followed up. Of them, we excluded patients with ischemic etiology or myocarditis, those receiving a biventricular assist device, those with insufficient data, those who had received concomitant aortic valve (AV) replacement for significant aortic regurgitation, and those who had been followed up for <6 months. From among the 86 remaining patients with non-ischemic cardiomyopathy, background-matched 20 patients with a PF LVAD and 20 with a CF LVAD, who were chosen using propensity score-matching analyses (as described later), were enrolled.

All patients had received guideline-directed medical treatment, and none of them had any absolute contraindications for heart transplant at the time of LVAD therapy. The CF LVAD was approved from 2011 in Japan, and was indicated for patients who were listed as heart transplant recipients before the surgery. No patients were assigned to INTERMACS profile 1. The PF LVAD was available during the entire study period, irrespective of preoperative heart transplant listing or INTERMACS profile 1.

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LVAD and CF LVAD support. The same procedure was also executed either just before explantation of the LVAD or after 6 months, and that timing was assumed to be the endpoint. Opening of the native AV was observed for 1 m in the M-mode. Less than 30% of opening per native heartbeat was defined as “native AV remaining closed.”

De novo aortic regurgitation equivalent to or worse than mild regurgitation was defined as AI, as in previous studies.

We initiated weaning protocols after patients were deemed potential candidates for weaning of LVAD on the basis of sufficient improvements in LVEF and exercise tolerance. The “off test” for PF LVAD or the “pump down test” for CF LVAD was performed, with echocardiography and hemodynamic studies for 10 min without LVAD support, accompanied by successive “volume challenge tests” with 10 ml/kg of saline for 15 min. If the results indicated success, the patient was scheduled for explantation of the LVAD.

Written informed consent was given by all the participants. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, University of Tokyo.

Preoperative Variables
Preoperative data, including demographics and laboratory variables, were obtained 24 h before the surgery. Hemodynamic and echocardiographic data were obtained 1 week before the operation. The LV ejection fraction (LVEF) in the 2- and 4-chamber views was calculated by the Simpson method. The grade of valve regurgitation was scored as follows: 0, no regurgitation; 1, trace; 2, mild; 3, moderate; and 4, severe. The doses of β-blocker and angiotensin-converting enzyme inhibitor were corrected as equivalent doses of carvedilol and enalapril, respectively.

Postoperative Variables
Echocardiography was performed 1 and 3 months after LVAD implantation. LVEF was calculated at least 3 times from the data obtained at the different times and then averaged, because the absolute value of LVEF varies according to time during PF LVAD and CF LVAD support. The same procedure was also executed either just before explantation of the LVAD or after 6 months, and that timing was assumed to be the endpoint. Opening of the native AV was observed for 1 m in the M-mode. Less than 30% of opening per native heartbeat was defined as “native AV remaining closed.”

Weaning Protocol
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Statistical Analysis
Propensity score-matching analyses were used to select the background-matched patients who received a PF or CF LVAD. In the analyses, age, HF duration, cumulative dose of β-blocker, INTERMACS profile, and the plasma level of B-type natriuretic peptide were uptitrated in consideration of hemodynamics. A PF LVAD was regulated in a full-fill full-empty manner. The rotation speed of the CF LVAD was adjusted according to hemodynamic and echocardiographic data.

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Pulsatility and AI During LVAD Therapy

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Clinical Course During 6-Month LVAD Support

The echocardiographic variables before and after the operation in the PF and CF groups are presented in Figure, and variables at the endpoint were compared between the groups (Table 2). The LV diastolic diameter decreased significantly in both groups (Figure A). The LVEF increased significantly in the PF group, but remained unchanged in the CF group (Figure B). At the endpoint, the diameters of the AV ring and the sinus of Valsalva remained unchanged in the PF group, but had increased significantly in the CF group (Figures C, D).

The rate of AV opening increased significantly in the PF group, but remained unchanged in the CF group (Figure E). The rate of AI increased significantly in the PF group, whereas few patients (10%) in the CF group experienced AI (Figure F). Patients in the PF group had a higher pulse pressure than those in the CF group. There were no differences in the dose of anti-HF medications between the groups.

The PF LVAD was explanted in 5 patients (25%), and a CF LVAD was explanted only in 1 patient (5%). No patients died during the study period.

Results

Preoperative Baseline Characteristics

The preoperative baseline characteristics of the patients are presented in Table 1. The CF LVAD group included the following models: 11 EVAHEART; 3 DuraHeart; 4 HeartMate II; 2 Jarvik 2000. All patients had an etiology of non-ischemic cardiomyopathy. There were no significant differences in the background variables of both groups.

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The PF LVAD was explanted in 5 patients (25%), and a CF LVAD was explanted only in 1 patient (5%). No patients died during the study period.
Younger age, shorter HF duration, and insufficient preoperative β-blocker treatment are predictors of LVRR during LVAD treatment. Therefore, we used the recently developed propensity score-matching technique for the analysis, and matched all the patients’ backgrounds to reduce selection bias and purely compare pump efficacy.

Pulsatility, LVRR, AV Opening, and AI Prevention

The ultimate goal indicating recovery is the achievement of LVRR and explantation of the LVAD. However, LVRR during LVAD therapy is a gradual phenomenon, and even partial recovery of the LVEF is associated with better clinical outcomes, including improved exercise tolerance and reduced readmission rate due to cardiovascular events.

We assessed LVRR at 6 months after LVAD, because many authors had shown that 6 months was sufficient to complete LVRR.

In this study, the LVEF increased significantly during PF LVAD support compared with CF devices. Although clinical backgrounds were not necessarily matched completely, some authors showed more volume unloading with PF devices, while others showed that a PF pump was better than a CF pump considering the improvement in LVEF or explantation in the clinical setting.

Correlation Between LVAD Flow and Clinical Outcome

Among patients with a CF LVAD, there were no significant differences in VAD flow irrespective of the existence of AV opening and AI (Tables 3A, B). There was no significant correlation between the amount of VAD flow and LV/aortic geometric or functional parameters (Table 3C).

Discussion

In this study, improvement in the LVRR and less frequent AI was observed at 6 months after LVAD implantation in the PF group, as compared with the propensity score-matched CF group. This is the first report discussing the frequency of AI between background-matched PF and CF groups.

Background Matching Using the Propensity Score

Some authors have compared the clinical outcome between PF and CF LVADs, but all studies contained a patient selection bias because no randomization trials had been performed considering both pumps.

Patients with ischemic etiology have less chance of achieving LVRR compared with those with non-ischemic cardiomyopathy, and patients with fulminant myocarditis often experience LVRR. Younger age, shorter HF duration, and insufficient preoperative β-blocker treatment are predictors of LVRR during LVAD treatment. Therefore, we used the recently developed propensity score-matching technique for the analysis, and matched all the patients’ backgrounds to reduce selection bias and purely compare pump efficacy.

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Although the precise mechanism by which a PF device has an advantage in achieving LVRR remains unclear, “pulsatility” may be an important factor. PF devices unload the ventricle only during some part of the cardiac cycle, whereas CF devices unload the left ventricle continuously throughout the cardiac cycle. In acute animal models, pulsatile unloading preserved more normal physiologic values, whereas continuous unloading altered the physiologic profile of myocardial and vascular hemodynamic energy utilization. Experimental animal models also demonstrated that prolonged complete LV unloading increased the ratio of the myocardial fibrotic area, myocardial apoptosis, and cardiac stiffness probably related to disuse of the left ventricle. Ootaki et al showed the decrease in coronary blood flow by strong continuous LV unloading. A PF LVAD was associated with less increased stimulation of the inflammatory system when compared with a CF LVAD. Considering these reports, preserved pulsatility by intermittent LV unloading may contribute positively to successful LVRR, although the required amount of pulsatility remains uncertain.

AI opening is a sufficient condition to avoid AI. In other words, no patients experience AI when their AV is open. AV opening is achieved when the LV systolic pressure overcomes the pressure of the aortic root. Therefore, LVRR is key to achieving AV opening and preventing AI. In this study, few patients consistently experienced AI owing to LVRR during PF LVAD therapy.

Non-Pulsatility, Aortic Root Remodeling, and AI Development

In this study, patients in the CF group had a lower pulse pressure, larger diameter of the aortic root, and more frequent AI. The CF LVAD induces turbulence in the aortic root, which will increase wall shear stress and retrograde pressure on the aortic root. Degenerative remodeling of the aortic root, accompanied by thinning of the aortic wall, occurs under non-pulsatile circumstances because of apoptosis of smooth muscle cells and fragmentation of elastic fibers. Such remodeling of the aortic root, together with degeneration of the native AV, induces AI. Consistently, some studies have showed that less pulsatility is associated with AI.

Future Directions

Although we demonstrated the advantages of a PF LVAD in LVRR and AI prevention, the overall advantage of a CF LVAD, including better survival, has been demonstrated previously. Currently, owing to the limited evidence, we do not at all suggest the use of a PF LVAD in the era of the CF pump. Instead, preserving “pulsatility” during CF LVAD treatment may be the future step.

For example, a centrifugal pump, which preserves relatively higher pulse pressure compared with an axial pump, may be recommended for achieving LVRR and preventing AI. The Jarvik 2000 has an intermittent low-speed mode, which reduces the rotation speed intermittently, and is expected to open the AV and prevent AI. However, AI developed in both patients receiving a Jarvik 2000 in the present study. Infrequent opening of the AV (ie, 8 per min) may be insufficient to prevent AI, although a future large-scale study is warranted. The HeartWare LVAD has a cyclic controlled speed change function (Lavare Cycle) mode, which allows for changes in LV filling and flow rate though the LVAD (ie, every minute during a 3-s cycle). The HeartMate III LVAD has an induced pulse mode for achieving an increased level of pulsatility with CF assistance. Preserving pulsatility during CF LVAD therapy may be the future direction for better LVRR and AI prevention.

Study Limitations

The present study was performed in a small population from a single center. The number of enrolled patients was considerably reduced by the propensity score-matching analyses, because the patients’ backgrounds differed greatly between the PF LVAD and CF LVAD groups. Therefore, the results may not simply be adopted in the overall population with end-stage cardiomyopathy. The findings should be confirmed in future studies of large populations from many centers. We matched patients’ backgrounds using propensity score-matching analysis in a retrospective manner. Prospective randomization for receiving PF and CF LVADs may be impossible in the current CF era. Although all background information was matched, a PF LVAD is extracorporeal, and a CF LVAD is implantable. Therefore, restrictions to the daily activity of patients with a PF LVAD might have affected the results. The flow volumes are different in PF and CF LVADs, and the effect of flow volume in LVRR and AI remains controversial. However, there were no significant correlations between flow volume and clinical outcomes in the patients with a CF LVAD. Thus, changes in the flow volume within the physiological range may not affect LVRR and AI.

Conclusions

Compared with a CF LVAD, a PF LVAD may be better in improving LVRR and preventing AI. Therefore, it may be best to incorporate pulsatility into current CF LVADs while retaining their existing benefits.

Disclosures

The authors declare that they have no conflicts of interest.

References