Implication of Preoperative Existence of Atrial Fibrillation on Hemocompatibility-Related Adverse Events During Left Ventricular Assist Device Support

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Background: Hemocompatibility-related adverse events (HRAEs) are substantial issues in patients with left ventricular assist devices (LVADs). Atrial fibrillation (AF) is associated with worse prognosis in patients with heart failure (HF), but its effect on HRAEs following LVAD implantation remain uncertain.

Methods and Results: Data from the Japanese Mechanically Assisted Circulatory Support registry of consecutive patients who received HeartMate II LVADs and were followed for 1 year were retrospectively reviewed. Among 190 patients, 23 had AF and 167 had sinus rhythm. The AF group had comparable baseline characteristics with the non-AF group except for their higher age (53 vs. 42 years, P<0.001). Following LVAD implantation, most cases of AF (73%) persisted. Antiplatelet therapy, anticoagulation therapy, and LVAD speed following LVAD implantation were comparable between groups (P>0.05 for all). The 1-year survival free from HRAEs was comparable between groups (83% vs. 76%, P=0.52). Event rates of the breakdown of HRAEs were comparable between groups except for a relatively higher rate of surgically managed pump thrombosis in the AF group (0.16 vs. 0.04, incidence rate ratio 3.75, 95% confidence interval 0.87–16.1, P=0.075). These trends still remained with propensity score-matched comparison.

Conclusions: Existence of AF had no effect on the development of HRAEs following LVAD implantation. The need to aggressively treat AF before or after LVAD implantation needs further investigation.

Key Words: HeartMate; Hemocompatibility; Japanese Mechanically Assisted Circulatory Support Registry (J-MACS); Left ventricular assist device (LVAD)

Atrial fibrillation (AF) and heart failure (HF) are closely related, as the presence of one increases the likelihood of the other.¹ The original Framingham Heart Study that followed patients between 1980 and 2012 showed that among 1,737 individuals, 37% with new AF had HF and among 1,166 individuals, 57% with new HF had AF.² A meta-analysis of 16 studies involving 53,969 HF patients demonstrated that AF was independently associated with death, with an odds ratio of 1.4 in 7 randomized trials, and 1.15 in 9 observational studies.³ The high mortality of patients with concomitant HF and AF is largely attributable to the combination of both pump failure and thromboembolic events.

Although rhythm and/or rate control therapies are attempted to manage AF in HF patients, the optimal strat-
Pre-LVAD AF and HRAEs

Methods

Patient Selection

Data from consecutive HF patients who underwent HeartMate II LVAD implantation as bridge to transplantation at 30 Japanese institutions between April 2014 and January 2017 and were followed for 1 year were retrospectively collected from the J-MACS registry. Patients were assigned to the AF group if they had AF or atrial flutter and all others were assigned to the non-AF group. Patients with a pacemaker were excluded. All participants gave informed consent at each institute before LVAD implantation. The use of the J-MACS registry was approved before the initiation of this study.

Follow-up Protocol

All LVAD patients were observed for 1 year at each institute. Patients were managed by expert LVAD teams according to guideline-directed therapy, including an appropriate dose of aspirin, warfarin dosed to a target

| Table 1. Comparison of the Background Characteristics of the 2 Groups |
|-----------------|-----------------|-----------------|-------------|
| **Demographics** | **Total** (n=190) | **AF group** (n=23) | **Non-AF group** (n=167) | **P value** |
| Age, years | 44 (31, 52) | 53 (47, 58) | 42 (30, 50) | <0.001* |
| Sex, male | 138 (73%) | 16 (70%) | 131 (78%) | 0.24 |
| Body surface area, m² | 1.64±0.15 | 1.68±0.14 | 1.63±0.16 | 0.2 |
| Ischemic etiology | 24 (13%) | 1 (4%) | 23 (14%) | 0.18 |
| Diabetes mellitus | 36 (19%) | 3 (13%) | 33 (20%) | 0.69 |
| Peripheral artery disease | 1 (1%) | 0 (0%) | 1 (1%) | 0.88 |
| Chronic obstructive pulmonary disease | 2 (1%) | 0 (0%) | 2 (1%) | 0.76 |
| **INTERMACS level** | | | | |
| 1 | 21 (11%) | 4 (17%) | 17 (10%) | – |
| 2 | 71 (37%) | 10 (43%) | 61 (37%) | – |
| 3 | 89 (47%) | 7 (30%) | 82 (49%) | – |
| 4–7 | 9 (5%) | 2 (9%) | 7 (4%) | – |
| **Concomitant therapies** | | | | |
| Continuous intravenous inotropes | 139 (73%) | 18 (78%) | 121 (72%) | 0.38 |
| Intra-aortic balloon pumping | 47 (25%) | 6 (26%) | 41 (25%) | 0.53 |
| Respirator | 10 (5%) | 0 (0%) | 10 (6%) | 0.27 |
| Extracorporeal membrane oxygenation | 3 (2%) | 0 (0%) | 3 (2%) | 0.88 |
| Continuous hemodialysis filtration | 1 (1%) | 0 (0%) | 1 (1%) | 0.88 |
| **Medications at 1 month following LVAD implantation** | | | | |
| INR (n=184) | 2.25±0.56 | 2.39±0.66 | 2.23±0.55 | 0.3 |
| LVAD speed (n=173) | 8,600 (8,400, 8,800) | 8,600 (8,400, 8,800) | 8,600 (8,400, 8,800) | 0.62 |
| Aspirin (n=184) | 168 (91%) | 21/22 (95%) | 147/162 (91%) | 0.4 |
| β-blocker (n=184) | 165 (90%) | 18/22 (82%) | 147/162 (91%) | 0.18 |
| Angiotensin-converting enzyme inhibitor (n=184) | 136 (74%) | 12/22 (55%) | 124/162 (77%) | 0.030* |
| Aldosterone antagonist (n=184) | 132 (72%) | 13/22 (59%) | 119/162 (73%) | 0.13 |
| Amiodarone (n=184) | 33 (18%) | 6/22 (27%) | 27/162 (17%) | 0.18 |
| Diuretics (n=184) | 84 (46%) | 10/22 (45%) | 74/162 (46%) | 0.58 |

Normally distributed variables compared by unpaired t-test; non-normally distributed variables compared by Mann-Whitney U test; categorical variables compared by Fisher’s exact test. *P<0.05. INTERMACS, interagency registry for mechanically assisted circulatory support; INR, prothrombin time with international ratio; LVAD, left ventricular assist device.

The effect of AF in the Japanese LVAD population should be assessed separately given the patients’ unique HRAE profile. In this study, we investigated the effect of pre-LVAD AF on HRAEs following LVAD implantation using data from the Japanese Mechanically Assisted Circulatory Support registry (J-MACS).
international normalized ratio (INR) of 2.0–2.5, and adequate LVAD speed adjustment.\textsuperscript{13}

**Variables Evaluated**

Pre-LVAD baseline characteristics were obtained and hemodynamics data before LVAD implantation were obtained when available. Following LVAD implantation, data from ECG performed 1 month post-LVAD were obtained if available. The dose of aspirin, prothrombin time with INR, and LVAD speed at 1 month after LVAD implantation were obtained.

During the 1-year observation period, death or clinical adverse events attributable to LVAD-related bleeding or thrombosis, which were defined as HRAEs as detailed previously,\textsuperscript{11} were censored. Breakdowns of the HRAEs were followings.

**Statistical Analysis**

Statistical analyses were performed with SPSS Statistics 22 (SPSS Inc, Armonk, IL, USA). Two-sided P-values <0.05 were considered to be significant. Continuous variables are expressed as mean and standard deviation and compared between groups by unpaired t-test when normally distributed. When non-normally distributed, they were expressed as median and interquartile and compared between groups by Mann-Whitney U test. Categorical variables are expressed as numbers and percentages and compared between groups by Fisher’s exact test.

Kaplan-Meier analyses using the log-rank test were performed to assess the event-free survival of the 2 groups. Cox proportional hazard ratio regression analyses were also performed to investigate the effect of pre-LVAD AF and other variables on HRAEs. Variables with P<0.05 in the univariate analysis were enrolled into the multivariate analysis. The breakdown of HRAEs was expressed as events per patient-year and compared between groups by negative binomial regression analyses.

We performed a propensity score analysis, matching for age, post-LVAD aspirin use, INR, and use of angiotensin-converting enzyme inhibitors to collect a ratio of 1:2 of the AF and non-AF groups, considering the effect of these 4 variables on HRAEs. A propensity score was calculated using logistic regression modeling including all 4 variables and paired participants were selected based on the propensity scoring.

**Results**

**Baseline Characteristics**

In total, 326 patients underwent HeartMate II LVAD implantation and were followed for 1 year. Of them, 136 were excluded because of undetectable rhythm related to pacemaker support. As a result, we enrolled a total of 190 patients whose pre-LVAD rhythm data were available. Age was 44 (31, 52) years old, 52 of 190 (27%) were male, and 24 of 190 (13%) had ischemic HF etiology (Table 1).

There were 23 patients in the AF group and 167 in the non-AF group, and there were no statistically significant differences in their baseline characteristics except for higher age in the AF group (53 vs. 42 years old; P<0.001). As for pre-LVAD hemodynamics (n=59/190), there were no statistically significant differences between groups except for higher right atrial pressure (RAP) in the AF group (13±4 vs. 8.2±4.4 mmHg, P=0.017; Supplementary Table 1).

At 1 month following LVAD implantation, aspirin dose,
During the 1-year observation period, 4 of 23 patients in the AF group and 39 of 167 in the non-AF group experienced HRAEs. As a result, 1-year survival free from HRAEs was statistically comparable between the groups (83% vs. 76%, \( P=0.52 \); Figure 2). When we set \( \alpha \) of 0.05 and \( 1-\beta \) of 0.8, enrolling 23 patients in the AF group and 167 patients in the non-AF group, the estimated difference in the survival rate required to show statistical significance was calculated as 40% (e.g., 50% in the AF group vs. 90% in the non-AF group). Cox proportional hazard ratio regression analyses showed that the existence of pre-LVAD AF was not a significant factor affecting post-LVAD HRAEs in the univariate and multivariate analyses (\( P>0.05 \) for both). Instead, patients’ age and no aspirin use were statistically comparable between the groups (\( P>0.05 \) for both; Table 1). There were no statistical differences in the rates of other medications between groups except for a lower rate of angiotensin-converting enzyme inhibitors in the AF group (55% vs. 77%, \( P=0.036 \)).

**Trend in AF Following LVAD Implantation**

There were 28 patients whose post-LVAD ECGs were unavailable (Figure 1). Among the AF group, most patients had persistent AF following LVAD implantation (16 of 22). In contrast, post-LVAD de novo AF was observed in only 3 of 140 patients and sinus rhythm persisted following LVAD implantation in the remaining 137 patients.

**Survival Free From HRAEs Following LVAD Implantation**

During the 1-year observation period, 4 of 23 patients in the AF group and 39 of 167 in the non-AF group experienced HRAEs. As a result, 1-year survival free from HRAEs was statistically comparable between the groups (83% vs. 76%, \( P=0.52 \); Figure 2). When we set \( \alpha \) of 0.05 and \( 1-\beta \) of 0.8, enrolling 23 patients in the AF group and 167 patients in the non-AF group, the estimated difference in the survival rate required to show statistical significance was calculated as 40% (e.g., 50% in the AF group vs. 90% in the non-AF group). Cox proportional hazard ratio regression analyses showed that the existence of pre-LVAD AF was not a significant factor affecting post-LVAD HRAEs in the univariate and multivariate analyses (\( P>0.05 \) for both). Instead, patients’ age and no aspirin use were statistically comparable between the groups (\( P>0.05 \) for both; Table 1). There were no statistical differences in the rates of other medications between groups except for a lower rate of angiotensin-converting enzyme inhibitors in the AF group (55% vs. 77%, \( P=0.036 \)).

**Table 2. Cox Proportional HR Analysis to Investigate the Effect of Baseline Characteristics on Post-LVAD HRAEs**

<table>
<thead>
<tr>
<th>Existence of pre-LVAD AF</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>0.91 (0.32–2.58)</td>
<td>0.87</td>
<td>0.60 (0.21–1.72)</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>1.31 (1.03–1.66)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.63 (0.87–3.06)</td>
<td>0.13</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>0.33 (0.05–2.19)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.30 (0.58–2.92)</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.02 (0.99–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>INTERMACS level</td>
<td>1.02 (0.73–1.43)</td>
<td>0.92</td>
</tr>
<tr>
<td>Preoperative continuous intravenous inotropes</td>
<td>1.16 (0.59–2.28)</td>
<td>0.68</td>
</tr>
<tr>
<td>Preoperative intra-aortic balloon pumping</td>
<td>0.86 (0.43–1.74)</td>
<td>0.68</td>
</tr>
<tr>
<td>INR &gt;3.0 at 1 month</td>
<td>2.21 (0.93–5.25)</td>
<td>0.073</td>
</tr>
<tr>
<td>INR &lt;1.5 at 1 month</td>
<td>2.02 (0.80–5.15)</td>
<td>0.14</td>
</tr>
<tr>
<td>LVAD speed at 1 month</td>
<td>1.00 (0.99–1.00)</td>
<td>0.37</td>
</tr>
<tr>
<td>No aspirin use at 1 month</td>
<td>3.21 (1.49–6.94)</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*\( P<0.05 \). AF, atrial fibrillation; HR, hazard ratio; HRAE, hemocompatibility-related adverse event. Other abbreviations as in Table 1.

**Figure 3. Rates of the breakdown of hemocompatibility-related adverse events. Groups were compared by negative binomial regression analyses. AF, atrial fibrillation; IRR, incidence rate ratio; PT, pump thrombosis.**
at 1 month were significant risk factors (P<0.05 for both; Table 2).

Breakdown of HRAEs
Event rates for each category of the HRAEs were statistically comparable between groups (Figure 3). The rates of bleeding and medically managed pump thrombosis were statistically comparable between the groups (P=0.66 and P=0.79, respectively). The rate of surgically managed pump thrombosis tended to be higher in the AF group (incidence rate ratio 3.75, 95% confidence interval 0.87–16.1, P=0.075). LVAD flow at 1 month tended to be lower in the AF group (4.4±0.5 vs. 4.8±0.6 L/min, P=0.069). The rates of major stroke and death were statistically comparable between groups (P>0.05 for both).

Propensity Score-Matched Analysis
We statistically prepared 22 background-matched patients in the AF group and 44 patients in the non-AF group patients (Supplementary Table 2). All 4 matched variables had standardized differences <0.2 (Supplementary Figure 1). C-statistics before and after background matching were 0.642 and 0.507, respectively. Survival free from HRAEs still remained statistically comparable between groups (82% vs. 77%, P=0.70; Supplementary Figure 2).

Discussion
In this study, we investigated the effect of pre-LVAD AF on HRAEs following LVAD implantation using J-MACS registry data. The main findings were: (1) 12% had AF before LVAD implantation; (2) patients in the AF group were older and had higher RAP compared with the non-AF group before LVAD implantation; (3) following LVAD implantation, most cases of pre-existing AF (73%) persisted; (4) survival free from HRAEs was comparable irrespective of the existence of pre-LVAD AF; (5) incidences of the breakdown of HRAEs were comparable between groups; and finally (6) these trends persisted in the background-matched comparison.

Prevalence of Pre-LVAD AF
Prevalence of AF before LVAD implantation was 12% in the J-MACS registry data. We should state that we excluded subjects whose underlying rhythm could not be interpreted because of the placement of pacemaker. Although the incidence of AF in HF patients can vary depending on various factors, such as the severity of HF, patient’s age, the era of observation, definition of AF (paroxysmal or persistent), and history of rhythm control therapy, the overall rate is approximately 20–50%. The relatively lower prevalence of AF in the J-MACS registry may represent a recent aggressive rhythm control strategy with catheter ablation together with antiarrhythmic medications for patients with advanced HF, targeting improvement of cardiac contractility, quality of life, and exercise performance (data not shown).

Pre-LVAD AF and Hemodynamics
Before LVAD implantation, RAP was higher in the AF group, which was not surprising because the AF group had more progressive right-sided HF. Progressive HF leads to mechanical stretch, inappropriate neurohormonal activation, and fibrosis of the atrial myocardium, all of which cause AF. Additionally, AF reduces atrial kick and ventricular filling, which further increases the RAP.

Although we did not have the hemodynamic data following LVAD implantation in this study, it is reported in another study that patients with AF had higher RAP during LVAD support. Also, the preoperative potential for right ventricular failure, as we observed in this study (i.e., elevated RAP), often worsens following LVAD implantation.

Trend in AF Following LVAD Implantation
In most cases AF persisted even after LVAD implantation. The AF observed in the current Japanese LVAD candidates (i.e., INTERMACS 2–3) may be refractory to “upstream treatment” with strong LV unloading because of progressive remodeling of the left atrium, with little potential for reversal. In other words, despite mechanical LV unloading, these patients cannot recover from the adverse effects of AF, including reduced atrial kick and increased risk of thrombus formation.

AF and HRAEs During LVAD Support
Survival free from HRAEs was comparable irrespective of the existence of pre-LVAD AF, and the trend remained in the background-matched comparison. Considering this finding, it may be reasonable to avoid unnecessarily aggressive rhythm control, which can be a high risk for patients with advanced HF and hemodynamic deterioration.

Particularly, the incidence of major stroke, which is one of the major comorbidities in Japanese LVAD patients, was statistically comparable. When we considered the CHA2DS2-VASc risk stratification score to estimate the effect of AF independently of LVAD on the development of thrombotic stroke, all candidates had at least 1 point for HF (estimated risk of stroke: 0.6% per year) and at most 7 points (estimated risk of stroke: 11.2% per year), considering that all patients were under 65 years of age.

Results of large randomized control trials, including SPAF, AFASAK, BAAAF, and CAFA, show that the estimated risk reduction with anticoagulation therapy ranges between 45% and 82%, or approximately 60%. The post-LVAD INR averaged 2.25±0.56, which is within the therapeutic range not only for HeartMate II management but also for the prevention of stroke in AF patients. Therefore, the estimated risk of stroke should decrease to approximately 0.24–4.48% per year (0.6×0.40=0.24 and 11.2×0.40=4.48). In contrast, the actual rate of major stroke in the non-AF group in this study was extremely high (~18% per year) despite no existence of AF. Considering this result, most of the thrombus formation during LVAD support may come from the device itself and not from the left atrium, irrespective of the existence of AF. In other words, stroke may be caused by device-related thrombus rather than AF.

The clinical effect of AF on LVAD patients varies in several studies, probably because of the variety of device types, the magnitude of the antiplatelet and anticoagulation therapies, and the definition of each event. Nevertheless, a recently published meta-analysis that investigated 11 cohort studies including 6,351 LVAD patients concluded that AF was not associated with overall thromboembolic, stroke, and pump thrombosis events.

Bleeding rates were comparable irrespective of AF, mainly because of comparable therapeutic parameters, including antiplatelet and anticoagulation therapies, and LVAD speed settings, between groups. Also, our team
recently proposed that the main mechanism of bleeding in LVAD patients is development of arterial venous malformations via angiogenesis and initiation of an inflammatory signal cascade, both of which may not be associated with AF.

The event rate of surgically treated pump thrombosis tended to be higher in the AF group. The precise mechanism remains uncertain, but preoperative right-sided HF in the AF group may persist following LVAD implantation (data not shown), which may reduce forward blood flow into the device and increase the risk of pump thrombus formation. Consistently, LVAD flow tended to be lower in the AF group. Post-LVAD longitudinal echocardiographic and hemodynamic assessments, as well as device parameters, would better clarify the detailed mechanism among right HF, LVAD flow, and pump thrombosis in patients with AF.

The causes of pump thrombosis are multifactorial. Particularly in patients with AF, as well as other risk factors such as advanced right ventricular failure, elevated serum creatinine level, pulmonary hypertension, high/low body mass index, narrow angle between inflow cannula and pump body, and the opening of the native aortic valve, special attention and management may be required during LVAD therapy to prevent pump thrombosis. An effort to maintain higher LVAD speed, sufficient anticoagulation therapy, and careful monitoring of the serum lactate dehydrogenase level may also be needed to maintain appropriate LVAD flow. Inotropes or adjustment of diuretics using hemodynamic and echocardiographic ramp tests may be attempted to improve right heart function.

Future Directions and Study Limitations
The existence of AF may not increase the risk of HRAEs following LVAD implantation. If LVAD implantation is scheduled, preoperative aggressive rhythm control may not be necessary to prevent HRAEs. However, the effect of AF on other outcomes, including exercise capacity and myocardial recovery, may be promising because of the improvement in right heart function. In contrast, when LVAD implantation is not yet scheduled, aggressive rhythm control may stabilize hemodynamics before bridging to surgery.

This study has several limitations. This is a Japanese multicenter study of patients with the HeartMate II LVAD, and the results may not be applicable to other countries or devices. The main finding (survival free from HRAEs) was “negative” in this study. In a small cohort such as this, statistically negative results may not necessarily indicate “similarity” and we should careful when interpreting the results. Nevertheless, we want to emphasize that this cohort was the current maximum LVAD population data in Japan. Because of the nature of a multicenter registry study, detailed data collection is difficult. Particularly, we could not obtain the original rhythm for patients with pacemakers and thus they were excluded. Nevertheless, we believe that the patients with pacing devices should be excluded, as we did in this study.

When patients with HF and AF receive pacing therapy, their cardiac function may improve with regular ventricular pacing despite residual AF. In other words, despite persistent AF, the clinical effect may be different between those with and without pacing. Furthermore, it is still controversial whether biventricular pacing or right ventricular pacing improves clinical outcomes during LVAD support.

We recently showed that right ventricular pacing improved patients’ quality of life, exercise capacity, and risk of ventricular tachyarrhythmias compared with biventricular pacing, potentially because of left ventricular suction. Therefore, those with pacing should be considered separately. Nevertheless, we should again state that the prevalence of pre-LVAD AF is likely inaccurate in this study because we excluded those who were paced.

Although it is known that the preoperative potential of right-sided HF is a risk factor for post-LVAD right-sided HF, we did not have any post-LVAD hemodynamic data in this study. We did not analyze other outcomes, including left-sided and/or right-sided HF, infection, and aortic insufficiency, and the effect of AF on these comorbidities remains uncertain. Also, therapeutic parameters at the first month were comparable between the groups, but we did not compare their long-term trends. Left atrial appendage ligation may be performed at LVAD implantation to prevent thrombotic events in some cases, but we did not have this surgical data.

Conclusions
We could not demonstrate a significant effect of the existence of preoperative AF on mortality and HRAEs following LVAD implantation from the current maximum LVAD cohort in Japan. Optimal patient selection for pre-LVAD rhythm control therapy is a future consideration.

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Supplementary Files

Please find supplementary file(s):