Organ Transplant Act in July 2010, but the number is still very low in international terms and the mean waiting period was >1,150 days at the end of June 2016. Despite this extremely long waiting time, it is almost impossible for patients with severe biventricular failure to be safely bridged to heart transplantation.

The aim of this retrospective study was to evaluate the historical improvement and limitations in the treatment of severe biventricular failure, and to provoke a discussion about heart allocation system in Japan.

Methods

Patients

Ethics committee approval was obtained for this retrospective study. Individual consent was waived. From October 2005 to August 2017, 170 patients had undergone 188 implantable continuous-flow LVAD implantations at the present institute. Of the 170 patients, 158 were supported...
with isolated LVAD, and this group of patients was named group-LVF. Those patients who initially required temporary mechanical right heart support but who later had removal of the RV assist device (RVAD) were also included in this group. The other 12 patients required long-term mechanical right heart support or continuous i.v. inotropic right heart support under continued hospitalization, and this group of patients was named group-BVF. Patient characteristics and clinical outcomes were compared between the 2 groups.

Device Selection for RVAD
The first choice of device as mechanical right heart support at the present institute was temporary extracorporeal centrifugal pumps such as Capiox (Terumo, Tokyo, Japan), Gyropump (Medtronic, Minneapolis, MN, USA), or Rotaflo (Maquet, Rastatt, Germany). After hemodynamic stabilization and the recovery of end-organ function, the patient was weaned off the temporary RVAD as far as possible, as described previously. If not possible, temporary RVAD was converted to durable RVAD such as Nipro paracorporeal pneumatic pump (Nipro, Osaka, Japan). Nipro pump was the only durable device approved in Japan to be used as RVAD. If right heart failure was so severe that the surgeon found that weaning from the temporary RVAD was not possible in 2 weeks, a durable pump was used instead of the temporary centrifugal pump from the beginning. Implantable continuous flow devices such as Jarvik2000 (Jarvik Heart, New York, NY, USA) and HVAD (Medtronic) were also used as durable RVAD. Such implantable devices were available only in a very limited number of patients as part of clinical investigations.

Statistical Analysis
Continuous variables are presented as mean±SD, and categorical variables as numbers with or without proportions. All continuous variables were checked for normality using the Shapiro-Wilk test and normal probability plot. For univariate analysis, normally distributed variables were compared using Student’s t-test, non-normally distributed variables were compared using the Mann-Whitney U-test, and categorical variables were compared using chi-squared analysis or Fisher’s exact test, as appropriate. Survival curves for group-LVF, group-BVF and Nipro biventricular assist device (BiVAD) patients were prepared using the Kaplan-Meier method and were compared using the pairwise log-rank test. We also used the Kaplan-Meier method for the simulation of survival in group-BVF. Kaplan-Meier survival curve simulation was carried out under the condition that all the patients in group-BVF who died on LVAD support >1 year after LVAD implantation had received heart transplantation at 365 days after LVAD implantation and survived thereafter.

All P-values are 2-sided, and P<0.05 was considered to indicate statistical significance. Statistical analysis was performed using JMP Pro 13.0 (SAS Institute, Cary, NC, USA).

Results
Preoperative Characteristics and Clinical Outcomes
Table 1 lists the patient characteristics. Mean patient age tended to be younger in group-BVF (34.3±11.7 years) than in group-LVF (42.3±14.8 years, P=0.0670) and there were more female patients in group-BVF (58.3%) than in group-LVF (29.8%, P=0.0403). The main etiologies of heart failure in group-BVF were idiopathic cardiomyopathy and myocarditis, and no patients had ischemic cardiomyopathy in this group. The mean Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile number was smaller in group-BVF than in group-LVF (1.5±0.7 vs. 2.6±0.7, P<0.0001), suggesting more severe preoperative conditions in group-BVF than in group-LVF. LVAD type had no apparent impact on the requirement of right heart support.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group-LVF (n=158)</th>
<th>Group-BVF (n=12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.3±14.8</td>
<td>34.3±11.7</td>
<td>0.0670</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>29.8</td>
<td>58.3</td>
<td>0.0403</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.60±0.22</td>
<td>1.53±0.20</td>
<td>0.2758</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>84</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>dHCM</td>
<td>22</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>INTERMACS profile</td>
<td>2.6±0.7</td>
<td>1.5±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Device (LVAD)</td>
<td></td>
<td></td>
<td>0.2682</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>49</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Jarvik2000</td>
<td>35</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>DuraHeart</td>
<td>33</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>EVAHEART</td>
<td>26</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HeartWare</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Data given as mean±SD, %, or n. BVF, patients who required long-term mechanical or inotropic right heart support; DCM, dilated cardiomyopathy; dHCM, dilated phase hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVF, patients with isolated left ventricular assist device.
New Heart Allocation System to Save BVAD Patients

Table 2. Group-BVF: Patient Characteristics

<table>
<thead>
<tr>
<th>Patient ID no.</th>
<th>Age (years)/sex</th>
<th>Etiology</th>
<th>LVAD</th>
<th>Right heart support</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30/F</td>
<td>Fulminant myocarditis</td>
<td>Nipro → DuraHeart</td>
<td>Nipro → Jarvik2000 RVAD</td>
<td>Died on BiVAD (539 days)</td>
</tr>
<tr>
<td>2</td>
<td>35/F</td>
<td>Fulminant myocarditis</td>
<td>Nipro → DuraHeart</td>
<td>Nipro → Jarvik2000 RVAD</td>
<td>Discharged home → HTx (884 days)</td>
</tr>
<tr>
<td>3</td>
<td>27/F</td>
<td>ARVC</td>
<td>Jarvik2000</td>
<td>Jarvik2000 RVAD</td>
<td>Discharged home → HTx (1,245 days)</td>
</tr>
<tr>
<td>4</td>
<td>36/M</td>
<td>Post-HTx vasculopathy</td>
<td>DuraHeart → Nipro</td>
<td>Inotropes → EC-centrifugal RVAD → Nipro RVAD</td>
<td>Died on BiVAD (225 days)</td>
</tr>
<tr>
<td>5</td>
<td>24/M</td>
<td>dHCM</td>
<td>DuraHeart</td>
<td>EC-centrifugal RVAD → Nipro RVAD</td>
<td>Died on BiVAD (448 days)</td>
</tr>
<tr>
<td>6</td>
<td>32/M</td>
<td>Fulminant myocarditis</td>
<td>EVAHEART</td>
<td>EC-centrifugal RVAD → Jarvik2000 RVAD</td>
<td>Died on BiVAD (553 days)</td>
</tr>
<tr>
<td>7</td>
<td>13/F</td>
<td>Danon’s disease</td>
<td>HVAD</td>
<td>HVAD RVAD</td>
<td>Discharged home → HTx (826 days)</td>
</tr>
<tr>
<td>8</td>
<td>45/F</td>
<td>dHCM</td>
<td>Jarvik2000</td>
<td>Inotropes</td>
<td>HTx (801 days)</td>
</tr>
<tr>
<td>9</td>
<td>40/M</td>
<td>dHCM</td>
<td>Jarvik2000</td>
<td>EC-centrifugal RVAD</td>
<td>HTx (310 days)</td>
</tr>
<tr>
<td>10</td>
<td>59/F</td>
<td>DCM</td>
<td>Jarvik2000</td>
<td>Inotropes</td>
<td>Died on LVAD+inotropes (141 days)</td>
</tr>
<tr>
<td>11</td>
<td>42/F</td>
<td>Fulminant myocarditis</td>
<td>HeartMate II</td>
<td>EC-centrifugal RVAD → Nipro RVAD</td>
<td>Died on BiVAD (250 days)</td>
</tr>
<tr>
<td>12</td>
<td>28/M</td>
<td>dHCM</td>
<td>DuraHeart</td>
<td>Inotropes → Nipro RVAD</td>
<td>Died on BiVAD (1,407 days)</td>
</tr>
</tbody>
</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; BiVAD, biventricular assist device; EC, extracorporeal; HTx, heart transplantation; RVAD, right ventricular assist device. Other abbreviations as in Table 1.

Table 3. Successful Bridge to HTx

<table>
<thead>
<tr>
<th></th>
<th>Group-LVF (n=158)</th>
<th>Group-BVF (n=12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>57 (36.1)</td>
<td>5 (41.7)</td>
<td>0.6981</td>
</tr>
<tr>
<td>Waiting time at status 1 (days)</td>
<td>975±274</td>
<td>703±397</td>
<td>0.0441</td>
</tr>
<tr>
<td>Rank on the waiting list†</td>
<td>8.3±21.7</td>
<td>34.2±55.6</td>
<td>0.0325</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). †At the time of heart transplantation. Abbreviations as in Tables 1,2.

Table 2 lists the characteristics and the clinical outcomes of the 12 patients in group-BVF. Temporary RVAD with extracorporeal centrifugal pumps were used as initial RVAD in 4 patients (patients 5,6,9,11). After attempts to wean off RVAD had failed, the temporary RVAD was converted to Nipro RVAD in 2 patients and to Jarvik2000 RVAD in 1. The other patient was successfully bridged to heart transplantation with LVAD and temporary RVAD (patient 9). Two patients with fulminant myocarditis (patients 1,2), who were referred to the present institution under veno-arterial extracorporeal membrane oxygenation support with arrested heart, were implanted with Nipro BiVAD as the initial operation. No cardiac functional recovery was observed even after inflammation of the myocardium had resolved, and Nipro BiVAD was converted to implantable BiVAD with DuraHeart LVAD and Jarvik2000 RVAD.7–9 Two patients with severe right heart failure: 1 due to arrhythmogenic RV cardiomyopathy (patient 3) and 1 due to secondary cardiomyopathy (Danon’s disease, patient 7) were implanted with implantable BiVAD (Jarvik2000 BiVAD and HVAD BiVAD, respectively) at the initial operation.8,9,10,11 Four patients (patients 4,8,10,12) required continuous injection of inotropes although they were able to be separated from cardiopulmonary bypass during the initial operation. One of them later developed end-organ dysfunction and was implanted with the Nipro RVAD (patient 12). One patient with cardiac allograft vasculopathy (patient 4) underwent DuraHeart LVAD implantation, but heart failure remained because of low LVAD flow due to right heart failure and small LV chamber. LVAD inflow was changed from LV apex to left atrium, and the LVAD was exchanged to extracorporeal device. The patient could not be weaned off cardiopulmonary bypass without mechanical right heart support during this operation.

Heart Transplantation

Of the 170 patients, 57 in group-LVF and 5 in group-BVF were successfully bridged to heart transplantation (Table 3). Mean waiting time at status 1 (active waiting duration on Japan Organ Transplantation Network waiting list under mechanical circulatory support or inotropic support) was significantly shorter in group-BVF than in group-LVF (703±397 days vs. 975±274 days, P=0.0441). Patients in group-BVF received heart transplantation when they were at a significantly lower rank on the waiting list (34.2±55.6 vs. 8.3±21.7, P=0.0325). This means that many patients in group-BVF received heart transplantation from more marginal donors who patients at the higher rank of the waiting list had rejected, compared with
2000 to October 2010 (n=16) was compared with that of patients in group-BVF (Figure 2). One- and 2-year survival in the Nipro BiVAD group were 12.5% and 0%, respectively, whereas 1- and 2-year survival in group-BVF were 75.0% and 50.0%, respectively. Survival in group-BVF was significantly higher than that in the Nipro BiVAD group (P=0.0002).

Poor Outcome Compared With LVAD Patients

Biventricular Failure Patients

Improved Survival

As a historical control, survival of patients who underwent Nipro BiVAD support from May 2000 to October 2010 (n=16) was compared with that of patients in group-BVF (Figure 2). One- and 2-year survival in the Nipro BiVAD group were 12.5% and 0%, respectively, whereas 1- and 2-year survival in group-BVF were 75.0% and 50.0%, respectively. Survival in group-BVF was significantly higher than that in the Nipro BiVAD group (P=0.0002).

Figure 1. Survival after heart transplantation (HTx) in patients with isolated left ventricular assist device (group-LVF) and in patients who required long-term mechanical or inotropic right heart support (group-BVF).

Figure 2. Survival after left ventricular assist device (LVAD) implantation in patients with Nipro biventricular assist device (BiVAD) and in patients who required long-term mechanical or inotropic right heart support (group-BVF).

Figure 3. Survival after left ventricular assist device (LVAD) implantation in patients with isolated LVAD (group-LVF) and in patients who required long-term mechanical or inotropic right heart support (group-BVF). Green circle, heart transplantation; red circle, death after heart transplantation.

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Group-LVF</th>
<th>Group-BVF</th>
<th>Nipro BiVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-LVF</td>
<td>57</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Group-BVF</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Group-LVF</th>
<th>Group-BVF</th>
<th>Nipro BiVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-LVF</td>
<td>158</td>
<td>87</td>
<td>67</td>
</tr>
<tr>
<td>Group-BVF</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Group-LVF</th>
<th>Group-BVF</th>
<th>Nipro BiVAD</th>
</tr>
</thead>
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<tr>
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<td>67</td>
</tr>
<tr>
<td>Group-BVF</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>
transplantation in Japan was longer than 2 years, >2 years even though the average waiting time for heart
BiVAD implantation were devastating. No patient survived
thereafter (Figure 4). Death after heart transplantation was
counted as it was. There was no significant difference in
survival between the groups (P=0.2424).

Discussion
In the present study we found that the survival of the patients who underwent BiVAD implantation significantly
improved in the era of implantable continuous-flow devices
compared with that in the era of paracorporeal pulsatile
device. The survival of BiVAD patients, however, was still
significantly worse than that of isolated LVAD patients.
Waiting time for heart transplantation was significantly
shorter for BiVAD patients than for isolated LVAD
patients because BiVAD patients accepted more marginal
donors than LVAD patients. Nevertheless, survival after
heart transplantation was equivalent in the 2 groups.

There are several reasons for the improvement in survival
of the patients who underwent BiVAD implantation. One
of the reasons is obviously the improvement in device
technology. In the 6th annual report of INTERMACS
published in 2014, Kirklin et al reported significantly
improved survival in patients who were implanted with
continuous-flow device compared with patients who were
implanted with pulsatile device, both as LVAD and
BiVAD. In the present study, clinical outcomes of Nipro
BiVAD implantation were devastating. No patient survived
>2 years even though the average waiting time for heart
transplantation in Japan was longer than 2 years, and therefore, no patient was successfully bridged to heart
transplantation with the Nipro BiVAD. Although the right
heart supports used in patients in group-BVF varied, consisting of the Nipro pump, continuous-flow pumps,
extracorporeal centrifugal pumps, and inotropes (Table 2), all the patients in group-BVF were implanted with
implantable continuous-flow pumps as LVAD, and this
was a great advantage over the Nipro BiVAD.

Another reason is the utilization of continuous-flow
implantable pumps as RVAD. Five of 12 patients in
group-BVF were implanted with continuous-flow BiVAD
as part of clinical investigations. All 5 patients survived
longer than 1 year, and 3 of them survived longer than 2
years and were successfully bridged to heart transplantation. The clinical use of continuous-flow implantable BiVAD
was first reported by Frazier et al in 2004; they used the
Jarvik2000 in a salvage procedure for acute postoperative
right-sided heart failure. Although the patient died 12 days
after BiVAD implantation because of sepsis and hepatic
failure, they suggested that timelier implantation of the
BiVAD might be lifesaving. Since then, other investigators,
including us, have reported success with short- and long-
term implantable BiVAD support. Widespread use of
continuous-flow implantable BiVAD, however, is
limited because of technical and logistic challenges that
add to the complexity of device management. One of these
challenges is the anatomic limitation. The difficulty of
accommodating 2 pump housings and opposing outflow
canals has traditionally discouraged the use of BiVAD
therapy. Another substantial limitation of BiVAD therapy
is the need for duplicate equipment: 2 controllers, 4 active
batteries, and an additional backup power supply, all of
which constitute a physical and operational burden. Like-
wise, the need to manage and manipulate multiple con-
trollers increases the complexity of dual-device training.
Additionally, and the most importantly, there also exists
the reimbursement issues of the second pump. The use of
implantable continuous-flow device as an RVAD is not
approved in Japan nor in the USA, or in other European
countries.

Another possible explanation for improved survival in
BiVAD patients is the strategy in heart transplantation.
The mean waiting time for donor heart in group-BVF was
703±397 days, which was significantly shorter than that in
group-LVF (975±274 days, P=0.0441; Table 3). In Japan,
all the patients who are waiting for heart transplantation
with inotropic support, LVAD support or BiVAD support
are listed as “status 1” and are not distinguished by more precise clinical conditions. All the patients in status 1 are sorted only by the time on the list. Therefore, the only possible way to make the waiting time shorter than for other patients is to accept the marginal donor heart that is refused by the patients at a higher rank on the waiting list. The mean rank on the waiting list at the time of heart transplantation in group-BVF and LVF was 34.2±55.6 and 8.3±21.7, respectively, and the difference was significant (P=0.0325). This means that patients in group-BVF underwent heart transplantation when they were at a significantly lower rank on the waiting list than patients in group-LVF. The use of so-called marginal donors is now generally accepted and widespread. Historically, the upper age limit for heart donation was 40–45 years, but there is no definitive reason why selected older donor hearts cannot be used if structurally normal.18 Prieto et al reported that there was no difference in long-term survival between recipients of older hearts and those who received hearts from younger donors and suggested that donors should not be excluded based solely on age.20 Also in the present study, the post-transplant survival in group-BVF was not significantly inferior to that of group-LVF, although the patients in group-BVF were considered to have received hearts from more marginal donors than in group-LVF. It is also true, however, that when utilizing marginal donor hearts, we must carefully consider donor and recipient characteristics to minimize deaths on the waiting list and to maximize graft survival outcomes. Fudim et al reported worse graft survival with utilization of marginal donor organs compared with utilization of standard organs.19 Nevertheless, when these transplant recipients were compared with patients who remained on optimal medical therapy, survival and quality of life were significantly improved.20,21

The fact that the survival of patients with biventricular failure might be improved (at least partly) by shortening the waiting time for heart transplantation prompted the next clinical question: what if these patients could receive heart transplantation even earlier? Considering that the patients with biventricular failure who die ≤1 year after LVAD implantation may be too sick to undergo heart transplantation, we carried out Kaplan-Meier survival curve simulation under the condition that all the patients in group-BVF who died on LVAD support >1 year after LVAD implantation had received heart transplantation at 365 days after LVAD implantation and survived thereafter. On this survival curve simulation, no significant difference was seen in survival between the 2 groups. This suggests that if the patients with severe biventricular failure could receive heart transplantation 1 year after LVAD implantation (not from marginal donors but from standard donors), survival in biventricular failure patients would be as good as that in isolated LVAD patients. There are a few options to enable biventricular failure patients to receive heart transplantation at 1 year. For example, the simplest way is to set a new status over “status 1” that gives priority to BiVAD patients who are waiting for >1 year. Patients in this new status have top priority to receive heart transplantation, and heart transplantation may be available for them around 1 year after BiVAD implantation. Another option is to give triplicate waiting points for BiVAD patients. Given that the average waiting time in status 1 was 1,157 days in 2016 in Japan, a patient with BiVAD could expect a donor heart in approximately 385 days under this system.

**Study Limitations**

We recognize several limitations in the present study, including those related to a single-center retrospective analysis. The number of patients in this study was relatively low, limiting statistical power. Because of the small number, we needed to analyze patients on different types of right heart support in the same cohort. Although it is difficult to conduct this kind of study in a prospective way, it is necessary to re-evaluate these data in a multicenter study. The setting of heart transplantation in Japan, especially the waiting time, is totally different from that in other countries. Therefore, the suggestion of the new allocation system could be applied only in Japan. We recognize that the simulation method we used in this study is too simple, and that the simulation does not precisely predict the survival of patients in the real world. More precise simulation requires large-scale data on patient survival after heart transplantation, which we do not have. Moreover, in the suggestion of the new allocation system, we did not consider the negative impact on the survival of isolated LVAD patients if we give the priority for heart transplantation to the BiVAD patients. We believe, however, that such data as presented in this study could trigger a discussion about the heart allocation system in this country.

**Conclusions**

Survival of those with severe right heart failure after LVAD implantation was still very poor compared with that of isolated LVAD patients, although it significantly improved compared with that of paracorporeal pulsatile BiVAD patients. A new heart allocation system that allows severe right heart failure patients to receive heart transplantation at around 1 year would enable rescue of the patients with severe right heart failure.

**Disclosures**

The authors declare no conflicts of interest.

**References**


