A Novel Extracorporeal Continuous-Flow Ventricular Assist System for Patients With Advanced Heart Failure
— Initial Clinical Experience —

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**Background:** Bridge-to-decision (BTD) devices providing temporary mechanical circulatory support should be introduced to patients with advanced heart failure. This study evaluated the effectiveness and safety of a BTD device comprising an innovative extracorporeal continuous-flow temporary ventricular assist device (VAD) driven by a novel hydrodynamically levitated centrifugal pump.

**Methods and Results:** Nine patients, comprising 3 with dilated cardiomyopathy, 3 with fulminant myocarditis, and 3 with ischemic heart disease, and 6 males, whose mean age was 47.7±8.1 years, were enrolled into the study. Six patients had Interagency Registry for Mechanically Assisted Circulatory Support profile 1, and 3 were profile 2. The primary endpoint was a composite of survival free from device-related serious adverse events and complications during circulatory support. Eight patients received left ventricular support, of whom 3 received concomitant right ventricular support using extracorporeal membrane oxygenation circuits, as a consequence of severe respiratory failure. One patient with fulminant myocarditis received biventricular support using the novel VAD system. After 19.0±13.5 days, 3 patients were weaned from circulatory support, because their native cardiac function recovered, and 6 patients required conversion to a durable device as a bridge-to-transplantation. One patient had non-disabling ischemic stroke episodes, and no patients died.

**Conclusions:** This novel extracorporeal VAD system with a hydrodynamically levitated centrifugal pump can safely and successfully bridge patients with advanced heart failure to subsequent therapeutic stages.

**Key Words:** Advanced heart failure; Bridge-to-decision; Bridge-to-transplantation; Mechanical circulatory support; Ventricular assist device
Novel Ventricular Assist System as a BTD Device

Written informed consent was obtained from the enrolled patients or their families at study enrollment.

Study Subjects and Sample Size
The study subjects comprised patients with advanced heart failure or refractory cardiogenic shock who were unresponsive to conventional medical and/or surgical treatments or mechanical circulatory support, including intra-aortic balloon pumps (IABPs), venoarterial extracorporeal membrane oxygenation (ECMO), percutaneous cardiopulmonary support (PCPS), and other VAD systems, and were eligible for rescue therapy using VADs as BTD or bridge-to-recovery strategies. Detailed information of inclusion criteria and exclusion criteria of this study were previously described (Supplementary Table 1).

A total of 9 patients were enrolled in the study. The study was planned using Simon’s minimax 2-stage design, as described previously.13 Briefly, the hypothesis to be tested was H0: P<P0 vs. H1: P>P1, where P was the probability of mortality at 30 days, a false-positive rate (α) ≤10% and a false-negative rate (ß) ≤10% were accepted, P0 was set at 50%, and P1 was set at 90%. Within these constraints, 4 patients were enrolled for the first stage. The study would stop if ≤2 patients survived, would continue until a total of 9 patients were accrued, and be declared a success if >7 patients survived.

Endpoints
The study’s primary endpoint was a composite of survival free from device-related serious adverse events and complications during device support. Regarding left ventricular (LV) assistance, withdrawal of the BTD device as a consequence of native LV functional recovery or exchange to a durable implantable VAD as a bridge-to-transplantation within 30 days after implantation was considered a study
success. Regarding right ventricular (RV) assistance, BTD device withdrawal as a consequence of native RV functional recovery within 30 days after implantation was considered a study success.

The secondary endpoints included the VAD support period, and changes in the brain natriuretic peptide (BNP) levels, LV ejection fraction (LVEF), and LV diastolic dimension (LVDd) at 7 days after device implantation and on the day of device withdrawal. To evaluate the effect of the device on end-organ function, changes in the creatinine (Cre), total bilirubin (T-Bil), and aspartate aminotransferase (AST) levels were assessed before and after VAD implantation. Changes in lactate acid dehydrogenase (LDH) and indirect bilirubin (I-Bil) during the device support period were also assessed to determine the occurrence of hemolysis.

**BTD Device**

The BTD device has been described in detail previously. Briefly, the VAD system comprises a disposable centrifugal flow pump with a hydrodynamically levitated bearing (BR16010), cannulae, an extracorporeal circuit, and metallic connectors (Figure 1). Flexible polyvinyl chloride (PVC) tubes (1/2 inch diameter) with hard tips are used for the inflow cannula (Figure 1A), a 12-mm diameter vascular prosthesis attached to a flexible PVC tube is used for the outflow cannula (Figure 1B), and custom-made metallic connectors are used to connect the cannulae and the extracorporeal circuit (Figure 1C). The extracorporeal circuit consists of a PVC tube (70 cm long and 3/8 inch wide) coated with T-NCVC® heparin (Toyobo, Osaka, Japan) (Figure 1D). The pump’s priming volume is 18 mL (Figure 1E). The impeller is embedded in a stationary casing and it rotates with a narrow clearance at both ends (Figure 1F). The blood film in this space serves as the oxygenation; P-LVAD, paracorporeal left ventricular assist device; T-Bil, total bilirubin; TCS, temporary circulatory support.

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**Table 1. Patients’ Baseline Demographic and Clinical Data**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Etiology</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>INTERMACS profile</th>
<th>Preoperative MCS Devices</th>
<th>Duration (days)</th>
<th>LVDd (mm)</th>
<th>LVEF (%)</th>
<th>T-Bil (mg/dL)</th>
<th>Cre (mg/dL)</th>
<th>BNP (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>56</td>
<td>M</td>
<td>AMI</td>
<td>170</td>
<td>60</td>
<td>1.69</td>
<td>1 (TCS)</td>
<td>C-ECMO</td>
<td>1 (TCS)</td>
<td>7</td>
<td>42</td>
<td>3</td>
<td>0.77</td>
<td>773.8</td>
</tr>
<tr>
<td>Case 2</td>
<td>54</td>
<td>F</td>
<td>DCM</td>
<td>158</td>
<td>56.4</td>
<td>1.57</td>
<td>2 (TCS)</td>
<td>None</td>
<td>None</td>
<td>11</td>
<td>64</td>
<td>10</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Case 3</td>
<td>50</td>
<td>M</td>
<td>OMI</td>
<td>184</td>
<td>86.9</td>
<td>2.1</td>
<td>2 (TCS)</td>
<td>P-LVAD</td>
<td>24</td>
<td>70</td>
<td>7</td>
<td>1.6</td>
<td>0.55</td>
<td>663</td>
</tr>
<tr>
<td>Case 4</td>
<td>48</td>
<td>F</td>
<td>DCM</td>
<td>160</td>
<td>40</td>
<td>1.37</td>
<td>2 (TCS)</td>
<td>IABP</td>
<td>1</td>
<td>66</td>
<td>20</td>
<td>0.7</td>
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<tr>
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<td>M</td>
<td>AMI</td>
<td>182</td>
<td>80</td>
<td>2.01</td>
<td>1 (TCS)</td>
<td>LVAD-ECMO</td>
<td>18</td>
<td>52</td>
<td>10</td>
<td>3.4</td>
<td>1.1</td>
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<td>Myocarditis</td>
<td>164</td>
<td>66</td>
<td>1.72</td>
<td>1 (TCS)</td>
<td>P-ECMO</td>
<td>1</td>
<td>47</td>
<td>8</td>
<td>0.7</td>
<td>0.77</td>
<td>392.6</td>
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<tr>
<td>Case 7</td>
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<td>Myocarditis</td>
<td>178</td>
<td>70</td>
<td>1.87</td>
<td>1 (TCS)</td>
<td>P-ECMO</td>
<td>2</td>
<td>52</td>
<td>5</td>
<td>1.2</td>
<td>3.94</td>
<td>226</td>
</tr>
<tr>
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<td>DCM</td>
<td>175</td>
<td>80</td>
<td>1.96</td>
<td>1 (TCS)</td>
<td>P-ECMO</td>
<td>1</td>
<td>62</td>
<td>5</td>
<td>1.7</td>
<td>1.57</td>
<td>471.9</td>
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<tr>
<td>Case 9</td>
<td>30</td>
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<td>Myocarditis</td>
<td>146</td>
<td>40</td>
<td>1.28</td>
<td>1 (TCS)</td>
<td>IABP</td>
<td>1</td>
<td>38</td>
<td>5</td>
<td>1</td>
<td>0.59</td>
<td>547.1</td>
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</tbody>
</table>

AMI, acute myocardial infarction; BNP, brain natriuretic peptide; BSA, body surface area; C-ECMO, central extracorporeal membrane oxygenation; CHDF, continuous hemodiafiltration; Cre, creatinine; DCM, dilated cardiomyopathy; F, female; IABP, intra-aortic balloon pumps; INTERMACS, interagency registry for mechanically circulatory support; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; M, male; MCS, mechanical circulatory support; OMI, old myocardial infarction; P-ECMO, peripheral extracorporeal membrane oxygenation; P-LVAD, paracorporeal left ventricular assist device; T-Bil, total bilirubin; TCS, temporary circulatory support.

**Surgical Procedures and Management of the Ventricular Assist System**

All of the surgical procedures were performed through a median sternotomy under a cardiopulmonary bypass. To implant the left VAD (LVAD), the outflow cannula was anastomosed to the ascending aorta, and the inflow cannula was anastomosed to the LV apex. The extracorporeal circuit was then connected to the pump and placed between the inflow and outflow cannula. To implant the right VAD (RVAD), the inflow cannula was placed at the RV apex, and the outflow cannula was anastomosed to the main pulmonary artery. If there was no surgical bleeding, heparin infusions began 24 h after surgery to maintain the activated partial thromboplastin time within 50–60 s. Aspirin (100 mg daily) and warfarin were introduced 24 h after surgery, and the warfarin dose was adjusted to maintain a target international normalized ratio of 3. Heparin infusion was then replaced by oral aspirin and warfarin.

**Statistical Analyses**

The continuous variables are expressed as the means and the standard deviations (SDs) or as the medians and the interquartile ranges (IQRs), as appropriate. The categorical variables are expressed as counts and frequencies. Comparisons between groups were performed using unpaired t-tests for normally distributed data, or the Mann-Whitney U-test for non-normally distributed data. The statistical analyses were performed using JMP software, version 13 (SAS Institute Inc., Cary, NC, USA).

**Results**

Four patients were enrolled to participate in the first stage of the study in accordance with the 2-stage design. As all of these patients survived >30 days, 5 additional patients were enrolled to participate in the second stage of the study. The first patient was enrolled on 6 October 2017, and the last patient was enrolled on 8 March 2018. Table 1 presents the patients’ baseline demographic and clinical data. All of the patients were Interagency Registry for
Mechanically Assisted Circulatory Support (INTERMACS) profiles 1 and 2 at enrollment, and 8 patients had received temporary circulatory support, including IABPs and/or PCPS, at study enrollment. All laboratory data were obtained while patients were on temporary mechanical circulatory support. Figure 2 provides an overview of the statuses of the study subjects at the time of enrollment, the devices used, and the outcomes. Table 2 provides detailed data describing the clinical parameters and each enrolled patient’s course, including their therapeutic strategies and outcomes. Five patients received LV support and 1 patient received biventricular support using the BTD device. The 3 remaining patients who had critical respiratory dysfunction caused by severe pulmonary congestion received LV support using the BTD device concomitant with RV support using an RVAD and a conventional ECMO circuit (RVAD-ECMO). Five patients with LVADs and 1 patient with a LVAD concomitant with a RVAD-ECMO could not be weaned from mechanical circulatory support, and they received an implantable durable LVAD as a bridge-to-transplantation. Two patients with LVADs concomitant with RVAD-ECMOs and 1 patient with a biventricular support assist device were successfully weaned from the VADs, because their native cardiac function recovered. The mean VAD support period was 19.0 ± 13.5 days (range, 9–48 days), and during the study period that included 7

| Table 2. Patients’ Clinical Parameters and Each Enrolled Patient’s Course, Including Therapeutic Strategies and Outcomes |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Operative time (min) | Bypass time (min) | Initial support strategies | Support time (days) | Pump speed (rpm) | Pump flow (L/min) | PCWP (mmHg) | PAP (mmHg) | RAP (mmHg) | CI (L/min⁻¹/m⁻²) | Adverse events | Outcome |
| Case 1 | 251 | 102 | LVAD | 21 | 3,400 | 4.15 | 4 | 23/9 (13) | 4 | 2.54 | Cerebral infarction | BTB |
| Case 2 | 274 | 142 | LVAD | 11 | 3,000 | 3.67 | – | 30/16 (22) | 10 | 2.7 | Cannula injury | BTB |
| Case 3 | – | – | LVAD | 10 | 4,000 | 5.24 | – | 28/12 (18) | 8 | 2.7 | None | BTB |
| Case 4 | 164 | 52 | LVAD | 13 | 3,030 | 3.51 | 9 | 30/15 (20) | 8 | 2.8 | None | BTB |
| Case 5 | 89 | – | LVAD | 34 | 4,810 | 5.18 | – | 18/11 (15) | 9 | 2.5 | None | BTB |
| Case 6 | 251 | 110 | BiVAD (BR16010) | 7 | 3,900 | 5.00 | – | 20/11 (14) | 8 | 3 | None | BTR |
| Case 7 | 174 | 63 | LVAD (BR16010) + RVAD-ECMO | 9 | 3,210 | 4.20 | – | 16/13 (14) | 5 | 2.1 | Symptomatic epilepsy | BTR |
| Case 8 | 288 | 100 | LVAD (BR16010) + RVAD-ECMO | 16 | 3,330 | 3.45 | – | 21/14 (16) | 7 | 2.1 | Cardiac tamponade | BTR |
| Case 9 | 211 | 78 | LVAD (BR16010) + RVAD-ECMO | 48 | 3,020 | 3.52 | 6 | 18/12 (14) | 12 | 2.87 | Cardiac tamponade | BTB |

BiVAD, biventricular assist device; BTB, bridge-to-bridge; BTR, bridge-to-recovery; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; LVAD, left ventricular assist device; RAP, right atrial pressure; RVAD, right ventricular assist device.

Figure 2. Overview of how patients were enrolled. The statuses of the patients at study enrollment, the initial form of ventricular assist device therapy, and the outcomes are shown. BiVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; i-LVAD, implantable left ventricular assist device; LVAD, left ventricular assist device; RVAD, right ventricular assist device; VA, venoarterial; VAD, ventricular assist device.
days after device removal, 1 patient experienced 2 non-disabling ischemic stroke episodes, and none of the patients died. Regarding other device- or surgery-related complications, 2 patients developed cardiac tamponade that required chest reopening, and a cannula injury was detected in 1 patient that probably occurred when the cannula and circulatory circuit were being connected using the metallic connectors. With respect to hemolysis, values of LDH and I-Bil during the support period are shown in Supplementary Table 2. Although there was elevation in LDH in some cases early after conversion or implantation of a VAD, the values decreased with time, and there are no clinically meaningful elevations suggesting occurrence of hemolysis.

Figure 3 presents the changes in the BNP levels, LVEF, and LVDd. The median BNP level decreased significantly from 547.1 (IQR, 309–875) pg/mL at study enrollment to 278.7 (IQR, 185–391) pg/mL at VAD removal. The mean LVDd decreased significantly from 54.6±11.0 mm at study enrollment to 44.9±11.1 mm at 7 days post-VAD implantation, with no further decreases at VAD removal. The median LVEF increased significantly from 8% (IQR, 5–15%) at study enrollment to 15% (IQR, 15–37.5) at VAD removal. BNP, brain natriuretic peptide; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction.

BTD therapy using our novel extracorporeal CF temporary VAD system and newly developed centrifugal flow blood pump, is a promising approach for patients with acutely deteriorating advanced heart failure. All of the enrolled patients with INTERMACS profiles 1 or 2 were successfully bridged to subsequent therapeutic stages, which included weaning them from the VADs as a consequence of native cardiac recovery and conversion to a durable implantable LVAD as a bridge-to-transplantation. Non-disabling strokes occurred in 1 patient; however, this patient was successfully bridged to a durable LVAD after 21 days of support. No other major critical adverse events occurred during support for a total of 171 days (mean, 19±13.5 days), except for cardiac tamponade.

VAD therapy for patients with critical conditions is always challenging. The prognoses for patients with lower INTERMACS profiles, for example, profile 1, are worse than those for patients with higher INTERMACS profiles after VAD implantation. Rescuing patients with critical
after implantation.

In addition to the system’s hemodynamic reliability and lower thrombogenicity, the small console is an important practical feature of this device. For patient transportation, the frame has wheels and a small turning circle, and the console itself, which weighs only 8 kg, is easily detached from the frame and placed on a bed or stretcher. The internal battery, which remains charged for ~60 min, should contain sufficient energy to enable patient transportation in different clinical settings. The portability of this device is also another clinical superiority compared to other conventional VAD systems such as NIPRO VAD.

The device’s lowest rotational speed of 3,000 rpm caused some inconvenience when we performed the LVAD off/weaning tests, because the device can provide almost full circulatory support at this rotational speed, depending on the patient’s size, and it is difficult to evaluate native cardiac function during these tests. However, during LVAD off/weaning tests, we clamp the outflow side of the circuit to restrict the blood flow volume, and because the blood flow volume is clearly indicated on the console’s screen, fine adjustments can be made during these tests.

This study’s design is an important aspect of this investigation. Simon’s minimax 2-stage design, which was adapted for this study, is often applied to phase II clinical studies that evaluate the safety and efficacy of targeted treatments in single-arm trials. The study’s design involved separating the patients into 2 groups or stages, and as the efficacy of the targeted treatment was greater than the predetermined threshold after the completion of the first
stage, the second stage proceeded. In the current study, 4 patients were enrolled to participate in the first stage, followed by 5 patients in the second stage. Because the 2-stage design is usually applied to clinical trials of cancer treatments, we propose that this design could be applied to evaluate the efficacy of medical devices in critically ill patients.

The study’s limitations include its implementation at a single center, and the relatively small sample size. We calculated the number of study subjects required based on Simon’s minimax 2-stage design, as described in the methods section. On the basis of the current study’s findings, large scale, multicenter, prospective post-marketing surveillance studies, not only for LVAD use, but also for RVAD use, are recommended.

In conclusion, BTD strategies that involved a novel extracorporeal CF ventricular assist system and a hydrodynamically levitated centrifugal pump (BR16010), safely and successfully bridged patients with advanced heart failure to their next therapeutic stages. The current device can be used as a LVAD and a RVAD, which allows it to be used on patients with different types of advanced heart failure. We plan to use this device as a portable ECMO system in the future.

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Disclosures
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IRB Information
National Cerebral and Cardiovascular Center Institutional Review Board; Reference Number: NCVC-BTD_01.

References

Supplementary Files
Please find supplementary file(s):