Change of Coronary Flow by Continuous-Flow Left Ventricular Assist Device With Cardiac Beat Synchronizing System (Native Heart Load Control System) in Acute Ischemic Heart Failure Model

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Background: A novel control system for the EVAHEART left ventricular assist device (LVAD), known as the Native Heart Load Control System (NHLCS), can change the device's rotational speed (RS) in synchrony with the heartbeat. The system enhanced coronary flow (CoF) with the counter-pulse mode in normal goats' hearts, so we examined the change in CoF in goats with acute ischemic heart failure (HF).

Methods and Results: We studied 14 goats (56.1±6.9 kg) with acute ischemic HF induced by coronary microsphere embolization. We installed EVAHEART and ran the device in 4 modes [continuous support, circuit-clamp, counter-pulse (raise RS in diastole), and co-pulse (raise RS in systole)] with 50% or 100% bypass in each mode. In comparison with the circuit-clamp mode, CoF was 121.0±14.1% in the counter-pulse mode and 102.9±7.9% in the co-pulse mode, whereas it was 113.5±10.6% in the continuous mode, with 100% bypass (P<0.05). The same difference was confirmed with 50% bypass. The results indicated that a LVAD in an acute ischemic heart enhanced CoF, and that CoF was greater in the counter-pulse mode and smaller in the co-pulse mode relative to the continuous mode.

Conclusions: By using NHLCS to change CoF, recovery of native heart function with a LVAD has a better prognosis. (Circ J 2013; 77: 995–1000)

Key Words: Acute ischemic heart failure; Coronary flow; Left ventricular assist devices; Native Heart Load Control System

Patients with severe heart failure (HF) are treated with a multidisciplinary approach of medical management, including left ventricular assist device (LVAD) and heart transplantation, and the prognosis has tremendously improved these days. But because of the scarcity of donor hearts available in Japan, the number of patients receiving LVAD is rapidly increasing. So, there is an urgent need to find methods to improve the course of LVAD patients, especially aiming for a ‘bridge to recovery (BTR)’ with restoration of native heart function.5-7

Needless to say, now is the time for continuous flow (cf) LVAD. By virtue of its small size, it can be installed inside the body, allowing patients to be discharged from hospital. The risk of infection is considered small. The favorable clinical outcomes reported thus far are a promising sign.8 Many reports have compared the clinical outcomes or effects on circulatory dynamics between pulsatile and cf-LVAD.8-29

We think that the merit of pulsatile LVADs to provide physiological circulation cannot be completely denied. We therefore developed a novel driving system, the Native Heart Load Control System (NHLCS), for cf-LVADs. With this system, we can drive the cf-LVAD in synchrony with the cardiac beat. Such a pulsatile driving technique had not been tried or discussed before our group’s recent report.30-36 Using this system in normal goats’ hearts, we found that coronary flow (CoF) could be altered according to the control mode.31 If we can achieve strong CoF by controlling the rotation of the cf-LVAD, in synchrony with the cardiac beat, we may have a...
better chance of improving the function of the LVAD-supported native heart. For clinical situations, however, it is necessary to prove the fact in models of HF. So here we report that we could change CoF using our novel control method in a goat model of acute ischemic HF.

Methods

Animals
We studied 14 goats (56.1±6.9 kg) with acute ischemic HF induced by coronary microsphere embolization. The animals used in this study were maintained in accordance with the guidelines of the Committee on Animal Studies at the National Cerebral and Cardiovascular Center. This study was approved by the National Cerebral and Cardiovascular Center Animal Investigation Committee.

Surgical Protocol: Implantation of LVAD
The animals were tranquilized with ketamine hydrochloride (8–10 mg/kg IM), and then intubated and mechanically ventilated. Anesthesia was maintained with isoflurane (1–3 vol/100 ml in oxygen). The animals were draped and surgically prepared in right lateral recumbency. A left thoracotomy was performed and the 5th costal bone was resected. We preserved the left internal thoracic artery and vein to measure arterial pressure (AoP) and central venous pressure (CVP), and also to collect data for blood gas analysis. Blood flow in the ascending aorta, LVAD, and coronary artery (left main trunk, LMT) was measured by flow meter: electromagnetic

flow meter (16–22 mm diameter, EMF-1000, Nihon Kohden, Tokyo, Japan) for the aorta and ultrasonic flow meters (3–4 mm HQD3FSB and 16 mm TS420, respectively; Transonic Systems, Ithaca, NY, USA) for the LMT and LVAD. After heparinization (200 U/kg), a centrifugal LVAD, the EVAHEART, was installed. Inflow cannulas from the LV apex and the outflow conduit to the descending aorta were also installed. A 6Fr conductance catheter (2S-RH-6DA-116, Taisho Biomed Instrument, Osaka, Japan) and a 4Fr micro-tip catheter pressure transducer (Millar Instruments, Houston, TX, USA) were inserted into the LV from the anterior wall to collect data for the pressure-volume curve. These vital data were recorded in Labchart5 (ADInstruments, Bella Vista, NSW, Australia).

Creating the Model of LV Dysfunction
To make the acute ischemic HF model, we micro-embolized the left anterior descending coronary artery (LAD) according to procedures described previously. A multipurpose Judkins catheter (4Fr, Create Medic, Yokohama, Japan) was introduced through a long sheath (4Fr×17 cm) into the left carotid artery toward the LAD under fluoroscopic guidance. We then injected the microspheres (50 μm) into the LAD [=0.3 million particles (0.005 million/kg)]. At 10 min after the injection, we observed the animal’s general condition, including the aortic flow. If the aortic flow was more than 60% of the baseline value, we added half the amount of microspheres (0.0025 million/kg) arbitrarily, so the total amount was 0.30±0.14 million. After 30 min of further observation, we collected data to stabilize and optimize cardiac function.
Study Protocol: LVAD Control Method

We controlled the AoP and CVP to ensure stable conditions during the examination without changing the afterload and preload of the heart. Heart rate was also controlled. We controlled these values by adjusting the volume of infusion and changing the depth of anesthesia, not by using vasodilator or catecholamine. We used 2% lidocaine (1 mg · kg\(^{-1}· h^{-1}\)) and produced gentle waveforms of AoP and pump flow in the diastolic phase. The CoF in the diastolic phase was higher in this mode than in the other modes. There were no significant differences in bypass rates among the modes, except for the circuit-clamp mode.

We defined the systolic and diastolic phases as 35% and 65% of the RR interval, respectively, and we input the duration of each phase according to the heart rate. Our controller can change the RS of each phase, detecting the R wave from ECG. The bypass rate was calculated by dividing the pump flow rate by the sum of the pump and aortic flow rates.

Using this controller, we compared 4 driving modes in this study. The first one was the “circuit-clamp” (pump-off) mode, clamping the LVAD circuit so as to evaluate the conditions of the native heart. The next was the “continuous support” mode, driving the LVAD continuously at a stable rotation speed, which is the mode generally used in clinical situations. The third mode was the “counter-pulse”, in which we set the RS of the systolic phase to approximately 700 rpm, the LVAD system’s minimum speed, and adjusted the RS of the diastolic phase to achieve a bypass rate of 50% or 100%. The fourth mode was “co-pulse” mode, in which we set the RS of the diastolic phase to approximately 1,000 rpm to avoid reverse flow inside the LVAD circuit, and adjusted the RS of the systolic phase to achieve a bypass rate of 50% or 100%. We obtained data 5 min after setting each mode, which we considered to be sufficient time to stabilize the condition. In this study, we mainly evaluated CoF.

Results

Figure 1 shows representative ECG and the waveforms of pressure and flow. In the counter-pulse mode, increased RS produced gentle waveforms of AoP and pump flow in the diastolic phase. The CoF in the diastolic phase was higher in this mode than in the other modes. There were no significant differences in bypass rates among the modes, except for the circuit-clamp mode.

The hemodynamic parameters in each mode are shown in the Table. There were no significant differences in heart rate, CVP, AoP, total flow, or bypass rate among the 3 driving modes (continuous, counter-pulse, co-pulse).

Figure 2 shows the CoF in each mode as a percentage of that in the circuit-clamp mode (=100%). The CoF was higher in the counter-pulse mode than in the continuous mode (P<0.05) with both the 50% and 100% bypass rate. With the 50% bypass rate, the CoF was 112.5\(\pm\)4.3% in the counter-pulse mode, 102.9\(\pm\)7.9% in the co-pulse mode and 106.4\(\pm\)5.7% in the continuous support mode. The same trend was detected with the 100% bypass rate, where the CoF was 121.0\(\pm\)14.1% in the counter-pulse mode, 102.9\(\pm\)7.9% in the co-pulse mode and 113.5\(\pm\)10.6% in the continuous support mode.

Figure 3 shows the end-diastolic pressure (EDP) of the LV in each mode as a percentage of that in the circuit-clamp mode (=100%). The LVEDP was lower in the counter-pulse mode and higher in the co-pulse mode than in the continuous mode (P<0.05) for both the 50% and 100% bypass rate. With the 50% bypass rate, the LVEDP was 74.9\(\pm\)4.2% in the counter-pulse mode, 98.9\(\pm\)6.6% in the co-pulse mode and 89.3\(\pm\)5.1% in the continuous support mode. The same trend was detected with the 100% bypass rate, where the LVEDP was 49.2\(\pm\)3.9% in the counter-pulse mode, 71.0\(\pm\)5.1% in the co-pulse mode and 59.1\(\pm\)4.7% in the continuous support mode.

Discussion

The effect of LVAD pulsatility has been argued for a long time. The counter-pulse, which produced gentle waveforms of AoP and pump flow in the diastolic phase, increased RS. The CoF in the diastolic phase was higher in this mode than in the other modes. There were no significant differences in bypass rates among the modes, except for the circuit-clamp mode.

We controlled these values by adjusting the volume of infusion and changing the depth of anesthesia, not by using vasodilator or catecholamine. We used 2% lidocaine (1 mg · kg\(^{-1}· h^{-1}\)) and produced gentle waveforms of AoP and pump flow in the diastolic phase. The CoF in the diastolic phase was higher in this mode than in the other modes. There were no significant differences in bypass rates among the modes, except for the circuit-clamp mode.

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**Table.** Vital Data at Baseline and After Embolization of the Heart in Various Modes of the Continuous-Flow LVAD With Native Heart Load Control System

<table>
<thead>
<tr>
<th>Bypass rate (%)</th>
<th>HR</th>
<th>AoP (mmHg)</th>
<th>CVP (mmHg)</th>
<th>LVP (mmHg)</th>
<th>Total flow (L/min)</th>
<th>Pump flow (L/min)</th>
<th>50% bypass</th>
<th>Circuit-clamp</th>
<th>Continuous</th>
<th>Counter-pulse</th>
<th>Co-pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% bypass</td>
<td>76.3(\pm)11.7</td>
<td>80.6(\pm)14.6</td>
<td>11.2(\pm)5.6</td>
<td>74.6(\pm)14.7</td>
<td>4.8(\pm)1.2</td>
<td>0.0(\pm)0.0</td>
<td>81.9(\pm)15.6</td>
<td>12.3(\pm)4.0</td>
<td>1.6(\pm)0.8</td>
<td>53.4(\pm)8.4</td>
<td>52.6(\pm)9.3</td>
</tr>
<tr>
<td>100% bypass</td>
<td>76.3(\pm)11.7</td>
<td>83.4(\pm)14.0</td>
<td>11.2(\pm)5.6</td>
<td>74.6(\pm)14.7</td>
<td>4.8(\pm)1.2</td>
<td>0.0(\pm)0.0</td>
<td>83.0(\pm)13.1</td>
<td>10.6(\pm)5.7</td>
<td>1.7(\pm)0.7</td>
<td>53.4(\pm)8.4</td>
<td>52.6(\pm)9.3</td>
</tr>
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</table>

Bypass rates were adjusted at 50% and 100% in each mode. Aortic flow in the circuit-clamp mode decreased to approximately 60% of the baseline value. There were no significant differences in the data for the LVAD. AoP, arterial pressure; CVP, central venous pressure; LVAD, left ventricular assist device.
The effect of long-term support with cf-LVAD remains unknown or is not considered beneficial. Among the clinical outcomes, unfavorable results with pulsatile LVAD have been reported, but this may stem from the higher risks of complication with pulsatile LVAD. Because we consider that the merit of its ability to provide physiological circulation should not be completely excluded, we developed our novel driving system, the NHLCS, for the cf-LVAD.

Needless to say, CoF is considered the most important factor in determining the native heart’s condition. To avoid myocardial ischemia, it is important to maintain appropriate CoF. Therefore, we considered CoF carefully when evaluating our new system. Apparently, LVADs may increase CoF by their ability to raise aortic perfusion and decrease LVEDP. Thus, many researchers have discussed the effect of LVADs on myocardial perfusion, but it remains incompletely understood.

The vascular system is thought to be affected by pulsatility, because it is always exposed to changes in AoP, blood flow, and growth factors. Nishimura et al. reported that long-term non-pulsatile LVAD caused marked structural changes in the aortic wall, and atrophic changes in aortic smooth muscle cells. They also reported that the systemic vascular resistance response to norepinephrine decreased markedly with non-pulsatile flow.

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A counter-pulse effect may be useful for increasing coronary perfusion with increasing aortic pressure in the diastolic phase. The vascular system is thought to be affected by pulsatility, because it is always exposed to changes in AoP, blood flow, and growth factors. Nishimura et al. reported that long-term non-pulsatile LVAD caused marked structural changes in the aortic wall, and atrophic changes in aortic smooth muscle cells. They also reported that the systemic vascular resistance response to norepinephrine decreased markedly with non-pulsatile flow.
continuous support and counter-pulse modes in our model of acute ischemic HF. In models of the normal heart, CoF decreased and coronary artery resistance increased.\(^{(30,31)}\) which we initially thought may have been attributable either to mechanical collapse of the coronary vascular bed with pump support or to increased vascular tone through the autoregulatory system. However, if the coronary vascular bed always collapses with LVAD, then the LVAD should also decrease CoF in models of acute HF. So the hypothesis that the LVAD may induce collapse of the coronary vascular bed is contradictory. The autoregulatory system, which changes coronary artery resistance according to the demands of myocardial perfusion, may be more accountable for these results.\(^{(31)}\) If the LVAD creates excessive CoF, which is the situation in the normal heart, coronary artery resistance may increase and lead to a decrease in CoF at last. If the native heart in acute failure needs more myocardial perfusion, resistance may be decreased and CoF increased.

If we shift our frame of reference to the change in CoF according to the driving mode, we find that CoF always increased in the counter-pulse mode and decreased in the co-pulse mode, regardless of the heart’s condition. In the counter-pulse mode, the reduction in LVEDP\(^{(36,37)}\) and diastolic flow support may lead to increased CoF as the difference between aortic pressure and the internal pressure of the cardiac muscle increases. When compared with intraaortic balloon pumping (IABP), the counter-pulse mode of the NHLCS has a more active effect on reducing LVEDP, so it may be considered to be more effective for enhancing CoF.\(^{(44,45)}\) On the other hand, in the co-pulse mode, CoF was reduced for the opposite reason. In fact, we have proved that LVEDP is reduced in the counter-pulse mode and enhanced in the co-pulse mode. We also observed a change in aortic pressure in the diastolic phase according to the driving mode. From the standpoint of coronary vascular resistance, the change in LVEDP with the driving mode also affects the resistance by wall tension. It is possible that metabolic, neurologic, or some other factors are responsible for the change in resistance. Further examination to elucidate the change in coronary vascular resistance and the determinant factors affecting it is in progress.

We have at least proved the possibility of changing the native heart load from the aspect of CoF with bypass rates of 50% and 100%. This means that we freely can produce a desirable CoF for native heart conditions by choosing the driving mode of the cf-LVAD. A bypass rate of 100% simulates a patient with acute HF needing full support. Excessive CoF may be beneficial in that situation and the counter-pulse mode with 100% bypass may be suitable. On the other hand, a bypass rate of 50% simulates weaning from the LVAD in the recovery stage. We can reduce the bypass rate for the purpose of both evaluating native heart function and training the native heart. If we can increase the strain to the native heart with the co-pulse mode (ie, no enhancement of CoF by the LVAD), it may be useful for training or for confirming the possibility of weaning from the LVAD.

We have shown the possibility of changing the CoF by a cf-LVAD using a pulsatile driving technique, but it remains unknown whether the oxygen in the coronary perfusion was used effectively. Further examination is in progress, including an analysis of myocardial oxygen consumption and the LV pressure–volume curve. Furthermore, we are now attempting to show the same result with the CoF using models of chronic HF.

### Conclusions

Our experiment on goats with acute ischemic HF have revealed that the LVAD was able to change the level of CoF. Flow was higher with the counter-pulse mode and lower with the co-pulse mode, relative to the continuous support mode, which usually applies to clinical use. This result means that we can change the CoF by controlling the LVAD’s rotation in synchrony with the heartbeat. With the ability to freely change CoF by cf-LVAD using our NHLCS, establishing a BTR may have a better prognosis, especially for patients with HF of ischemic etiology.

### References


