Autosynchronized systolic unloading during left ventricular assist with a centrifugal pump

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Objectives: The purpose of this study was to investigate how the inflow cannulation site of the left ventricular assist system with a centrifugal pump would influence cardiac function on failing heart models.

Methods: In 10 sheep, a left ventricular assist system was instituted by an outflow cannula in the descending aorta, two inflow cannulas in the left atrium and the left ventricle, and connecting those cannulas to a magnetically suspended centrifugal pump. A conductance catheter and a tipped micromanometer for monitoring the pressure-volume loop were also inserted into the left ventricle. Myocardial oxygen consumption was directly measured. Heart failure was induced by injection of microspheres into the left main coronary artery. The assist rate was varied from 0% to 100% at each inflow cannulation site.

Results: The pump flow with left ventricular cannulation increased during the systolic phase and decreased during the diastolic phase, whereas it was constant with left atrial cannulation. Ejection fraction with left atrial cannulation decreased as the assist rate increased, whereas that with left ventricular cannulation was maintained up to 75% assist. The external work with left atrial cannulation decreased gradually as the assist rate increased, whereas the external work with left ventricular cannulation did not decrease until the assist rate reached 75%. The myocardial oxygen consumption in both cannulations decreased proportionally as the assist rate increased; they were significantly less with left ventricular cannulation at the 100% assist rate than with left atrial cannulation.

Conclusion: Left ventricular cannulation during left ventricular assistance maintains ejection fraction and effectively reduces oxygen consumption.

The left ventricular assist system (LVAS) helps save patients with profound heart failure. So far, the LVAS has used mainly pulsatile pumps,¹⁻³ although nonpulsatile pumps such as axial pumps have also been applied with favorable results.⁴⁻⁷ The magnetically suspended centrifugal pump (MSCP) is a type of nonpulsatile centrifugal pumps without a shaft.^{8,9} The impeller of the MSCP is suspended between the walls of the pump casing by magnetic forces and rotates without

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Figure 1. Schematic drawing of the experimental preparation. **MSCP**, Magnetically suspended centrifugal pump; **CS**, coronary sinus; **PA**, pulmonary artery; **Ao**, aorta; **RA**, right atrium; **LA**, left atrium; **LV**, left ventricle.

Figure 2. Rotational speed of the pump during LVAS at various assist rates. **LAC**, Left atrial cannulation; **LVC**, left ventricular cannulation; †† $P < .01$ compared with left atrial cannulation.

contact inside the casing. We^{10,11} previously reported that the MSCP showed long durability and antithrombogenicity in long-term animal experiments. It is expected that the MSCP will be used in patients whose failing heart will recover after long-term assistance, and testing is now at the preclinical stage.

Recently, there have been several reports of failing hearts that have recovered after long-term use of the LVAS, which was removed successfully.¹²⁻¹⁵ A decrease in the afterload

of a native heart may play an important role in its recovery after failure.

Nonpulsatile pumps whose flow changes automatically according to changes in afterload are more advantageous than pulsatile pumps that are usually operated in an asynchronous mode. Furthermore, the blood drainage site of LVAS may influence the recovery process.

In our animal studies using MSCP, we inserted an inflow cannula into the left ventricle (LV) because the pump flow could be obtained more easily than that from left atrial (LA) cannulation. Although LV cannulation is commonly used with pulsatile pumps, that is merely applied with centrifugal pumps. Some previous studies compared LA versus LV cannulation during LV assist with pulsatile pumps,¹⁶⁻¹⁹ whereas few have examined the use of centrifugal pump.²⁰

The purpose of the present study was to investigate how the inflow cannulation site of the LVAS using MSCP would influence cardiac function in failing heart models. The hemodynamic effects of LV cannulation during use of the LVAS were compared with those of LA cannulation. To assess the hemodynamic performance of the LV, we investigated the pressure-volume loop in the LV in conjunction with continuous measurement of myocardial oxygen consumption (MVO_2).

Methods

Experimental Preparations

Ten sheep weighing from 36 to 48 kg (mean 41 ± 3 kg) were used in this study. The sheep were anesthetized with an intravenous

Figure 3. Left ventricular pressure-volume loops during LVAS at various assist rates. A, Left atrial cannulation. B, Left ventricular cannulation.

Figure 4. Simultaneous measurement of aortic pressure (AP), left ventricular pressure (LVP), and pump flow wave during LVAS at left atrial cannulation (LAC, top) and left ventricular cannulation (LVC, bottom) at various assist rates.

Figure 5. Systolic aortic pressure during LVAS at various assist rates. SAP, Systolic aortic pressure; MAP, mean aortic pressure; LAC, left atrial cannulation; LVC, left ventricular cannulation; * $P < .05$ compared with no assist (paired t test). Repeated-measures ANOVA: SAP cannulation: $F = 4.59$, $P < .0608$; SAP assist rate: $F = 1.73$, $P < .1644$; SAP cannulation $\times$ assist rate: $F = 0.86$, $P < .4946$. MAP cannulation: $F = 0.01$, $P = .9445$; MAP assist rate: $F = 13.43$, $P < .0001$; MAP cannulation $\times$ assist rate: $F = 0.94$, $P = .4529$.

injection of sodium thiopental. They then underwent endotracheal intubation and were maintained on a ventilator with oxygen mixed with halothane. After the left thoracotomy with resection of the fifth and sixth ribs and transverse splitting of the sternum, the left internal thoracic artery was cannulated for aortic pressure monitoring. The hemiazygos vein was ligated, and a reversible occluder was placed around the inferior vena cava. After heparinization (200 U/kg), a 10-mm outflow cannula was sutured to the descending aorta, an inflow cannula (10 mm) was inserted into the LA appendage, and the cannulas were connected to the inlet and outlet ports of the MSCP to establish LA-aorta LVAS. During the LVAS, another inflow cannula (10 mm) was inserted into the LV through a sutured cuff on the apex. This cannula was connected to the inlet port with an Y-shaped connector, so that the cannulation site could be quickly alternated.

A conductance catheter (ANP 455; Sentron, Roden, The Netherlands) and a tipped micromanometer catheter (model SPC-500; Millar Instruments, Inc, Houston, Tex) for monitoring the pressure-volume loop were also inserted into the LV. All measurements were sampled simultaneously at 333 Hz, stored on a floppy disk, and analyzed with LYCOM Sigma-5 analyzer (CardioDynamics, BV, Zoetermeer, The Netherlands).

Blood flow from the coronary sinus was measured by institution of a bypass circuit (5 mm) from the coronary sinus via the hemiazygos vein to the right atrium. The ostium of the coronary sinus was then doubly ligated, and an oxygen saturation catheter (Opticath catheter, model P7110-EP-H 7.5F, Abbott Laboratories, North Chicago, Ill) was inserted into this circuit to continuously measure coronary sinus oxygen saturation. MVO_2 was calculated by multiplying the oxygen content difference between arterial and coronary sinus blood by the coronary sinus blood flow and was standardized by LV weight.

Microspheres numbering 1.8×10^6 (15 μ m in diameter, Techpolymer; Sekisui, Osaka, Japan) were injected into the left main coronary artery to induce heart failure according to previous studies.²¹⁻²³ Hemodynamic parameters including the ventricular end-systolic elastance (E_{max}) were compared before and after injection of microspheres. Figure 1 is a schematic drawing of the experimental preparation.

Study Protocol

Before the study protocol was started, the LVAS from both the LA and the LV cannulation sites were operated at their respective maximum rotational speeds to decide the maximum pumping flow, which was defined as the 100% assist rate. After measurement of the hemodynamic characteristics at the control (0%), the assist rate was increased in a stepwise fashion to 25%, 50%, 75%, and 100% of the maximum LV assist flow by alternating between LA and LV cannulation at each assist rate. The following parameters at each assist rate were measured: heart rate, rotational speed, systolic arterial pressure, mean arterial pressure, LV end-systolic pressure, LV end-diastolic pressure, LV end-systolic volume, LV end-diastolic volume, ejection fraction, external work derived from the pressure-volume loop, coronary sinus flow, and oxygen saturation in the coronary sinus. The arterial oxygen saturation was measured only at control and was regarded as the same throughout the rest of the protocol. All measurements were recorded during steady-state conditions for each setting of the assist rate and each cannulation site. After the end of the experiment, sheep were put to death with high-dose pentobarbital, and the wet weight of the sheep LV was recorded.

All animal handling and experiments were conducted to minimize stress and discomfort to sheep based on guidelines for Animal Experiments of Kyoto University, which conform to the law on the Guide for the Care and Use of Laboratory Animals in Japan.

All values were expressed as means $\pm$ SEM. The variables were analyzed by repeated-measures analysis of variance (ANOVA). If the result of the ANOVA was significant, a post hoc paired t test was performed.

Results

Heart failure developed after injection of microspheres. The hemodynamic parameters before and after injection of microspheres are summarized in Table 1. Aortic pressure decreased and LV end-diastolic pressure increased, while the end-systolic elastance decreased. The mean value of maximum pumping flow was 3.56 ± 0.67 L/min and there was little difference between maximum flow of LA and LV cannulation. As the assist rate increased in a stepwise fashion, the rotational speed proportionally increased in both LA and LV cannulation. The rotational speed of LA cannulation was higher than that of LV cannulation at each assist rate except 100% assist (Figure 2). Figure 3 illustrates the pressure-volume loops of LA and LV cannulation. With LA cannulation, LV end-diastolic pressure proportionally decreased as the assist rate increased. With LV cannulation, LV end-diastolic pressure did not change until 75% assist, and it decreased at 100% assist. As seen in Figure 4, the

Figure 6. Left ventricular end-systolic pressure (A) and left ventricular end-diastolic pressure (B) during LVAS at various assist rates. *ESP*, Left ventricular end-systolic pressure; *EDP*, left ventricular end-diastolic pressure; *LAC*, left atrial cannulation; *LVC*, left ventricular cannulation; $P < .01$ compared with left atrial cannulation; $*P < .05$, $**P < .01$ compared with no assist (paired *t* test). Repeated-measures ANOVA: *ESP* cannulation: $F = 77.90$, $P < .0001$; *ESP* assist rate: $F = 36.92$, $P < .0001$; *ESP* cannulation $\times$ assist rate: $F = 50.11$, $P < .0001$. *EDP* cannulation: $F = 2.58$, $P = 0.1427$; *EDP* assist rate: $F = 23.48$, $P < .0001$; *EDP* cannulation $\times$ assist rate: $F = 7.27$, $P = .0002$.

TABLE 1. Hemodynamic parameters before and after injection of microspheres

	HR (bpm)	SAP (mm Hg)	MAP (mm Hg)	LVEDP (mm Hg)	E _{max} (mL mm Hg ⁻¹)
Preinjection	120.6 $\pm$ 6.2	87.3 $\pm$ 3.6	74.3 $\pm$ 4.1	7.7 $\pm$ 1.5	5.13 $\pm$ 0.15
Postinjection	128.0 $\pm$ 9.4	78.3 $\pm$ 3.5	64.8 $\pm$ 3.5*	14.6 $\pm$ 2.1*	2.61 $\pm$ 0.18†

Mean $\pm$ SEM. *HR*, Heart rate; *SAP*, systolic aortic pressure; *MAP*, mean aortic pressure; *LVEDP*, left ventricular end-diastolic pressure; *E_{max}*, end-systolic elastance.

* $P < .05$ compared with preinjection.

† $P < .01$ compared with preinjection (paired *t* test).

pump flow with LV cannulation increased during the systolic phase and decreased during the diastolic phase, whereas it was constant with LA cannulation.

Systolic and mean arterial pressure gradually increased as the assist rate increased with both LA and LV cannulation (Figure 5). LV end-diastolic pressure of both groups decreased as the assist rate increased, whereas LV end-systolic pressure did not change up to 75% assist, but showed a slight increase with LA cannulation and a marked decrease with LV cannulation at 100% assist (Figure 6). In accordance with the change in the LV end-diastolic and end-systolic volume during assist, ejection fraction with LA cannulation decreased as the assist rate increased, whereas that with LV cannulation was maintained up to 75% assist (Figure 7). As a consequence of the reduction in LV end-diastolic volume, external work in the LA cannulation proportionally decreased as the assist rate increased. However, the external work with LV cannulation did not decrease until 75% assist rate and decreased equally at 100% assist

(Figure 8). There were significant differences in external work between LA and LV cannulation at 25%, 50%, and 75% assist rate. In both the LA and LV cannulation, the MVO_2 decreased proportionally as the assist rate increased in a similar manner. However, the MVO_2 at 100% assist rate was significantly less with LV cannulation (Figure 9).

Discussion

Several controversies have been reported with respect to the inflow cannulation site during use of the LVAS. The LA cannula is technically easier to insert and is less invasive than the LV cannula. On the other hand, LV cannulation is advantageous in terms of a lower incidence of embolic episodes and greater pump flow.^{17,18} In this study, rotational speeds with LV cannulation were lower than those with LA cannulation, suggesting that LV cannulation achieved pumping flow easily because of the increase in preload. With regard to the effect of myocardial unloading during use of the LVAS, the cannulation site is important. Pennock

Figure 7. Left ventricular end-systolic volume (A), left ventricular end-diastolic volume (B), and left ventricular ejection fraction (C) during LVAS at various assist rates. *ESV*, Left ventricular end-systolic volume; *EDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LAC*, left atrial cannulation; *LVC*, left ventricular cannulation; $P < .05$, $P < .01$ compared with left atrial cannulation; $*P < .05$, $**P < .01$ compared with no assist (paired t test). Repeated-measures ANOVA: *ESV* cannulation: $F = 12.13$, $P = .0069$; *ESV* assist rate: $F = 2.68$, $P = .0472$; *ESV* cannulation $\times$ assist rate: $F = 8.49$, $P < .0001$; *EDV* cannulation: $F = 1.73$, $P = .2208$; *EDV* assist rate: $F = 24.09$, $P < .0001$; *EDV* cannulation $\times$ assist rate: $F = 8.02$, $P < .0001$; *LVEF* cannulation: $F = 2.46$, $P < .1516$; *LVEF* assist rate: $F = 8.91$, $P < .0001$; *LVEF* cannulation $\times$ assist rate: $F = 0.75$, $P < .5668$.

and associates¹⁶ reported that LV cannulation reduced myocardial infarct size more than LA cannulation using a roller pump. Pantalos and coworkers¹⁹ reported that LV cannulation was superior to LA cannulation for myocardial unloading using pulsatile ventricular assist. However, Cohen and colleagues²⁰ reported that there was no significant difference between LA and LV cannulation in MVO_2 reduction when a centrifugal pump was used. In interpreting myocardial unloading in relation to cannulation site, the type of device should be considered. The results of the present study suggested that LA and LV cannulation reduced the MVO_2 equally up to a 75% assist rate, which was consistent

with the findings of Cohen,²⁰ Kawaguchi,²¹ Goldstein,²⁴ and their associates. Although a similar decrease in the MVO_2 at less than 100% assist was observed for both cannulation sites, we consider that LV cannulation could be advantageous even at 50% and 75% assist because of synchronized increase in pump output during the systolic phase. Since the pump flow of centrifugal pumps is inversely correlated with the pressure difference between inflow and outflow, an increase in LV pressure results in a decrease in the pressure difference and eventually an increase in pump flow. During assist in the systolic phase of the native heart, the LV is actually unloaded because of the increase in pump flow.

Figure 8. External work during LVAS at various assist rates. *EW*, External work; *LAC*, left atrial cannulation; *LVC*, left ventricular cannulation; $P < .05$, $P < .01$ compared with left atrial cannulation; $*P < .05$, $**P < .01$ compared with no assist (paired *t* test). Repeated-measures ANOVA: Cannulation: $F = 8.94$, $P = .0152$; assist rate: $F = 34.40$, $P < .0001$; cannulation $\times$ assist rate: $F = 2.09$, $P = .1029$.

Figure 9. Myocardial oxygen consumption during LVAS at various assist rates. *MVO₂*, Myocardial oxygen consumption; *LAC*, left atrial cannulation; *LVC*, left ventricular cannulation; $P < .05$, $P < .01$ compared with left atrial cannulation; $*P < .05$, $**P < .01$ compared with no assist (paired *t* test). Repeated-measures ANOVA: cannulation: $F = 5.93$, $P = .0376$; assist rate, $F = 32.16$, $P < .0001$; cannulation $\times$ assist rate: $F = 7.88$, $P = .0001$.

Thus, during use of the LVAS with a centrifugal pump, LV cannulation is superior to LA cannulation in terms of myocardial unloading.

Since the external work should correlate with the MVO_2 ,²⁵ the external work with LA cannulation decreased linearly between 25% and 75% along with a proportional reduction in MVO_2 . In contrast, the external work with LV cannulation did not decrease proportionally, despite the same reduction in the MVO_2 as that for LA cannulation. In other words, with LV cannulation there was dissociation between the external work and the MVO_2 at 50% and 75% assist rates. We infer that this dissociation of external work and MVO_2 is due to the effect of synchronization during the systolic phase when substantial energy is required. This effect is applicable only at 50% and 75% and diminishes at 100% full assist because of the predominant venting effect at this level.

Ejection fraction was also maintained with LV cannulation, consistent with clinical results that were reported for patients with a pulsatile device.¹⁵ Although it remains unclear whether better ejection fraction would be important during LVAS, we speculate that maintaining ejection fraction could prevent disuse atrophy of the heart and might be advantageous for recovery of the heart. Thus, LV cannulation effectively reduces oxygen consumption without compromising cardiac wall motion.

The MSCP used in the present study is one of several types of centrifugal pumps. It eliminates a shaft and seal and allows long-term operation. The results of this study are not uniquely characteristic to the MSCP and would be applica-

ble to any type of centrifugal pump, because all centrifugal pumps show a similar correlation between pump flow and the inflow and outflow pressure difference.

Pulsatile assist devices are usually operated in an asynchronous mode with either LA or LV cannulation, although a synchronous mode is ideal for better myocardial unloading. A synchronous mode with a pulsatile device sometimes causes inadequate pump flow and necessitates sensing parameters such as an electrocardiograph. When a centrifugal pump was used with LV cannulation, the pump flow automatically increased during the systolic phase and decreased during the diastolic phase, similar to synchronization during the systolic period as seen in Figure 4. This autosynchronized systolic unloading could eliminate the need for sensors and reduce oxygen consumption, thus improving the recovery rate of the native heart after long-term assist.

One limitation of this study was that we did not observe the long-term effect and focused only on the acute phase during assist. Although hemodynamic effects during the acute phase would continue in theory, remodeling and changes at the molecular level during the chronic phase were unclear. It is not possible to predict when heart failure will recede and the LVAS can be removed. Another limitation was the model of heart failure we used, that is, injection of microspheres 15 μ m in diameter into the coronary arteries. Microspheres of this size cause global ischemia and not myocardial infarction. We used this technique to mimic global cardiac dysfunction that is similar to dilated cardiomyopathy. However, it was unclear whether this heart failure model was clinically relevant.

In conclusion, we have investigated the impact of the inflow cannulation site during use of the LVAS with a centrifugal pump in a failing heart model. LV cannulation appears to maintain ejection fraction and provides effective reduction in oxygen consumption, because the pump flow increases automatically during the systolic phase and decreases during the diastolic phase. This autosynchronized systolic unloading would obviate the need for any sensors in the living body and reduce oxygen consumption.

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