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ORIGINAL ARTICLE

Artificial Heart (Basic)

Quantification of interventricular dyssynchrony during continuous-flow left ventricular assist device support

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Abstract

Under continuous-flow left ventricular assist device (CF-LVAD) support, the ventricular volume change and cardiac cycle between the left ventricle (LV) and right ventricle (RV) become dyssynchronous due to the shortening of the LV systole. The purpose of this study was to quantify interventricular dyssynchrony based on different CF-LVAD support conditions and assess its relationship with LV unloading. In this study, we evaluated seven goats (body weight 44.5 ± 6.5 kg) with normal hearts. A centrifugal LVAD was implanted under general anesthesia. We inserted the conductance catheters into the left ventricle (LV) and right ventricle (RV) to assess the volume signal simultaneously. We defined the interventricular dyssynchrony as a signal (increase or decrease) of LV volume (LVV) change opposite to that of RV volume (RVV) (i.e., $(d\mathrm{LVV}/dt) \times (d\mathrm{RVV}/dt) < 0$). The duration of interventricular dyssynchrony (DYS) was reported as the percentage of time that a heart was in a dyssynchronous state within a cardiac cycle. The mean DYS of normal hearts, hearts with LVAD clamp and hearts supported by LVADs with a bypass rate of 50%, 75% and 100% were 5.6 ± 1.6%, 8.7 ± 2.4%, 8.6 ± 2.8%, 15.1 ± 5.1%, and 25.6 ± 8.0%, respectively. Furthermore, the DYS was found to be associated with the degree of LV stroke volume reduction caused by LV unloading. These findings may be useful for understanding interventricular interactions and physiology during CF-LVAD support. Influences on the right ventricular function and heart failure models warrant further study.

Keywords Continuous-flow left ventricular assist device · Interventricular dyssynchrony · Conductance method · Pressure–volume loop

Introduction

Continuous-flow left ventricular assist devices (CF-LVADs) have been proven to be a successful treatment option for patients with end-stage heart failure [1–4]. However, a significant percentage of these patients develop right ventricular failure, which adversely affects their prognosis [5–7].

Although the benefits of LVADs on left ventricle (LV) function, including its ability to induce LV unloading and improve organ function have been well documented, the complex interactions of LVAD on right ventricle (RV) performance are not sufficiently understood. The RV is coupled in parallel to the LV via their shared interventricular septum and pericardium. As such, they are interdependent [8–10]. One of the possible physiological factors for this interdependence is the change in the LV's cardiac cycle caused by LV unloading. During LVAD support, the continuous pumping of blood directly from the LV, independent of cardiac cycle phase, results in a decrease of isovolumic periods. In this case, the systolic phase of the LV becomes shorter than that of the RV and the pressure–volume loop transforms from its normal trapezoidal shape to a triangular shape when the aortic valve does not open, thereby disallowing the ejection of blood from the LV through the aortic valve [2, 11]. This results in the loss of an ejection period, which causes

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a lack of synchronicity between the LV's and RV's systolic and diastolic periods. Although this phenomenon may be understood as mechanical interventricular dyssynchrony, due to the continuous LV unloading unique to CF-LVAD support, there have been no reports regarding its precise mechanism and quantitative evaluation. In this study, we assessed interventricular dyssynchrony during CF-LVAD support using conductance methods [12]. The aim of this study was to quantify the mechanical interventricular dyssynchrony during CF-LVAD based on different CF-LVAD support conditions and assess its relationship with the LV unloading to provide more information on interventricular interactions and physiology in this context.

Materials and methods

Study subjects

We studied seven goats (body weight 44.5 ± 6.5 kg). All animals were handled humanely, in compliance with the ethical principles of laboratory animal care. The research protocols were approved by the ethics committee of National Cerebral and Cardiovascular Center.

Surgical procedure

Initially, general anesthesia was induced with intramuscular ketamine (10 mg/kg) and maintained by isoflurane inhalation (1–3% in oxygen). Thereafter, the goats were placed in the right lateral recumbent position, intubated, and mechanically ventilated. Next, left thoracotomy was performed via the fifth intercostal space. To monitor the arterial pressure (AoP), pressure lines were then placed in the posterior auricular artery. Afterwards, the centrifugal LVAD (EVAHEART ®; Sun Medical Technology Research Corporation, Nagano, Japan) was implanted as follows:

1. The outflow graft was anastomosed to the descending thoracic aorta using a 4-0 polypropylene running suture;
2. the apical cuff was anastomosed on the cardiac apex with 8–10 interrupted 2-0 pledgeted Ticron sutures;
3. systemic heparinization (200 U/kg) was performed; and
4. the cardiac apex was incised and the inflow cannula of the centrifugal LVAD was inserted into the LV and fixed to the apical cuff.

The inflow and outflow cannulas were connected to the extracorporeal circuit with metallic connectors. The pump was primed, connected to the extracorporeal circuit, and initiated. After the implantation of the centrifugal LVAD, we used an electromagnetic flow meter (TS 420 ultrasonic flow meter: 14–18 mm in diameter; Transonic Systems, Ithaca, NY, USA) for the pulmonary artery. The LVAD pump flow (PF) was measured at the outflow graft using a ultrasonic flow meter (TS420, Transonic, NY, USA) with a probe diameter of 12 mm.

Then, 6-Fr conductance catheters (Taisho Biomed Instrument, Osaka, Japan) were inserted into the LV from the descending thoracic aorta and into the RV from the main pulmonary artery to obtain their pressure–volume data.

Measurements

The conductance catheters enabled the continuous measurement of five segmental volume slices perpendicular to the ventricular long axis. These catheters were connected to a PowerLab (ADInstruments, Australia) to obtain segmental and total LV and RV volumes (LVVs and RVVs, respectively), LV and RV pressures (LVPs and RVPs, respectively), electrocardiographic data, pulmonary artery flow data and pump flow data. Pressure–volume loops were continuously drawn, and the pressure–volume relationship was assessed throughout the experiment. The bypass rate was calculated as a percentage by dividing the pump flow by the main pulmonary artery flow representing total systemic flow and then multiplying the result by 100 (i.e., full-bypass LVAD was defined as having a bypass rate of 100% and half-bypass LVAD was defined as having a bypass rate of 50%). "LVAD clamp" means that the outflow graft was clamped so that the LVAD did not work.

Cardiac function and nonuniform mechanical performance

Global ventricular function was assessed by measuring stroke volume (SV), stroke work (SW), end-diastolic and end-systolic volumes (EDVIs and ESVIs), and end-systolic and end-diastolic pressures (ESPs and EDPs).

Definition and quantification of interventricular dyssynchrony

Nonuniform performance between the LV and RV was determined from their conductance signals. At each point in time, ventricular volume signals were considered dyssynchronous if the change in the total RVV was opposite to the simultaneous change in the total LVV (i.e., if the RVV increases and the LVV decreases and vice versa). As such, interventricular dyssynchrony was mathematically defined as follows:

$$(d\mathrm{LVV}/d\mathrm{t}) \times (d\mathrm{RVV}/d\mathrm{t}) < 0.$$

Furthermore, the duration of interventricular dyssynchrony (DYS) was calculated as the percentage of time within a cardiac cycle that the change in the RVV was opposite to the simultaneous change in the total LVV.

Relationship between the DYS and LV stroke volume

The relationship between the DYS and left ventricular stroke volume (LVSV) was analyzed to assess the influence of LV unloading on interventricular dyssynchrony. To exclude the impact of the differences in ventricular volume among the subjects, LVSV ratios were used for this comparison and were calculated as follows:

$$\text{LVSV ratio} = (\text{LVSV in each bypass rate})/(\text{LVSV with clamping LVAD}) \times 100.$$

The DYS and LVSV ratios for each subject were plotted using a scatter plot for the following LVAD support conditions: hearts with LVAD clamp and hearts supported by LVADs with a bypass rate of 50%, 75% and 100%.

Statistical analysis

All numerical data were presented as mean ± standard deviation (SD). The comparison of data between each LVAD support condition was analyzed by a repeated-measure analysis of variance (ANOVA), followed by the Dunnett's multiple comparison test. All analyses were two-sided and a p value of < 0.05 was considered to be statistically significant. All data were analyzed using JMP® 14 (SAS Institute Inc., Cary, NC, USA).

Results

Interventricular dyssynchrony according to the bypass rate

The hemodynamic parameter values for each corresponding LVAD support condition are described in Table 1. The mean LVPs were significantly lower when LVAD support was implemented than before LVAD implantation. Moreover, the mean LVESP was significantly lower when full-bypass LVAD support was implemented than before LVAD implantation. None of the RV pressure and volume parameters showed any significant changes between before and after LVAD administration.

Figure 1 shows samples of the pressure–volume data waveforms of ventricular volume changes occurring before LVAD implantation and during the implementation of half-bypass and full-bypass LVAD support. It was apparent that dyssynchronous states occurred much more often when full-bypass LVAD support was implemented than during

Table 1 Mean hemodynamic parameter values for each LVAD support condition

Hemodynamic parameters	Pre-LVAD implantation	LVAD clamp	LVAD 50% bypass	LVAD 75% bypass	LVAD 100% bypass
Heart rate (bpm)	94.4 ± 10.4	92.9 ± 26.4	95.3 ± 24.4	96.6 ± 21.6	95.7 ± 19.7
Mean AoP (mmHg)	78.5 ± 13.8	61.7 ± 17.5	63.8 ± 10.2	66.8 ± 11.4	66.6 ± 13.3
Pump flow (l/min)	0	0	1.51 ± 0.55	2.46 ± 0.70**	3.20 ± 0.93**
Total systemic flow (l/min)	3.88 ± 1.52	3.03 ± 0.97	3.05 ± 0.93	3.11 ± 0.99	3.18 ± 0.91
Mean LVP (mmHg)	44.2 ± 8.20	34.5 ± 10.5	27.3 ± 6.56*	26.2 ± 8.03*	22.0 ± 10.8*
Bypass rate (%)	0	0	49.8 ± 6.87	75.3 ± 5.20**	100.6 ± 10.3**
DYS (%)	5.57 ± 1.59	8.70 ± 2.38	8.63 ± 2.76	15.1 ± 5.13	25.5 ± 8.02*
Rotational speed (rpm)	0	0	1473 ± 256	1680 ± 246**	2023 ± 404**
Stroke work (mmHg•ml)	2097 ± 582	1799 ± 840	1630 ± 711	1525 ± 733	906 ± 782*
Stroke volume (ml)	21.9 ± 9.64	24.8 ± 8.53	15.6 ± 8.52	15.7 ± 7.18	14.1 ± 7.84
LVEDV (ml)	109 ± 15.1	105 ± 8.81	97.1 ± 12.3	94.9 ± 13.9	87.2 ± 13.5
LVESV (ml)	87.0 ± 9.81	80.5 ± 20.4	81.5 ± 12.1	79.2 ± 12.2	73.1 ± 9.85
LVEDP (mmHg)	7.06 ± 2.62	7.12 ± 2.19	7.28 ± 2.76	6.15 ± 2.81	4.03 ± 2.72
LVESP (mmHg)	88.6 ± 13.5	73.0 ± 12.7	72.6 ± 9.73	72.5 ± 10.8	62.6 ± 15.5*
RVEDV (ml)	82.8 ± 15.1	86.9 ± 8.81	84.7 ± 12.3	84.3 ± 13.9	84.5 ± 13.5
RVESV (ml)	61.7 ± 9.81	64.9 ± 10.4	63.2 ± 12.1	67.3 ± 12.2	65.0 ± 9.85
RVEDP (mmHg)	6.81 ± 2.62	5.03 ± 3.59	4.47 ± 2.94	4.72 ± 2.73	3.89 ± 2.78
RVESP (mmHg)	30.9 ± 9.06	30.2 ± 8.79	2.94 ± 8.57	31.0 ± 8.73	32.6 ± 9.57

*$p < 0.05$ if compared with pre-LVAD implantation values, **$p < 0.05$ if compared with 50% bypass LVAD support values

AoP aortic pressure, *LVP* left ventricle pressure, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end-systolic pressure, *LVEDP* left ventricle end-diastolic pressure, *LVESP* left ventricle end-systolic pressure, *RVEDV* right ventricle end-diastolic volume, *RVESV* right ventricle end-systolic pressure, *RVEDP* right ventricle end-diastolic pressure, *RVESP* right ventricle end-systolic pressure, *LVAD* left ventricular assist device

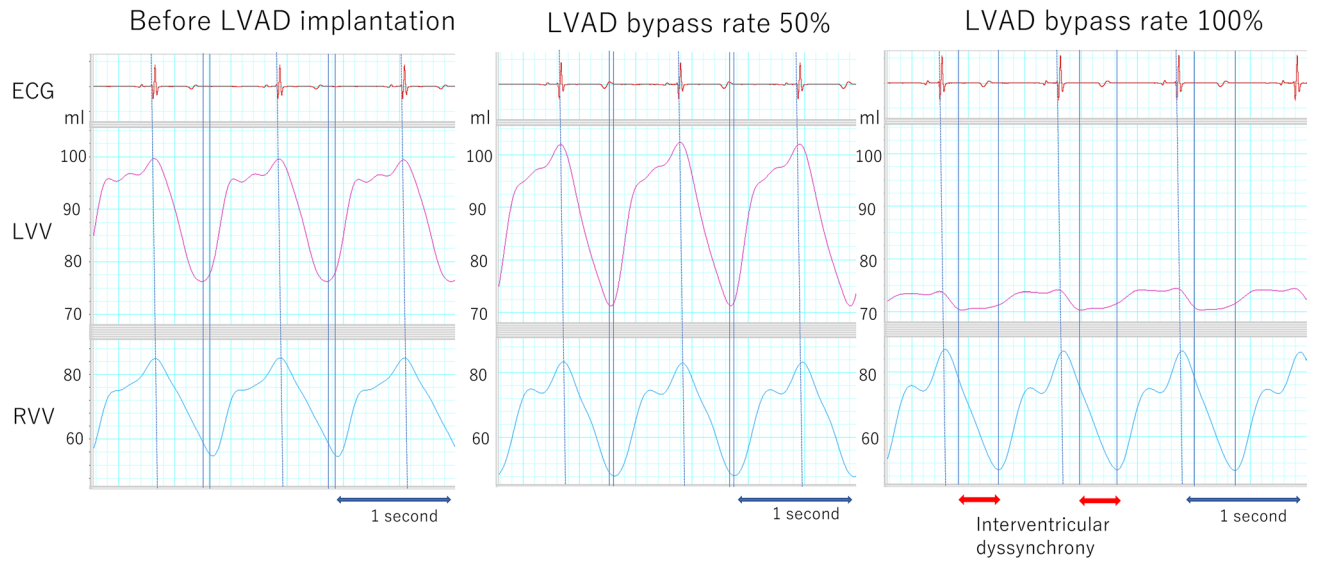

Fig. 1 Waveform of pressure–volume data of RV and LV at each support condition. *ECG* electrocardiography, *LVV* left ventricular volume, *RVV* right ventricular volume. Solid vertical line: minimum point of the ventricular volume; dotted vertical line: maximum of the ventricular volume

the other two LVAD support conditions. Dyssynchronous states were mainly observed during the end-systolic phase.

Figure 2 shows the typical pressure–volume relationships of the LV and RV before LVAD implantation and during half-bypass and full-bypass LVAD support implementation. During full-bypass LVAD support, the pressure–volume loop of the LV became triangle-shaped, but the pressure–volume loop of the LV was trapezoid-shaped before LVAD implantation and during the implementation of half-bypass LVAD support. The pressure–volume loops of the RV remained in a similar shape throughout all the LVAD support conditions.

Figure 3 shows the relationship between bypass rate and the DYS. The mean DYS of normal hearts (control), hearts implanted with LVAD clamps, and hearts supported by LVADs with a bypass rate of 50%, 75% and 100% were $5.6 \pm 1.6\%$, $8.7 \pm 2.4\%$, $8.6 \pm 2.8\%$, $15.1 \pm 5.1\%$, and $25.6 \pm 8.0\%$, respectively.

Relationship between interventricular dyssynchrony and LV unloading

The relationship between the DYS and LVSV ratios is shown in Fig. 4 in which a bimodal distribution can be observed. During LVAD clamp and 50% bypass LVAD support implementation, the DYS values were similar among the different rotational speeds (right side area). Alternatively, under 100% LVAD bypass conditions, a significantly smaller LVSV ratio and higher DYS than before 100% LVAD bypass implementation were observed (left side area). During the implementation of 75% bypass LVAD support, a bimodal DYS distribution was observed.

Discussion

This study quantified mechanical interventricular dyssynchrony during CF-LVAD based on different LVAD support conditions and assessed its relationship with LV unloading. These measurements were achieved by assessing the ventricular volumes with conductance methods simultaneously applied to the LV and RV of each subject.

Our primary findings are as follows:

1. Duration of the interventricular dyssynchrony becomes longer at higher bypass rate and was up to 25–30% of the cardiac cycle under LVAD full-bypass.
2. The duration of interventricular dyssynchrony was shorter when LVAD clamps were implemented and at half-bypass conditions ranging from 5 to 10% of the cardiac cycle.
3. The duration of interventricular dyssynchrony was associated with the degree of LV stroke volume reduction caused by LVAD unloading.

It is well known that intraventricular dyssynchrony plays a significant role in pathological conditions and its severity is associated with patients' responses to the cardiac resynchronization therapy and prognoses [13–15]. Interventricular dyssynchrony is another category of the ventricular dyssynchrony and observed in pathological conditions such as ischemia, hypertrophy or heat failure [16]. However, this subtype of interventricular dyssynchrony occurring due to LVAD support has not been reported with precision. Its assessment would be worthwhile in understanding the interactions between the LV and RV under the LVAD support.

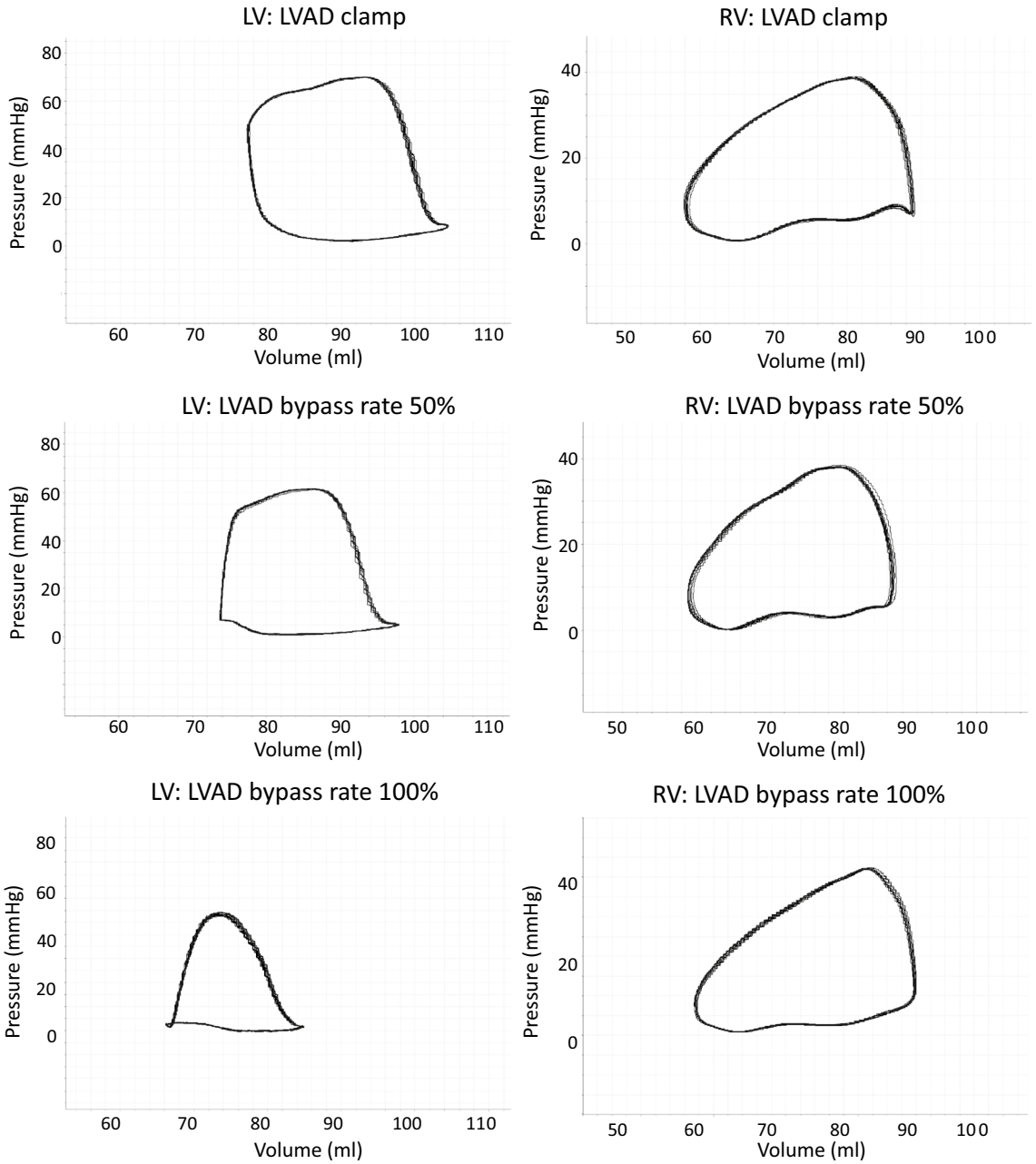

Fig. 2 Pressure–volume loop of each support condition

One of the proposed mechanisms for interventricular dyssynchrony caused by LVAD support is purely mechanical, the theory being that the decrease in LV systolic time caused by the LVAD suction is irrelevant to the cardiac cycle of the RV [17]. To assess the precise mechanism of this phenomenon and its relation to ventricular functional parameters and the status of the aortic valve, we applied a conductance method in this study. Interventricular dyssynchrony was successfully quantified and our primary findings indicated that the time in the dyssynchronous phase increases as LV is more aggressively unloaded by LVAD suction. The observed maximum DYS was up to 25–30% in this study group, but different DYSs may be observed with humans' large ventricle sizes and different types of LVAD support.

Based on the findings of the scatter plot analysis, we speculate that changes in the duration of interventricular dyssynchrony were caused by the following mechanisms: when the ejection period and the opening of the aortic valve were maintained with LVAD clamp and half-bypass LVAD support implementation, the DYS values were low and not significantly different among different rotational speeds. When the aortic valve did not open due to the high rotational

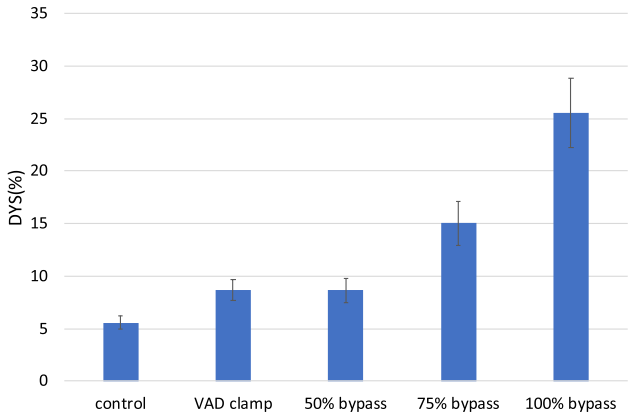

Fig. 3 Duration of interventricular dyssynchrony observed at each support condition

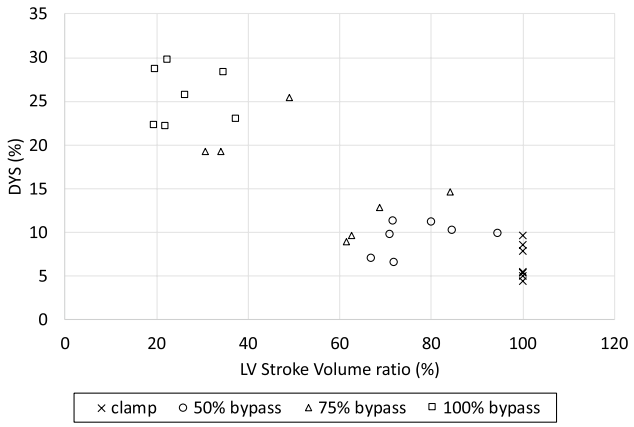

Fig. 4 Scatter plot of the relationship between left ventricular stroke volume ratio and the duration of interventricular dyssynchrony

speeds in full-bypass LVAD support, the ejection period was lost, thereby making the LV systole shorter than the RV systole. Subsequently, the DYS values during full-bypass LVAD support were significantly higher than those before full-bypass LVAD support implementation. The fluctuations in the DYS values during 75% bypass LVAD support may be explained by the inconsistent losses and reappearances of the ejection period, which were dependent on whether the aortic valve was open.

During the treatment of severe heart failure patients, high LVAD rotational speeds are often necessary to obtain sufficient systemic blood flow. It may be worth taking this phenomenon into account especially when aggressive LVAD support with concomitant high rotational speeds is required. Therefore, during LVAD support implementation, not only should dyssynchrony caused by preexisting heart failure be considered, but mechanical interventricular dyssynchrony caused by LVAD suction should be considered as well.

For the evaluation of the clinical impacts of interventricular dyssynchrony caused by LVAD support, further study is necessary to assess this phenomenon's influence on right ventricle function. One possibility is that the excessive and aggressive unloading by LVAD support could, in turn, cause right ventricle dysfunction due to the negative effects of dyssynchrony. If this is the case, LVAD support conditions that allow for adequate circulatory support, while limiting the incidence of dyssynchrony, would be desirable, especially for those undergoing LVAD support weaning.

Limitations

This study has several limitations. First, we only studied goats with normal heart conditions. Therefore, we have to assess interventricular dyssynchrony caused by LVAD in cases of heart failure for more robust and pertinent results that can be applied to a clinical setting. Second, further study regarding chronic phase is also necessary to appropriately assess the response of the heart in our study's context. Third, from the measurement principles of conductance catheter, the volume data of the right ventricle should be carefully assessed. To overcome this limitation, we only focused on the change of the RV volume, not the data itself. Lastly, DYS was observed in approximately 5% of the cardiac cycle even in the pre-LVAD condition, which means that the motions of the two ventricles are not completely synchronous in this condition. Although there have been no reports assessing DYS of an in situ normal heart, the influence of surgical intervention such as thoracotomy and pericardiotomy should also be taken into consideration when discussing interventricular dyssynchrony using conductance method.

Conclusion

Interventricular dyssynchrony during LVAD support was successfully assessed and quantified using a conductance method applied simultaneously for both the LV and RV. Moreover, our results show that there may be a relationship between DYS and LV unloading, since DYS increased when the LV was unloaded via the high rotational speeds during LVAD support. Further assessments regarding the effects of interventricular dyssynchrony during LVAD support on right ventricle function as well as how this phenomenon is affected in heart failure are required to gain further insight on interventricular interactions and physiological mechanisms in the context of LVAD support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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