

In vitro testing of an intra-ventricular assist device

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ABSTRACT

A novel pulsatile assist device, intra-ventricular assist device, was proposed to address various disadvantages existing in conventional pulsatile assist device, such as the large size, accessories and reduced pulsatility. The assist device was designed, fabricated and implanted into the sac from left ventricular apex in a home-designed mock circulatory system. In vitro test was carried out and results demonstrated that the response time did not vary with the heart rate, and co-pulsated synchronously with native heart by electrocardiograph. The key parameter, stroke volume of proposed device was precisely measured under different afterloads (60, 80, 100, and 120 mmHg), drive pressure (from 90 to 300 mmHg at 30 mmHg intervals), and heart rate (45–150 beats per minute). The measurement results revealed that the output characteristics of device, stroke volume increased with increasing drive pressure but decreased with increasing peripheral resistance, were consistent with the native heart. The proposed pump was then coupled with mock system that was set to a heart failure mode and the circulatory responses were tested. Results showed that the device improved left ventricular pressure from 106 to 158 mmHg, and stroke volume from 25.5 to 44 ml at 90 bpm.

KEYWORDS

heart failure;
hemodynamics; left
ventricular assist device;
mock circulatory system

Introduction

Left ventricular assist device (LVAD) is widely used to implant in heart failure (HF) patients. It helps the failing ventricle pumping blood from ventricle to the aorta. LVADs play an important role in the treatment of HF patients. In recent years, the permanent implantation (destination therapy) has become an option for this device [1]. Currently, pulsatile and non-pulsatile pump are available for clinical treatment, namely, continuous flow LVAD (CF-LVAD) and pulsatile flow LVAD (PF-LVAD). CF-LVADs generally provide non-pulsatile flow that has less pulsatility compared to the physiological flow. In most cases, CF-LVADs own much smaller size and lighter and be implanted intracorporeally. Therefore, they have better performance in terms of preventing infection arise from the smaller size [2,3]. However, they still have some significant issues, for example, the decreasing pulsatility and non-physiologically high levels of shear stress, the patients will suffer long-term complication such as gastrointestinal bleeding and aortic valve insufficiency [4].

On the other hand, in several studies, they believed that pulsatile flow is necessary. Variable speed mode of CF-LVAD increase the pulsatile pressure synchronized with ventricular beats, however, the pulsatility remained limited [5,6]. Additional, to prevent backflow, CF-LVADs should continue working. Although the old pulsatile pumps are larger size and heavier, they generate pulsating flow likes physiological flow. Last several years, some new pulsatile pumps have been studied, such as LibraHeart pulsatile LVAD. Therefore, the study of pulsatile pump is meaningful.

The proposed intraventricular assist device (iVAD) overcome the large size and accessory, which effectively improved the left ventricular perfusion in our previous simulation studies [7]. In this study, the performances of iVAD were assessed in mock circulatory system (MCS). Our goals were to measure the synchronization of iVAD with the ventricular pulsation at different heart rate (HR), the stroke volume (SV) at different driven pressure, and the assessment of ventricular perfusion with iVAD support.

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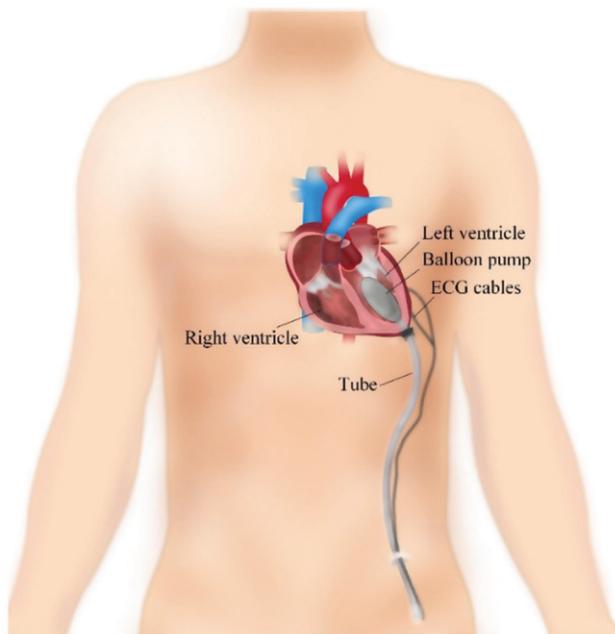


Figure 1. Schematic diagram of iVAD installation.

Materials and methods

iVAD

The iVAD is a new pulsatile pump that is implanted in the ventricle. It is powered by compressed air. The iVAD mainly consists of a balloon pump, a control unit and a drive unit. Figure 1 shows the parts of iVAD in the chest cavity. The balloon pump is placed in the left ventricle, at the same time, the control and drive units are placed in vitro. The inflated volume of the balloon used in this study is 50 cm^3 , and has a smaller implanted volume about 7 cm^3 when it is deflation (likes long cylinder, diameter 1 cm and length 5.6 cm), and thus creates a smaller operation wound. During the systole, the balloon is inflating and pushing the blood into aorta, and meanwhile increasing pressure of the left ventricle.

During the diastole, the deflated balloon causes the blood flow into the left ventricle. The iVAD co-pulsated with the ventricle. The ellipsoidal balloon is connected to the driveline, which is made of multi-layer polyurethane (PU). The innermost layer of which directly contacts with gas (air), whereas the outermost layer is covered with medical PU from Bayer. Additionally, unlike continuous operation of the non-pulsatile pumps, the iVAD can work intermittently. The pulsed mode of an iVAD is similar to that of IABP [8,9]. The iVAD synchronized with the electrocardiogram (ECG). The peaks of the ECG, R wave, are used to trigger the balloon pump of iVAD inflation. The time of systole was 35% of the cardiac cycle [10]. Figure 2 clearly elucidated the relationship between

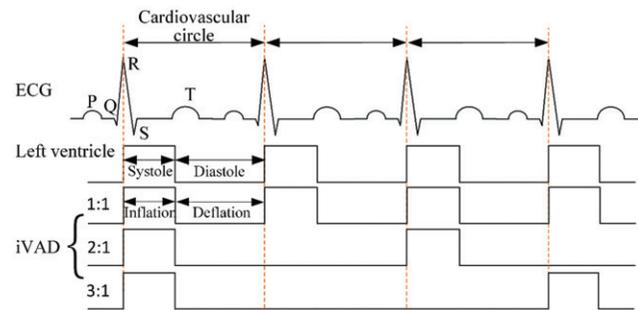


Figure 2. The pulsatile rhythm between the left ventricle and iVAD.

the ventricle and iVAD. Three drive mode, 1:1, 2:1 and 3:1 (that is, ventricle three times of beat, pump one beat), can be selected as needed.

Mock circulatory system

A mock circulatory system (MCS) is highly valuable because it minimizes the need for animal experiments in evaluating VADs [11]. The performance of iVAD is evaluating on the home-designed MCS, which comprises pulmonary and systemic circulations as shown in Figure 3. Four polyurethane cavities are represented as left and right ventricle, atrium respectively. These cavities were placed in acrylic chambers. The ventricular sac is a semi-ellipsoid (long axis – 180 mm and short axis – 62 mm) and its volume is approximately 181 cm^3 . Ventricular diastole and systole were controlled by two electropneumatic regulators (ITV2030-312BL, SMC Pneumatics, Tokyo, Japan) and two vacuum proportional valves (ITV2090-31N2BN5) and 3/2 way solenoid valves (VT325-025GS, SMC Pneumatics, Tokyo, Japan). They operated together to offer passively filled heart chambers and contractility. Artificial mechanical valves (SJM 23AJ-501 and SJM 27MJ-501, St. Jude Medical, USA) were employed as native heart valves. Additionally, resistance load reservoirs with adjustable pressure were employed to represent circulation resistance (afterload), whereas compliance reservoirs mimic blood vessel compliance. The tygon tubing connected the chambers and reservoirs. The whole system was filled with water at 37°C , that mimicked the blood. The flowrate and pressure were monitored and recorded by A data acquisition system (National Instruments, Austin, TX, USA) were monitored and recorded the pressure and flowmate.

Testing the synchronous drive mode

To improve the failing ventricular perfusion, the iVAD should be synchronously co-pulsation with the native

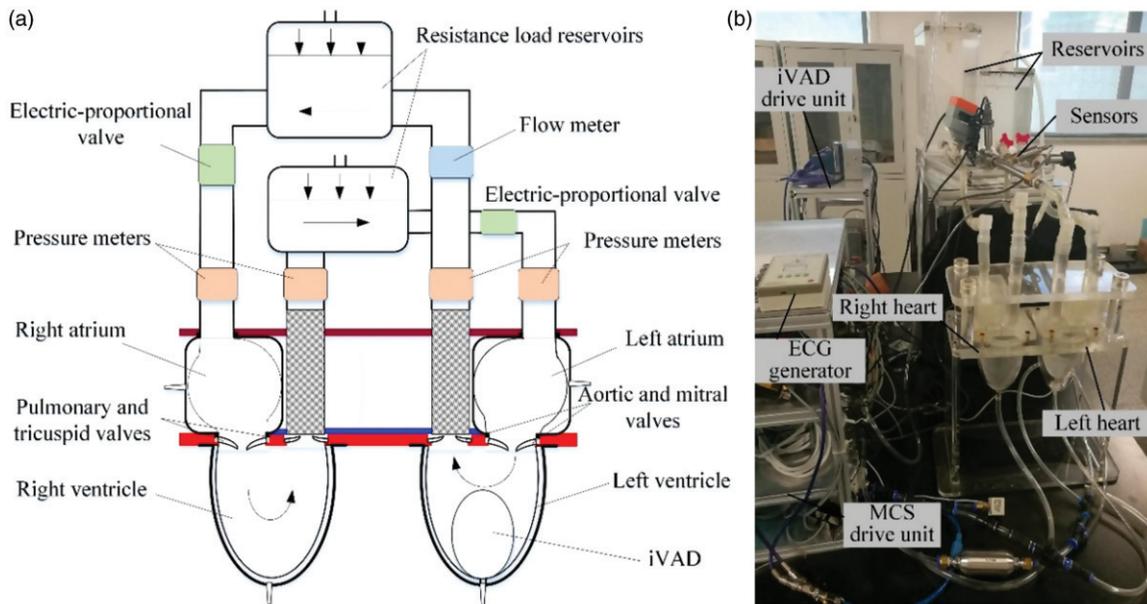


Figure 3. (a) Schematic of home-designed MCS, (b) Photo of the MCS.

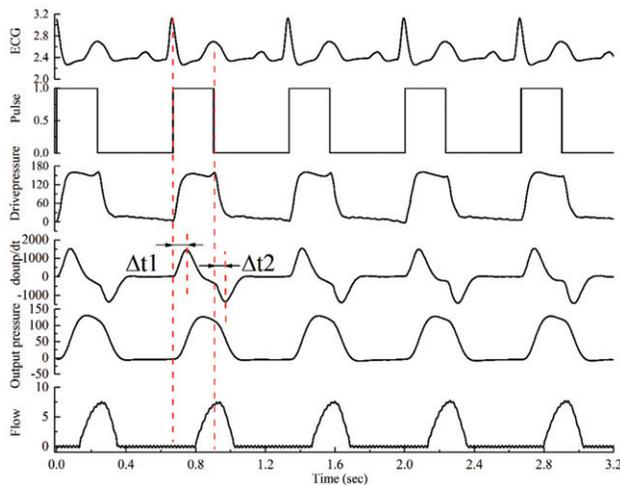


Figure 4. The timing relationship between ECG and aortic pressure and flow tested in MCS.

ventricle. A controller detecting peaks of R waves from ECGs (analog ECG generator, SKX-2000SUP+, Mingsheng, China) instantly triggered the iVAD to inflate behind the peaks for a configured delay time. In the experiment, the delay time was set to 0 ms. The previous 35% of RR interval is systolic time (iVAD is inflated), and 65% is the diastolic time (iVAD is deflated). Although synchronization of drive pressure and pulse was favourable (Figure 4), a certain delay in output pressure was inevitable. We then determined whether the time delays stemmed from the HR. Further experiments were conducted to investigate time delay in different HR conditions (from 50 to 150 bpm at intervals of 5 bpm). 15 and 80 mmHg were set as preload and afterload of MCS, respectively, and

drive pressure of iVAD was maintained at 150 mmHg. For each set of data, the number of samples did not decrease below 20.

Dynamic testing of iVAD

To test the stroke volume of iVAD, the balloon was coupled with MCS (Figure 3). The parameters of circulatory system as follows: preload of 15 mmHg and afterload of 60 mmHg, HR of 75 bpm and 150 mmHg drive pressure. The balloon volume is 50 cm³ (inflated cavity volume without plastic deformation). Further experiments, afterload was set to 80, 100, and 120 mmHg, respectively, drive pressures ranging from 90 mmHg to 300 mmHg at 30 mmHg intervals were adopted, and HR was increased from 45 bpm to 150 bpm by 15 bpm steps. FD-SS20A (KENYENCE, Japan) was employed to test the flowrate, and a micro-electro-mechanical system sensor CYY8 (Xian HangDong, China) was pressure sensor. SPAB-B2R-R18 (Festo, Germany) acquired drive pressure. All signals were filtered through a second-order Butterworth low-pass filter, and cutoff frequency was set to 20 Hz.

Testing of the iVAD support

In MCS, the pressure and other parameters were then compared under the following two conditions: baseline mode (hemodynamic simulation of HF without iVAD support) and assisted mode (iVAD support). Under HF, the weakened ventricle was unable to pump sufficient blood. The drive pressure was reduced and resistance increased to 90 mmHg, which was used

to simulate ventricular heart failure. Arterial pressure and cardiac output (CO) were failed to maintain the necessary perfusion to peripheral organs, which led to increase of HR by regulating of sympathetic nervous. Therefore, HR of 90, afterload of 80 mmHg, preload of 15 mmHg, and drive pressure of 120 mmHg (output pressure is about 100 mmHg) were selected for MCS of hemodynamics of failing ventricle. All measuring sensors or meters and signal processing were the same as those mentioned above.

Results

We concluded from Figure 4 that the pump synchronous co-pulsation with the native heart and offered a pulsatile flow similar to physiological flow. The output pressure curve displayed a plateau shape similar to that of normal ventricular pattern. Figure 4 also presented a multi-curve for iVAD testing, which included the results for ECG, drive pressure, and output flow. However, although the figure showed favourable drive pressure synchronization with the pulse, a certain response time was noticed in output pressure. Time differences (Δt_1 , Δt_2) between rising pulse edge and maximum output pressure derivative and between declining pulse edge and minimum output pressure derivative were used to represent inflation and deflation delays, respectively.

As shown in Figure 5, the average of 20 cycles of Δt_1 measured 35 ms (± 4 ms), and that of Δt_2 reached 52 ms (± 3 ms). Therefore, we concluded that time difference was a constant value independent of HR. Delay responses of iVAD may also be a fixed value independent of HR. The iVAD operated synchronously with the native heart, as shown by real-time ECG from an analogous human ECG generator.

Figure 6 reveals waveforms of SV and CO of the iVAD obtained through dynamic testing. The left panel and right panel denoted SV and CO, respectively, and (a, e), (b, f), (c, g), and (d, h) represent 60, 80, 100, and

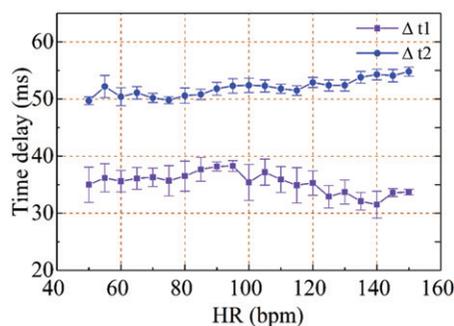


Figure 5. Time delays of drive pressure derivatives of the iVAD.

120 mmHg afterload, respectively. SV (mean of 20 cardiac cycles) increased with increasing drive pressure (P_d) of the iVAD. In Figure 6 above dash dot, SV exceeded 50 mL when in lower HR and higher drive pressure. The balloon underwent plastic deformation owing to the 0.2 mm thickness of balloon. SV decreased with increasing HR, however, CO increased first and then remained stable. Furthermore, CO increased with increasing drive pressure.

Figure 7 shows in detail LVP (the left ventricular pressure), AoP (aortic pressure), P_{drive} (iVAD drive pressure), ECG and P_{mock} (MCS drive pressure) under two test conditions. As illustrated in the figure, shapes of LVP and AoP curves were regular and similar to those of native ventricular and aortic patterns. Table 1 shows hemodynamic values for a healthy heart under HF condition and iVAD support conditions. In the non-assisted mode, maximum and minimum LVPs were found to be 107 and 0 mmHg at 75 bpm, respectively. Systolic and diastolic pressures reached 103 and 74 mmHg, respectively, whereas SV measured 28.9 ml. Such pressure and SV were lower than those of healthy heart. In other cases of HF conditions, the pressure is the same as that of 75 bpm and SV decreased with increasing HR. COs remain about 2.3 L/min. However, under iVAD support condition with 180 mmHg drive pressure, LVP, systolic pressure, SV, and CO remarkably increased to 155 and 143 mmHg, 54.4 ml and 4.1 L/min. LVP, systolic pressure, and SV changes corresponded to 44.9%, 38.8, and 88.2% increases, respectively. Hemodynamic parameters of systemic circulation reached normal human levels in the MCS after iVAD support. SV was below that of health heart but still supplied sufficient blood in resting state. When blood supply are insufficient, drive pressure of iVAD can be properly adjusted. In summary, an iVAD can effectively improve output pressure and SV of a failing ventricle in the MCS.

Discussion

In the experiments of the iVAD testing, we concluded that SV decreased with the increase of HR and afterload because of the iVAD incomplete inflation. To increase SV at high HR such as 120 bpm, the drive pressure can be set to 300 mmHg or higher. The drive pressure of the home-designed drive unit reaches to 500 mmHg at 30–150 bpm.

Figure 7 and Table 1 demonstrated that the iVAD could dramatically improve increased LVP, AoP and SV in the pathological heart. After iVAD support, the hemodynamics recovered to healthy levels. However,

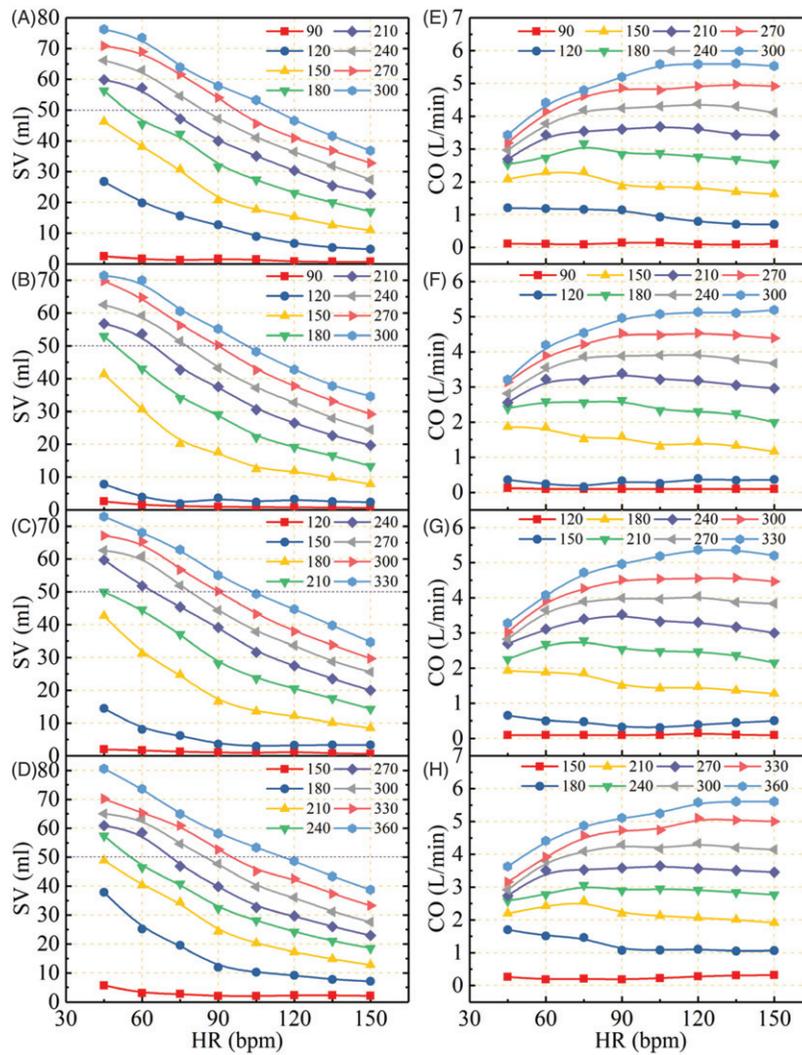


Figure 6. SV and CO of the iVAD varied with drive pressure at different HR and afterload. (a,e) 60 mmHg afterload, (b,f) 80 mmHg afterload, (c,g) 100 mmHg afterload, and (d,h) 120 mmHg afterload. The legend represents the drive pressure, mmHg.

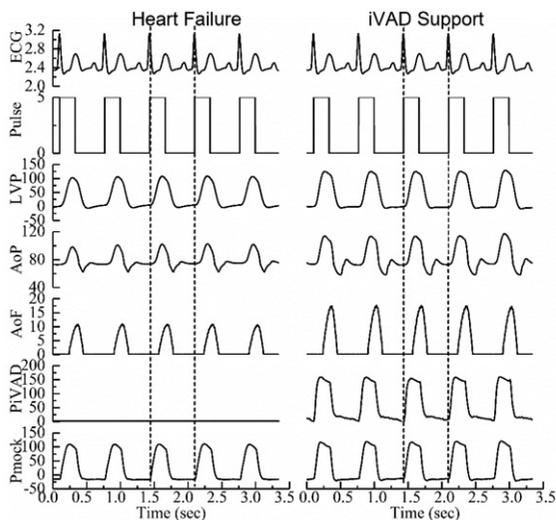
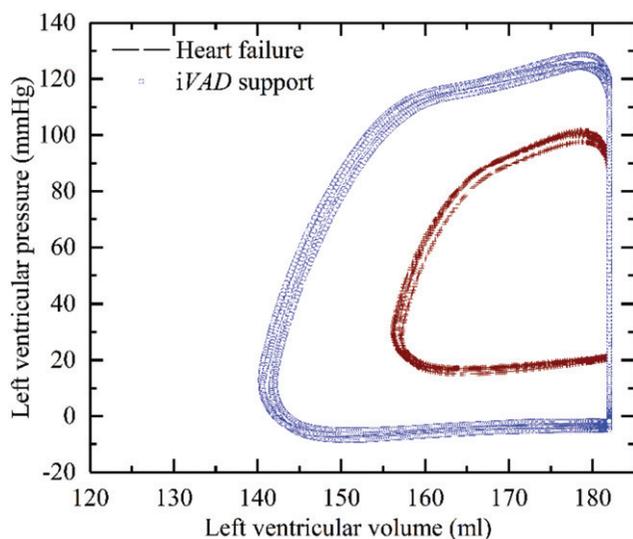


Figure 7. Pressure and flow waveforms under two conditions (baseline represent heart failure, and assisted mode represent iVAD support).

the changed HR and systemic peripheral resistance caused by neuromodulation were out of consideration in MCS. Figure 8 represents the left ventricular pressure-volume (P-V) loop before and after iVAD support. The ventricular volume in the motion cycle was not directly measured, however, the change in ventricular volume was indirectly calculated according to the flow in and out of the ventricle. The driving pressure was set to simulate heart failure condition, the end-diastolic pressure was 15 mmHg and the systolic pressure was 100 mmHg, respectively. The P-V loop translated to the top left and area increased after support. The ventricular ejection pressure and SV were significantly increased. Additionally, the positive and negative driving pressures of iVAD induced diastole and systole, which reduced the end-diastolic pressure from 15 to -12 mmHg and facilitated the return of artery blood to the heart chamber from the atrium. The decreased

Table 1. The failure heart hemodynamics before and after iVAD support.

Parameter	Healthy heart		Heart failure			iVAD support		
HR (bpm)	75	75	90	120	75	90	120	
LVP (mmHg)	120/10	107	106	106	155	158	156	
AoP (mmHg)	120/80	103/74	102/77	100/74	143/87	146/92	145/93	
SV (mL)	60–70	28.9	25.5	18.8	54.4	44	34.2	
CO (L/min)	4.5–5.25	2.2	2.3	2.3	4.1	4	4.1	

**Figure 8.** The pressure-volume loop of the failing ventricle before and after iVAD support at 150 mmHg drive pressure.

HR and system peripheral resistance was led by an increased AoP, which are beneficial for the ventricular recovery. Furthermore, the changes of pulmonary circulatory were not evident by iVAD supporting. Therefore, the related results did not display in this paper.

Although the proposed iVAD improved significantly LVP, AoP, and SV, one of the big challenges is the larger drive size. Hence, reduction in the size of the drive like the smaller and portable drive unit of the C-Pulse heart assist system [12,13] is required. In addition, the iVAD is designed for long-term support, preventing plastic deformation of the balloon is beneficial to life. Although durability and safety have not been confirmed, there is a risk of the balloon rupture. Therefore, it is crucial to improve the life of the balloon pump through structural optimization and the excellent fatigue performance of material. The fatigue performance of balloon needs to be further studies and experiments. Meanwhile, measures should be taken to prevent the balloon rupture. Moreover, the iVAD needs the balloon breakage monitoring micro-electromechanical sensor. Furthermore, the support model of implanting in the ventricle might be detrimental to myocardium, precipitate atrial fibrillation episodes and intrinsic coagulating situations owing to

change the flow field inside the ventricle. Last but not least, the inflated balloon implanted in ventricle may push the papillary muscles and chordae tendineae away, which may cause mitral regurgitation or damage the chorea and papillary muscles. These potential problems require additional studies and for long-term animal experiments.

Conclusions

In conclusion, given the in vitro testing results of iVAD, we concluded the following points: (a) the iVAD can be instantaneously synchronized in co-pulsation with the native heart, and response time will remain unchanged with HR. (b) The proposed device operated similar physiological flow, and regular output pressure is similar to ventricular pressure. (c) The iVAD support testing in a MCS showed that iVAD improved pulse pressure and SV for failing ventricles. Although the results are promising in a MCS, the potential problems need to be confirmed by further animal experiments and solved by clinical studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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