Hemodynamic effects of various support modes of continuous flow LVADs on the cardiovascular system: A numerical study

Authors' Contribution:
Study Design A
Data Collection B
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Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to determine the hemodynamic effects of various support modes of continuous flow left ventricular assist devices (CF-LVADs) on the cardiovascular system using a numerical cardiovascular system model.

Material/Methods: Three support modes were selected for controlling the CF-LVAD: constant flow mode, constant speed mode, and constant pressure head mode of CF-LVAD. The CF-LVAD is established between the left ventricular apex and the ascending aorta, and was incorporated into the numerical model. Various parameters were evaluated, including the blood assist index (BAI), the left ventricular external work (LVEW), the energy of blood flow (EBF), pulsatility index (PI), and surplus hemodynamic energy (SHE).

Results: The results show that the constant flow mode, when compared to the constant speed mode and the constant pressure head mode, increases LVEW by 31% and 14%, and EBF by 21% and 15%, respectively, indicating that this mode achieved the best ventricular unloading among the 3 support modes. As BAI is increased, PI and SHE are gradually decreased, whereas PI of the constant pressure head reaches the maximum value.

Conclusions: The study demonstrates that the continuous flow control mode of the CF-LVAD may achieve the highest ventricular unloading. In contrast, the constant rotational speed mode permits the optimal blood perfusion. Finally, the constant pressure head strategy, permitting optimal pulsatility, should optimize the vascular function.

MeSH Keywords: Blood Flow Velocity • Heart Failure • Ventricular Function, Left

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Background

The CF-LVADs are now widely used clinically in patients with advanced, chronic cardiac failure. The clinical results are gratifying, even after long-term support. Hemodynamic changes after CF-LVADs implantation have been evaluated quite extensively. Left ventricular volume is significantly reduced [1]. The pulsatility of blood flow is reduced as the rotational speed of the pump is increased [2]. The systemic vascular impedance is significantly increased [3]. In addition, changes in the coronary flow and circulation have been demonstrated [4,5]. The coronary flow is reduced as the CF-LVADs support is increased. This might be the consequence of a drop in the left ventricular work itself due to left ventricular unloading and a drop in myocardial oxygen demand. The decreased myocardial oxygen demand may lead to a reactive increase in the coronary vascular resistance through the auto-regulatory system.

The support modes of CF-LVADs could significantly impact the hemodynamic changes and patient outcomes. Differences in the support mode might even account for the differences in results in the patients receiving an LVAD as a bridge to recovery.

Many support modes, achieving various aims, have been designed for CF-LVADs, including Heart Mate II, Jarvik 2000, Heart ware, and BJUT-II VAD. For instance, the constant speed mode, driving the CF-LVADs with a stable rotational speed in the whole process, was first proposed for clinical practice [6,7]. Under this mode, the rotational speed of CF-LVADs is considered as the input of the controller, and the actual speed of CF-LVADs is regulated by the constant speed mode to track the desired one. To achieve a controllable performance of arterial perfusion, the continuous flow mode has been proposed [8–10]. Under this mode, the blood flow rate is chosen as the control input and the support mode regulates CF-LVADs to achieve the desired blood flow rate. Finally, as clinical experience in CF-LVADs improved, the role of the pressure gradient between the left ventricle and ascending aorta has become a very important indicator of the cardiovascular system. Hence, several support modes, choosing this pressure head as the control variables, were designed [11,12]. The pressure head across CF-LVADs, in this mode, is controlled by the controller to track its desired value. However, the precise mechanism of the changes in the hemodynamics and perfusion due to the different support modes remains unclear.

The present work is focused on the study on a circulatory model of the hemodynamic changes in the cardiovascular system under different modes of left ventricular support. Three support modes – "constant speed", "continuous flow", and "constant pressure head" – were studied. Numerical studies have been conducted to evaluate the performances of these 3 support modes. The following indices have been computed on the

Table 1. Abbreviations used in this manuscript.

Abbreviation	
HF	Heart failure
LVADs	Left ventricular assist devices
BAI	Blood assist index
LVEW	Left ventricular external work
EBF	Energy of blood flow
PI	Pulsatility index
EEP	Energy-equivalent pressure
SHE	Surplus hemodynamic energy
MAP	Mean arterial pressure

model: the blood assist index (BAI), the left ventricular external work (LVEW), the energy of blood flow (EBF), the pulsatility index (PI), and the surplus hemodynamic energy (SHE). The abbreviations used are shown in Table 1.

Material and Methods

The design of various support modes

In this paper, 3 support modes, used widely in clinical practice, were designed to evaluate the hemodynamic changes. The first support mode, named "constant speed", drives the CF-LVADs with a constant rotational speed during the whole cardiac cycle. The second control strategy, named "constant pressure head" [13], maintains a constant pressure across the CF-LVADs. For this support mode, the support level of CF-LVADs will be increased during the systolic period to achieve more blood perfusion. The support level is reduced during the diastolic phase to prevent suction. The third support mode, called "continuous flow", is driving the CF-LVADs with a stable flow output of the CF-LVADs.

To compare the respective hemodynamic effects of the 3 different modes, an equivalent support level is necessary. Consequently, the blood assist index (BAI) [14] was used as the indicator of the support level. BAI reflects the energy distribution between the CF-LVADs and the native heart, which is a ratio of the power of CF-LVADs and total power of the cardiovascular system. The validity of this index has been demonstrated in previous publications [15]. In this study, the BAI value was increased from 20% to 90% to cover all types of LVAD support. The 20% BAI value represents the minimal support level and the 90% BAI value represents the maximal unloading of the left ventricle.

In this article, the control variables of the 3 support modes – the rotational speed for constant speed mode, the pressure
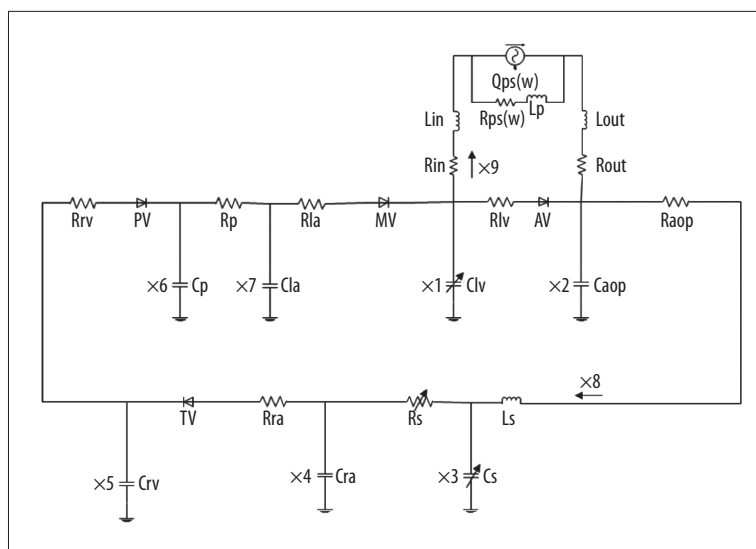
Figure 1. The bypass model of cardiovascular system and blood pump.

head for constant pressure head mode, and the pump flow for continuous flow mode – were regulated to increase the BAI value from 20% to 90%.

The combined model of cardiovascular system and CF-LVADs

A mathematical model of the cardiovascular-pump system was use to evaluate the hemodynamic effects of the different support modes. Figure 1 shows the complete electric circuit analogy of the cardiovascular model in relation to the CF-LVADs. The model includes the left atrium, the active left ventricle, the CF-LVADs, and the peripheral circulation system. The active left ventricle in this model is mimicked by a time-varying elastance function: $E(t)=1/C(t)$. In this work, the elastance function was defined as:

$$E(t) = (E_{max} - E_{min})E_n(t_n) + E_{min} \qquad (1)$$

Where E_{max} and E_{min} denote the maximum and minimum values of $E(t)$; and $E_n(t)$ represents the normalized time-varying elastance function [15,16]:

$$E_n(t_n) = 1.55 * [\frac{(t_n/0.7)^{1.9}}{1 + (t_n/0.7)^{1.9}}] * [\frac{1}{1 + (t_n/1.17)^{21.9}}] \qquad (2)$$

Where $t_n=t/t_{max}$ and $t_{max}=0.15*T_c+0.2$; T_c represents the cardiac cycle interval (i.e., $T_c=60/HR$, where HR represents the heart rate of the native heart). In this work, the HR was fixed at 75 bpm. This model was compared to clinical data, and the results demonstrate that the model can accurately mimic the hemodynamic performance of the circulatory system [17]. The complete description and the parameters' values (listed in Table 2) of the model were set as heart failure patient, as reported by Gu et al. [18].

According to previous research by our group, the mathematic model of CF-LVADs is described as a function of the flow rate, pressure head, and rotational speed of the pump, which is denoted by:

$$P_P(\omega, Q_{PO}) = 0.0115\omega^2 + 0.079\omega - 15.5 - (0.086\omega - 0.58)Q_{PO} + L_P\frac{dQ_{PO}}{dt} \qquad (3)$$

In which Q_{PO} represents the flow rate of the pump (L/min), P_P is the pressure head of the pump (mmHg), ω is the rotational speed (R/s), and L_P is the inertia of blood in intra-aorta pump. A detailed description of model of the BJUT-II VAD and its identification is reported in Chang [19]. Note that, although equation (3) is derived from BJUT-II VAD, it is confirmed to be appropriate for CF-LVADs placed between the left ventricular apex and the ascending aorta.

The hemodynamic analysis

The left ventricular external work (LVEW) as an index of cardiac recovery is defined to indicate the energy of native heart, denoted as:

$$\varpi_{LV} = \frac{1}{T_c}\int_0^{T_c} P_{LV}(t) * Q_{LV}(t)dt \qquad (4)$$

in which ωLV represents LVEW, $P_{LV}(t)$ is left ventricular pressure, $Q_{LV}(t)$ is left ventricular flow, and T_c is cardiac cycle.

The input work of systemic circulation as an index of blood perfusion was defined to indicate the energy of circulatory system, denoted as:

$$\varpi_{sys} = \frac{1}{T_c}\int_0^{T_c} P_{sys}(t) * Q_{sys}(t)dt \qquad (5)$$

in which ω_{sys} represents LVEW, $P_{sys}(t)$ is the left ventricular pressure, $Q_{sys}(t)$ is the left ventricular flow, and T_c denotes the cardiac cycle.

Table 2. Model parameters.

Parameter		Value	Physiological Meaning
Compliances (ml/mmHg)	C_{lv}	Time-varying	Left ventricular compliance Clv=1/E(t)
	C_{aop}	0.04	Aortic compliance
	C_s	Time-varying	System compliance Cs=C
	C_{ra}	4.4	Right atria compliance
	C_{rv}	4.8	Right ventricular compliance
	C_p	4.8	Pulmonary systemic compliance
	C_{la}	4.4	Left atria compliance
Resistances (mmHg·sec/ml)	R_{lv}	0.01	Left ventricular resistance
	R_{aop}	0.0398	Arterial resistance
	R_s	Time-varying	System resistance Rs=R
	R_{ra}	0.01	Right atria resistance
	R_{rv}	0.001	Right ventricular resistance
	R_p	0.02	Pulmonary systemic resistance
	R_{la}	0.01	Left atria resistance
	R_{in}	0.0677	Pump input resistance
	R_{out}	0.0677	Pump output resistance
Inertance (mmHg·sec²/ml)	Ls	0.0005	Inertance of blood in system
	Lp	0.0005	Inertance of blood in pulmonary
	Lin	0.00127	Inertance of input
	Lout	0.00127	Inertance of output
Valves	AV		Aortic valve
	TV		Tricuspid valve
	PV		Pulmonary valve
	MV		Mitral valve

Kawahito [20] proposed use of PI to evaluate the pulsatility blood flow of VADs. Research findings indicate that the change of pulsating flow was exponential, with different levels of assist ratio, in an animal experiment. In this article, the pulsatility index (PI) [21] is used to estimate pulsatility of blood pressure. In this paper, it is defined as follows:

$$PI = \frac{P_{SB} - P_{DB}}{MAP} \qquad (6)$$

in which P_{SB} is the systolic blood pressure, P_{DB} represents the diastolic pressure, and MAP is the mean arterial pressure.

The energy-equivalent pressure (EEP) formula is defined as the ratio of the area beneath the hemodynamic power curve (fFP_{dt}) to the area beneath the pump flow curve (fF_{dt}) during each pulse cycle [22]. It represents the hemodynamic energy per unit volume of blood. It is calculated as follows:

$$EEP = \frac{\int FP dt}{\int F dt} \qquad (7)$$

in which *F* is the blood flow (in liters per minute) and *P* represents the arterial pressure (in mmHg). SHE is calculated in response to EEP and MAP as follows:

$$SHE(ergs/cm^3) = 1332(\frac{\int FP dt}{\int F dt} - MAP) \qquad (8)$$

in which SHE represents the extra energy required for generation of pulsatile flow (PF) in terms of energy (not pressure) units and is thus a physiologically relevant measure of pulsatility because the generation of PF in the body is

Table 3. Comparison between simulating result and clinical data.

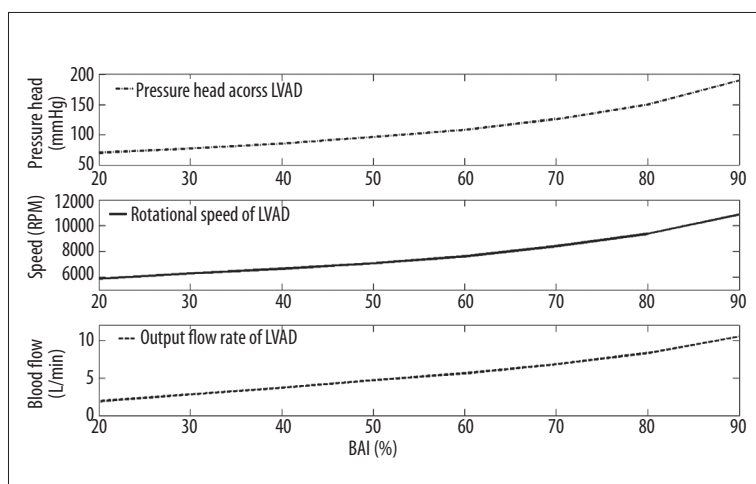|	Normal value	Clinical data	Before support	Error (%)
SBP (mmHg)	90~140	123	117	4.9
DBP (mmHg)	60~90	55	60	9
ESV (ml)	32~47	99.3	86	13.4
EDV (ml)	80~172	153.6	149	3
MAP (mmHg)	90~95	86	84	2.3

Figure 2. The relationship between the control variable of three support mode and the BAI.

dependent on an energy gradient rather than a pressure gradient [23].

Results

The hemodynamic effects of the different support modes of the CF-LVADs were evaluated in numerical studies. The characteristics of the model before CF-LVADs support were simulated to validate the model. The clinical data and the results of simulation are listed in Table 3. In this table, the normal value is derived from the literature [18], and the clinical value was measured in clinical practice at Peking University third hospital. The results show that the proportional error of the systolic pressure (SBP) and the diastolic pressure (DBP) is 4.9% and 9%, respectively. The proportional error of end-diastolic volume (EDV) and end-systolic volume (ESV) was 13.4% and 3%, respectively. The proportional error of MAP was about 2.3%.

Figure 2 shows the relationship between the control variables of the 3 support modes and the BAI value. In this study, the control variables of 3 support modes, including the pressure head across CF-LVADs, flow rate of CF-LVADs, and the rotational speed of CF-LVADs, were increased to achieve the BAI value increasing from 20% to 90%. For the constant speed mode, the

desired rotational speed of CF-LVADs is increased from 5880 RPM to 10 860 RPM. Similarly, the desired pressure head of CF-LVADs in constant pressure head mode is increased from 70 mmHg to 190 mmHg. The pump flow rate in the continuous flow mode increased from 1.9L/min to 10.5L/min.

Figure 3A shows the changes in the LVEW in the bypass model. Following the rise of BAI, the continuous flow has the minimum value of the LVEW. In the constant rotational speed mode and the constant pressure head mode, the LVEW is increased by 31% and 14%, respectively. In other words, the continuous flow control strategy may achieve higher ventricular unloading.

Figure 3B shows EBF in the bypass model. The 3 curves show the relationship between EBF and BAI in the bypass model. The constant rotational speed mode generates the highest energy of blood flow when compared to the continuous flow and the constant pressure head modes. EBF is improved by 21% and 15%, respectively. This suggests that the constant rotational speed mode has the best impact on the arterial perfusion.

Figure 4 represents the relationship between the pulsatility and the blood assist index. Before pump support,, PI was roughly 0.6. PI was reduced with the increase of BAI after support
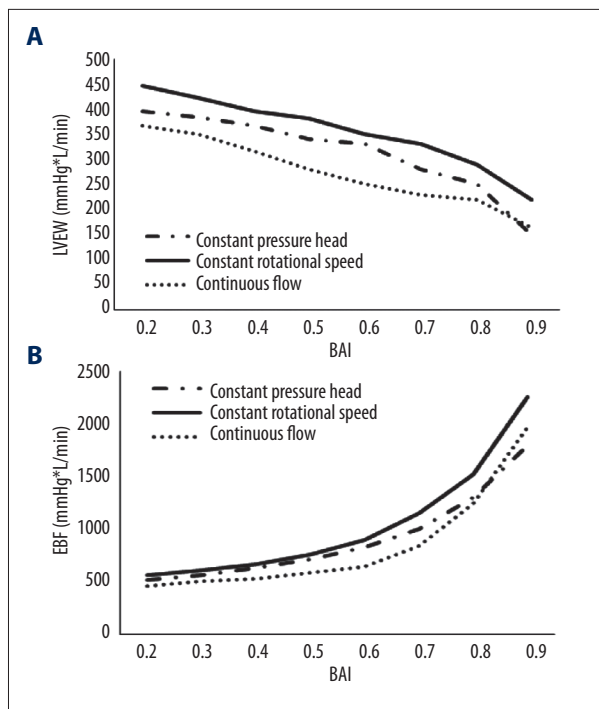
Figure 3. (**A**) The left ventricular external work of bypass model; (**B**) The energy of blood flow of bypass model.
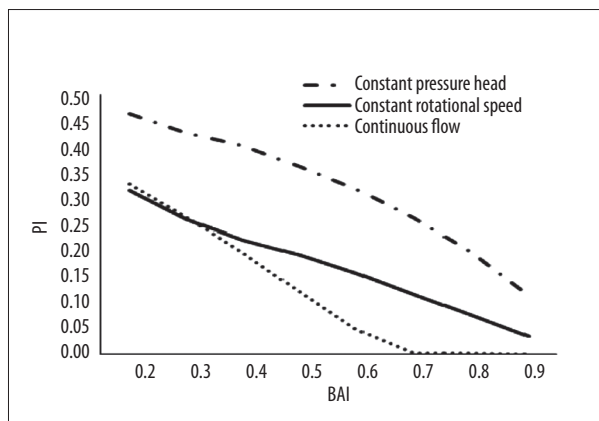

Figure 4. The curve of PI with the blood assist index.

Figure 5. The curve of the change of SHE along with the blood assist index.

Figure 6. The opening time of aortic valve.

with bypass pump in the 3 support modes. The continuous flow mode curve shows that, PI was significant decreased and leveled off at 0 during more than 70% of BAI. Comparing the 3 support modes, the constant pressure head mode had the maximum value, suggesting that this mode had the best impact on the vascular function.

Figure 5 shows the changes in SHE of the 3 support modes along with the increase of BAI. SHE was negatively related to BAI in the 3 modes. Among the 3 support modes, the constant pressure head mode achieved the highest SHE value at the same BAI level. In contrast, the continuous flow support mode had the lowest SHE value at each BAI level. This means
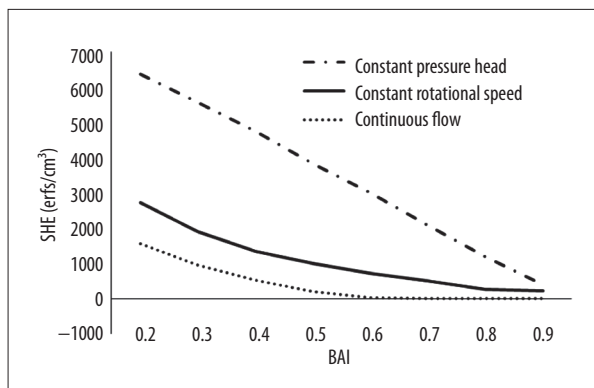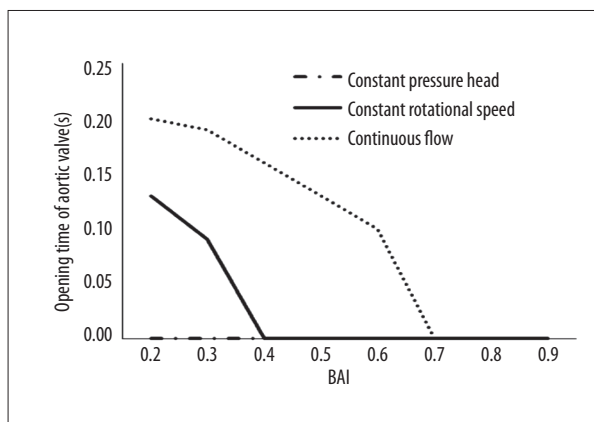
the constant pressure head mode has more benefit for restoring the pulsatility of blood pressure, compared with other 2 support modes.

Figure 6 shows the opening time of the aortic valves. In the simulated model, the aortic valves open when the ventricular pressure is higher than aortic pressure and close in the opposite situation. The aortic valves in the constant rotational speed mode and in the continuous flow support mode were closed at 40% and 70% BAI, respectively. This suggests that the continuous flow support mode may be optimal to protect the function of the native aortic valve.

Discussion

In the initial phase of the clinical experience, the studies on support modes of CF-LVADs using continuous flow pump mainly focus on the stability and the robustness. However, currently, many reports indicate that the support mode can directly change the hemodynamic state of the cardiovascular system. Differences in the support mode might explain the unpredictable results achieved in patients supported in myocardial

recovery and reverse left ventricular remodeling. Birks [24] et al. reported that the reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved in a substantial proportion of patients with CF-LVADs support. Ising [25] et al. reported that when the waveform of blood flow is designed to be synchronized with the cardiac beat, the pulsatility of the arterial blood flow increased significantly. Kishimoto [26] et al. found that when the rotational speed of the CF-LVADs is synchronized to the heart beat, the arterial perfusion is improved and the risk of aortic insufficiency is reduced. Similarly, Heredero et al. [27] reported that the synchronous mode of CF-LVADs operation may be satisfy the blood demand and restore the pulsatility of the aortic pressure. These studies show that the various support modes can significantly change the hemodynamic state of cardiovascular system.

However, the differences of the hemodynamic effects of the different support modes are not clear. The present work could provide insight into the precise mechanism involved and it also could give useful information on choosing the appropriate support modes in response to the condition of the patients and the final objective of the CF-LVADs support (bridge to cardiac replacement or bridge to recovery).

It has been generally believed that heart failure (HF) is a progressive and irreversible disease due to complex mechanisms of cardiomyopathy. However, there is increasing evidence that mechanical unloading obtained by the use of CF-LVADs may reverse the progression of HF, permit myocardial function recovery, and ultimately the explantation of the device [28]. For instance, Klotz et al. [29] reported that left ventricular function recovery is possible when given sufficient mechanical unloading. Manginas et al. [30] found that after CF-LVADs implantation, a transient increase occurs in the number of circulating progenitor cells, which may contribute to the improvement of tissue perfusion and cardiac recovery. Drakos et al. [31] reported that the sympathetic innervation in the failing heart was significantly improved by LVADs. Chen et al. [32] reported that LVADs support could alter the gene expression and found that there are 130 gene transcripts achieving the strict criteria for up-regulation and 49 gene transcripts for down-regulation after LVADs support. Saito et al. [33] found that cardiac fibrosis, which has a significant correlation with the cardiac function, was significantly reduced after support by LVADs. These various studies confirm that mechanical left ventricular unloading is the key factor in the improvement of the ventricular reverse remodeling.

In this paper, the LVEW was chosen as the indicator to evaluate the ventricular unloading performance of varied support modes. LVEW reflects the left ventricular load level, having a direct effect on the left ventricular reverse remodeling, in the whole cardiac cycle [34]. A lower LVEW value corresponds with a lower left ventricular load. In the present work, the continuous flow mode achieved the lowest LVEW value compared with other 2 support modes, indicating that the continuous flow mode can achieve better left ventricular unloading performance and promotes myocardial reverse remodeling.

EBF represents the input energy of blood, which is injected into the ascending aorta. A higher EBF value corresponds with more blood input energy. Generally, the aortic pressure and the blood flow are considered as the important indicators, reflecting the capacity of blood perfusion. However, the change of peripheral resistance of the circulatory system may affect the performance of aortic pressure and blood flow, which will reduce the accuracy of the evaluation. According to the hemodynamic theory, the energy is the essential reason for keeping the blood circulating. Hence, it is reasonable to think that in evaluation of the capacity of blood perfusion, neither use of aortic pressure nor direct blood flow, but rather a combination of them in the form of energy, is best. In the present work, the constant speed mode achieved the highest EBF among the 3 modes, meaning that the constant speed mode improves blood perfusion.

The above-mentioned results show that various support modes have different physiological significances and the operators should choose the appropriate support mode in response to patient state. If the aim of treatment is to satisfy the blood demand of the circulatory system, the constant speed mode will be chosen. In contrast, if the aim of treatment is to promote myocardial reverse remodeling, the continuous flow mode will be better.

The present study clearly shows that the different support modes of the CF-LVADs have a very different impact on the pulsatility. Both PI and SHE are important indicators of the pulsatility of aortic pressure or blood flow. The higher their values are, the higher the pulsatility of the pressure is. At the same support level, the constant pressure head strategy can achieve the highest pulsatility of the 3 support modes. The role of the pulsatility of the aortic blood flow is quite controversial and differing opinions have been published. However, it seems now that there is general agreement on some facts: the pulsatility is quite beneficial in patients in cardiogenic shock with peripheral organ dysfunction [35], and is less necessary in patients with an adequate peripheral end-organ function [36,37]. The effect of pulsatility on the vascular function is also quite controversial. Prolonged diminished pulsatility might lead to vascular stiffening, which increases the ventricular afterload, reduces myocardial perfusion because of early (systolic) AOP wave reflections, and attenuates baroreflex sensitivity [38]. Finally, pulsatility has an impact on the viscoelastic properties. With increased pulsatility, the viscoelastic interaction of the erythrocytes is reduced, which in turn reduces viscosity

and, therefore, blood flow resistance [39]. As a result, tissue oxygen delivery is enhanced in the renal circulation and brain compared with continuous-flow pump. Consequently, it can be assumed that the constant pressure head mode is optimal for restoring blood and vascular function.

The biomechanics of the aortic valve change during CF-LVADs support [40]. The clinical impacts of these changes are now clearly shown, as the number of patients on CF-LVADs support is increasing and as the time of support is prolonged over many months and even years [41]. Martina et al. [42] reported that 58% of patients who receive CF-LVADs treatment have commissural fusion of the aortic valve leaflets. Aggarwal et al. [43] reported that aortic insufficiency developed over time in a significant number of patients who received CF-LVADs treatment. The function of the aortic valve should be preserved by a selection of the optimal support mode for driving the CF-LVADs. The present data show that the aortic valve, if the constant pressure head mode is used, is always closed at a BAI ranging from 20% to 90%, as shown in Figure 6. The aortic valves in the constant rotational speed mode and in the continuous flow support mode are closed at 40% and 70% BAI, respectively. This suggests that the continuous flow support mode may be optimal to protect the function of the native aortic valve.

The limitations of study

The interaction between support modes and right ventricular function is a very important issue for heart failure patients with CF-LVADs support. Many studies found that left ventricular unloading can affect the position of the ventricular septum [44], and further affect the right ventricular function

[45,46]. For instance, if the left ventricular unloading level exceeds the normal range, the ventricular septum will be shifted to the left ventricle by the pressure gradient between left and right ventricles. This phenomenon will impair the right ventricular function. In the future, the mechanism of varied support modes on the left ventricular septum and right ventricular function will be studied.

These data, obtained in a simulation model, have to be confirmed by precise animal experimentation and the evaluation of the hemodynamic changes in the 3 different modes of function of a continuous flow CF-LVADs. They emphasize the need for precise study of hemodynamic and perfusion to optimize peripheral perfusion, and the possibility of left ventricular recovery and aortic valve preservation.

Conclusions

Three support modes of function of the CF-LVADs – the continuous flow mode, the constant rotational speed and the constant pressure head – were evaluated in a model using various parameters: the blood assist index (BAI), the left ventricular external work (LVEW), the energy of blood flow (EBF), pulsatility index (PI), and surplus hemodynamic energy (SHE). The numerical studies show that the various support modes can generate different hemodynamic effects on the cardiovascular system. The continuous flow appears to be most beneficial for protecting valve function. The constant rotational speed mode has the best performance in blood perfusion and ventricular unloading. Finally, the constant pressure head strategy can achieve the highest pulsatility of pressure, which may have benefit for keeping vascular functions.

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