Effects of Pulsatile Frequency of Left Ventricular Assist Device (LVAD) on Coronary Perfusion: A Numerical Simulation Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Left ventricular assist devices (LVADs) with counter-pulsation mode have been widely used to support left ventricular function and improve coronary circulation. However, the frequency characteristics of the coronary system have not been considered. The aim of this study was to investigate the effects of pulsatile frequency of LVADs on coronary perfusion.

Material/Methods: First, a lumped parameter (LP) model incorporating coronary circulation, systemic circulation, left heart, and LVAD was established to simulate the cardiovascular system. Then, the frequency characteristics of the coronary system were analyzed and the calculation results showed that the pulsatile frequency of the LVAD has a substantial effect on coronary blood flow. To verify the accuracy of the theoretical analysis, the hemodynamic effects of the LVAD on the coronary artery were compared under 4 support modes: co-pulsation mode, and counter-pulsation modes in synchronization ratios of 1: 1, 2: 1, and 3: 1.

Results: We found that the coronary flow increased by 5% when the working mode changed from co-pulsation to counter-pulsation in a synchronization ratio of 1: 1, and by an additional 6% when the working mode changed from counter-pulsation in a synchronization ratio of 1: 1 to counter-pulsation in a synchronization ratio of 3: 1.

Conclusions: This work provides a useful method to increase coronary perfusion and may be beneficial for improving myocardial function in patients with end-stage heart failure, especially those with ischemic cardiomyopathy (ICM).

MeSH Keywords: Coronary Vessels • Heart-Assist Devices • Myocardial Reperfusion • Pulsatile Flow

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Background

The heart failure (HF) caused by ischemic cardiomyopathy (ICM) is common and is mainly related to insufficient coronary perfusion [1–4]. In recent years, continuous-flow left ventricular assist devices (CFLVADs) have been widely used in destination therapy for end-stage heart failure, with high reliability and durability [5–7]. However, several studies have shown decreased coronary flow under CFLVADs support [8,9]. The main reasons for decreased coronary perfusion are the decrease of left ventricular work and myocardial oxygen demand [9,10]. Moreover, under constant rotational speed, the mechanical characteristics of CFLVADs are also responsible for diminished coronary flow [11].

To increase coronary flow, Ando et al. [11] proposed a counter-pulsation mode for CFLVADs to improve myocardial perfusion. Lim et al. [12] also reported that the LVAD with counter-pulsation mode achieved better physiological coronary blood perfusion. Naito et al. [13] presented a rotational speed modulation system for CFLVADs to decrease the left ventricular (LV) load and increase coronary flow. However, under long-term support, CFLVADs may impair arterial contractility and myocardial microvascular structure, thus limiting coronary flow and causing myocardial ischemia [14,15]. Therefore, the flow profiles and pulsatility of LVADs still need to be optimized to improve destination therapy.

The cardiovascular system is a complicated impedance network [16,17]. The frequency characteristics of the cardiovascular system are closely related to blood perfusion. Wang et al. [18] reported that the arterial system had an optimal perfusion at its natural frequency. Gao et al. [19] showed that the heart beat generally matched the frequency characteristics of the arterial system, with low power consumption. Zhuang et al. [20] reported that when the pump speed was consistent with the resonance frequency of the arterial system, the perfusion of the arterial system was effectively improved. Rebholz et al. [21] analyzed the interaction between the high-frequency operating LVAD and the cardiovascular system to reduce the pump body size. However, in these studies, the coronary system was not included and the frequency characteristics of the coronary system were not investigated. Coronary flow is an important factor in determining cardiac function. However, the effects of pulsatile frequency of the LVAD on coronary perfusion have not been reported.

In this study we investigated the effects of pulsatile frequency of the LVAD on coronary perfusion. Firstly, we established a lumped parameter (LP) model of the cardiovascular system and analyzed the effects of coronary system frequency characteristics on blood perfusion. Then, the effectiveness of the established cardiovascular model was verified by comparing the present results with those of a previous study. Finally,
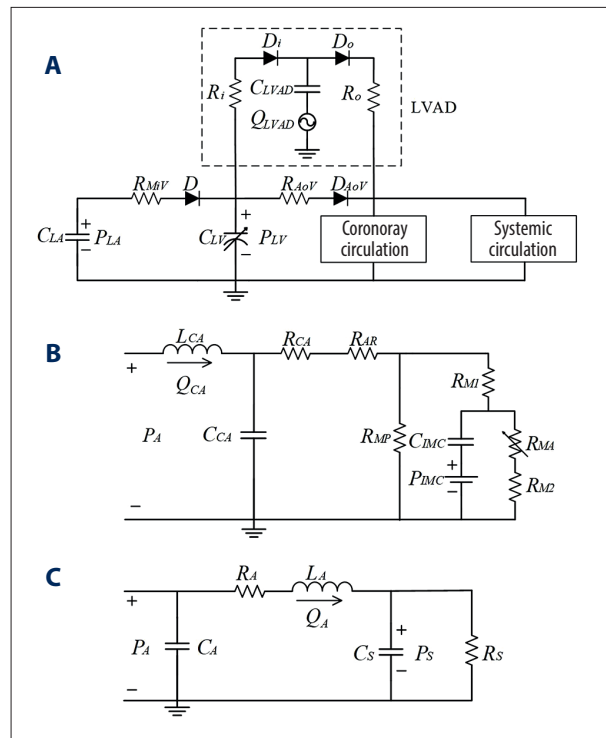
Figure 1. Circuit diagram of the cardiovascular system model. (**A**) Cardiovascular system and left ventricular assist device (LVAD), (**B**) Coronary circulation, (**C**) Systemic circulation. R – vascular resistance; C – vascular compliance; L – blood inertia; D – valve; P – pressure; Q – blood flow; LV – left ventricle; LA – left atrium; CA – coronary artery; A – aorta; S – total peripheral artery; MiV – mitral valve; AoV – aortic valve; AR – arteriolar resistance; IMC – intramyocardial vessels; R_{M1}, R_{MA}, R_{M2} and R_{MP} – the myocardial resistances.

the hemodynamic effects of the LVAD on the coronary artery were compared under 4 support modes: co-pulsation mode, and counter-pulsation modes in synchronization ratios of 1: 1, 2: 1, and 3: 1.

Material and Methods

In the cardiovascular system model, the equivalent circuit lumped parameter model is widely used to describe hemodynamic characteristics. As shown in Figure 1, the mathematical model consists of 2 components: the cardiovascular system and the LVAD. Kirchhoff's law is applied to the network nodes, which produces 14 first-order non-homogeneous differential equations. Then, these equations are solved in MATLAB (The Math Works, Natick, MA, USA) with the ODE23t algorithm. The initial values are estimated in a steady-state healthy hemodynamic system, as previously described [22,23].

Table 1. Parameter values of the lumped parameter model.

Parameters	Values	Parameters	Values
R_A	0.032 mmHg·s/ml	R_{M1}	9.751 mmHg·s/ml
R_S	1.2 mmHg·s/ml	R_{M2}	24.752 mmHg·s/ml
R_{MiV}	0.005 mmHg·s/ml	C_{LA}	4.4 ml/mmHg
R_{AoV}	0.005 mmHg·s/ml	C_{LVAD}	0.1 ml/mmHg
R_i	0.03 mmHg·s/ml	C_{CA}	0.00005 ml/mmHg
R_o	0.03 mmHg·s/ml	C_{IMC}	0.001 ml/mmHg
R_{CA}	1.5 mmHg·s/ml	C_A	0.08 ml/mmHg
R_{AR}	0.75 mmHg·s/ml	C_S	1.2 ml/mmHg
R_{MP}	37.5 mmHg·s/ml	L_{CA}	0.0652 mmHg·s^2/ml
R_{MA}	0.9 PLV mmHg·s/ml	L_A	0.0005 mmHg·s^2/ml

R_A – aorta resistance; R_S – total peripheral artery resistance; R_{MiV} – mitral valve resistance; R_{AoV} – aortic valve resistance; R_i – inlet valve resistance of LVAD; R_o – outlet valve resistance of LVAD; R_{CA} – coronary artery resistance; R_{AR} – arteriolar resistance; R_{MP}, R_{MA}, R_{M1}, and R_2 – the intramyocardial resistances; C_{LA} – left atrium compliance; C_{LVAD} – blood cavity compliance of LVAD; C_{CA} – coronary artery compliance; C_{IMC} – intramyocardial vessels compliance; C_A – aorta compliance; C_S – total peripheral artery compliance; L_{CA} – coronary artery inertance; L_A – aorta inertance.

Model of cardiovascular system

The cardiovascular system is modeled using a LP electric network, which includes 3 parts: left heart, systemic circulation, and coronary circulation. To analyze the frequency characteristics of the coronary system, the coronary circulation model was constructed from 3 main components: the coronary artery, the arteriolar resistance, and the myocardial vessels [24,25], as shown in Figure 1B. The coronary flow originates from the aorta root and flows into the vein [26]. The arteriolar resistance R_{AR} is mainly responsible for hyperemia and baseline conditions. Because ventricular pressure acts upon intramyocardial (IMC) vessels, the IMC pressure is represented by an external pressure element (P_{IMC} in Figure 1). The variable intramyocardial resistance R_{MA} depends on P_{IMC} and is modeled as $R_{MA}=0.9P_{IMC}$, $P_{IMC}=P_{LV}$ [25], where P_{LV} represents left ventricular pressure.

The left heart was modeled as a chamber pump with 2 valves that control the direction of ventricular blood flow. The ventricle was simulated with a commonly used time-varying elastance model [23,27], and the atrial compliance was characterized by a capacitor of electric analog [28]. The function C_{LV} (t) of ventricle compliance was adapted from a previous model [29]. The function C_{LV} (t)=1/E(t) can be calculated as:

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

$$E_n(t) = 1.55 \times \left[\frac{\left(\frac{t_n}{0.7}\right)^{1.9}}{1+\left(\frac{t_n}{0.7}\right)^{1.9}} \right] \times \left[\frac{1}{1+\left(\frac{t_n}{1.17}\right)^{21.9}} \right] \quad (2)$$

where $t_n=t/T_{max}$, $T_{max}=0.2+0.15t_c$, $t_c=60/HR$ is the cardiac cycle, and HR is heart rate. The $E_{max}=1.5$ mmHg under the healthy condition and the $E_{max}=0.713$ under the HF-III condition.

The systemic circulation was modeled by the aorta and the typical four-element Windkessel model (W4S) [23], as shown in Figure 1C. The aorta compliance is represented by C_A. In the W4S model, the model parameters are R_A, L_A, C_S, and R_S, which represent the aortic resistance, the aortic blood inertia, total arterial compliance, and total peripheral resistance, respectively. The parameters of the cardiovascular model were adapted from previous studies [22–29], as summarized in Table 1.

Model of LVAD

The LVAD model was established based on previous research [12,30]. The prototype of the LVAD is a pulsatile pneumatic ventricular assist device (the Hybrid Ventricular Assist Device; Korea Artificial Organ Center, Seoul, Korea) [30]. As shown in Figure 1A, the LVAD model consists of a flow generator (Q_{LVAD}), a blood cavity (C_{LVAD}), and 2 valves (D_i and D_o). The flow profiles of the proposed pump model are simulated directly as sinusoidal waves for simplification, as the sinusoidal-wave-flow profiles parameterized with the stroke volume, the pulsatile frequency, and the phase shift [21]. The phase shift φ was introduced to represent the time delay between the start of the native cardiac cycle and the middle of the pump systole. The starting point of the cardiac cycle was defined as the middle of native heart systole. As shown in Figure 2, the phase shift φ was simulated as 50%, 25%, and 16.6% to characterize the counter-pulsation mode with the synchronization
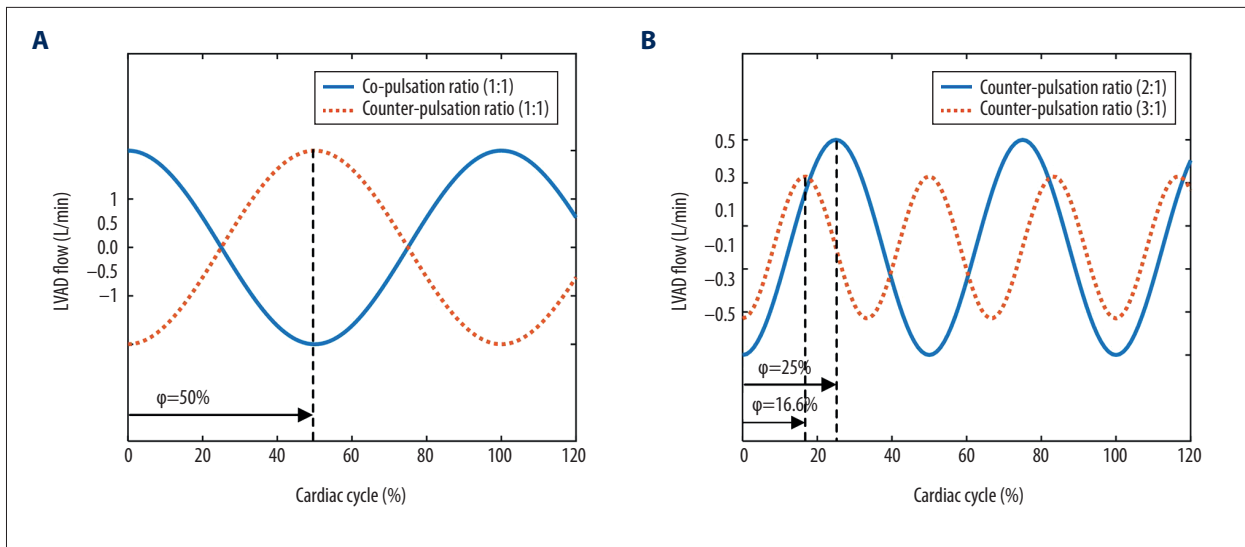
Figure 2. Flow waveforms of the LVAD in the co-pulsation mode and the counter-pulsation modes. The negative flows represent the pump's diastole and positive flows represent the pump's systole.

ratio of 1: 1, 2: 1, and 3: 1, respectively. To ensure comparable results for various operation modes, the stroke volume of the LVAD was further manually adjusted to keep mean aortic pressure and LVAD flow constant [12].

Frequency characteristics of the coronary system

The main factors affecting the coronary blood flow are blood pressure within the aortic root and vascular resistance. Generally, the coronary blood flow is about 250 ml/min and predominantly occurs during diastole [31]. Hence, the frequency characteristics of the coronary system were analyzed during diastole in our model. The diastolic ventricle pressure is very small and is close to zero. Therefore, the IMC pressure (P_{IMC}) and intramyocardial resistance (R_{MA}) can be ignored in the diastole. The relationship between the input impedance $Z_{(j\omega)}$ and frequency f can be expressed as:

$$Z(jw) = \frac{P_{cA}(j\omega)}{Q_{CA}(j\omega)} = \frac{P_A(j\omega)}{Q_{CA}(j\omega)} = \frac{jwL_{CA}a_1 + jwL_{CA}b_2 + a_1b_2}{a_1 + b_2} \quad (3)$$

where j is an imaginary unit and $\omega = 2\pi f$ is the angular frequency. The coefficients a_1 and b_2 can be calculated as:

$$a_1 = \frac{1}{jwC_{CA}}, \ a_2 = \frac{1}{jwC_{IMC}} \quad (4)$$

$$b_1 = R_{M1} + \frac{a_2(R_{M2}+R_{MA})}{a_2+R_{M2}+R_{MA}}, b_2 = R_{CA} + R_{AR} + \frac{b_1R_{MP}}{b_1+R_{MP}} \quad (5)$$

The magnitude of input impedance can be obtained by the above equations, as shown in Figure 3, showing that the magnitude of input impedance initially decreases and then increases with increasing frequency. The magnitude of impedance reaches the smallest value near 20 Hz, which is the smallest impedance frequency point. Further, the coronary impedance
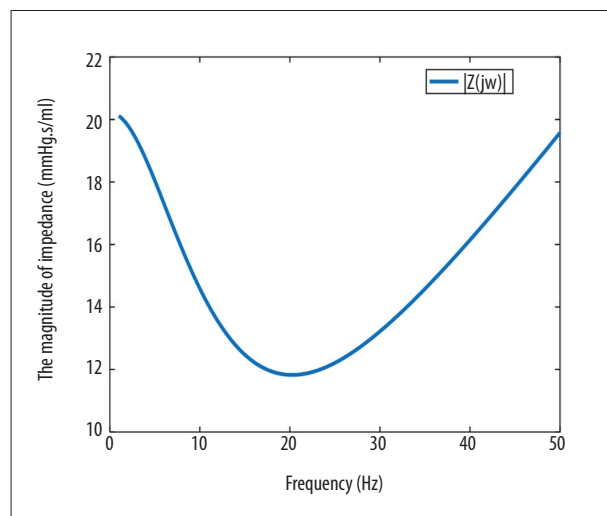
Figure 3. Frequency characteristics of the coronary system.

seriously restricts the coronary flow. Hence, the pulsatile frequency of LVAD can have a substantial influence on the coronary flow.

However, since the high pulsatile frequency requires more reliable and accurate control of the LVAD, the smallest impedance frequency is difficult to realize in clinical applications. Therefore, our study mainly investigated the effects of increased pulsatile frequency on coronary flow. In addition, when the pulsatile frequency increases by 2 Hz, the magnitude of coronary impedance decreases by about 4%. In other words, the coronary blood flow can increase by about 4% (10 ml/min) when the pulsatile frequency is 3 Hz.
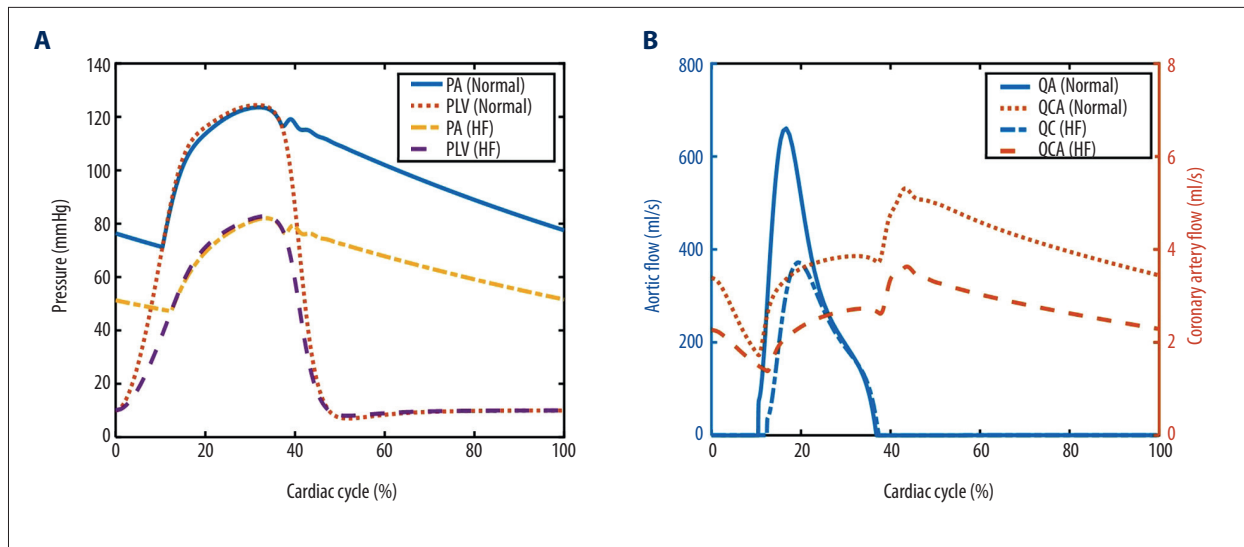
Figure 4. Simulated pressure waveforms (**A**) and flow waveforms (**B**) in the cardiovascular system. PA – aortic pressure; PLV – left ventricular pressure; QA – aortic flow; QCA – coronary artery flow.

Table 2. Key hemodynamic results for simulated normal and severe HF conditions (normal and HF-III, respectively).

Parameters	Normal range (reference [35,36])	Simulated normal results	Simulated HF esults
Diastole LV pressure (mmHg)	4–12	10	10
Systole LV pressure (mmHg)	90–140	125	83
Diastole aortic pressure (mmHg)	60–90	72	46
Systole aortic pressure (mmHg)	90–140	124	82
Cardiac output (L/min)	4.7–7.1	5.4	3.5
Coronary artery flow (ml/min)	200–300	234	157
Stroke volume (ml)	51–110	89	58

To further evaluate the effectiveness of coronary perfusion, the total input work (TIW) [20] and energy equivalent pressure (EEP) [32,33] were introduced. The TIW is an important index of hemodynamic power and is calculated as:

$$\text{TIW} = \frac{0.0022}{T_{\text{HR}}} \times \left(\int_0^{T_{\text{HR}}} P_{CA}(t) \times Q_{CA}(t)dt \right) \quad (6)$$

where T_{HR} is the cardiac cycle, $P_{CA}(t)$ is the coronary artery pressure, and $Q_{CA}(t)$ is the blood flow of the coronary artery. EEP denotes the hemodynamic energy per unit volume, which is defined as:

$$\text{EEP} = \left(\int_0^{T_{\text{HR}}} CF(t) \times CP(t)dt \right) / \left(\int_0^{T_{\text{HR}}} CF(t)dt \right) \quad (7)$$

where $CF(t)$ is the instantaneous coronary artery flow and $CP(t)$ is the instantaneous coronary artery pressure.

Results

Model verification

The simulated pressure and flow waveforms of the cardiovascular system are shown in Figure 4 and the key hemodynamic results for simulated normal and severe HF conditions are summarized in Table 2. In normal conditions, the peak systolic pressure of LV was about 125 mmHg and the cardiac output was approximately 5.4 L/min. However, the peak systolic pressure of LV declined to 83 mmHg and the cardiac output was about 3.5 L/min in the HF condition. We also found that the coronary flow of the HF condition had a 33% decrease compared with the normal condition, which was approximately consistent with previous reports [34].
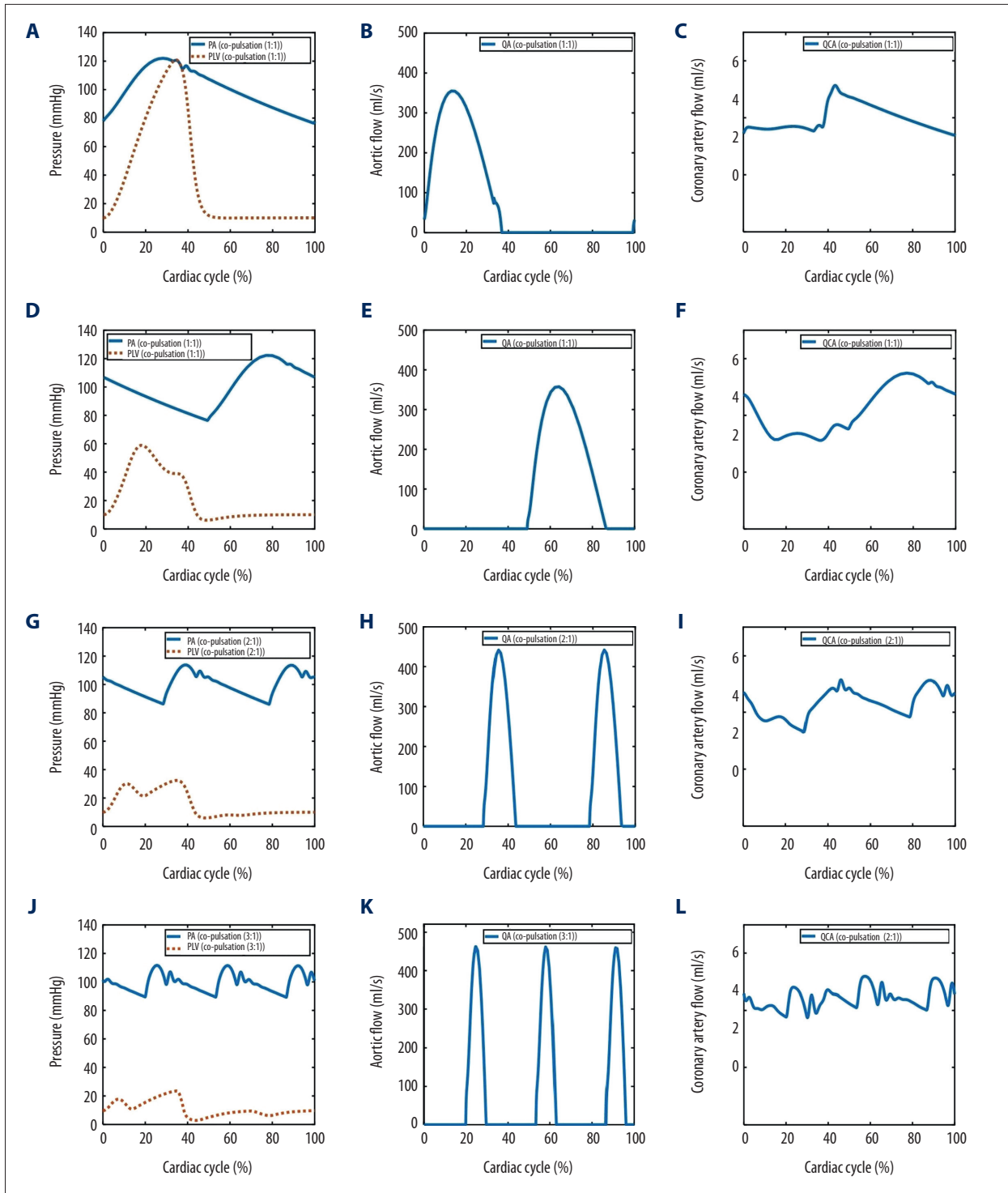
Figure 5. Simulated hemodynamic waveforms in the cardiovascular model with 4 different operation modes. (**A–C**) co-pulsation mode; (**D–F**) counter-pulsation mode; (**G–I**) counter-pulsation mode in a synchronization ratio of 2: 1; (**J–L**) counter-pulsation mode in a synchronization ratio of 3: 1.

Table 3. Simulated hemodynamic responses of the normal, severe HF, and HF with different modes of LVAD support (TIW – total input work; EEP – energy equivalent pressure).

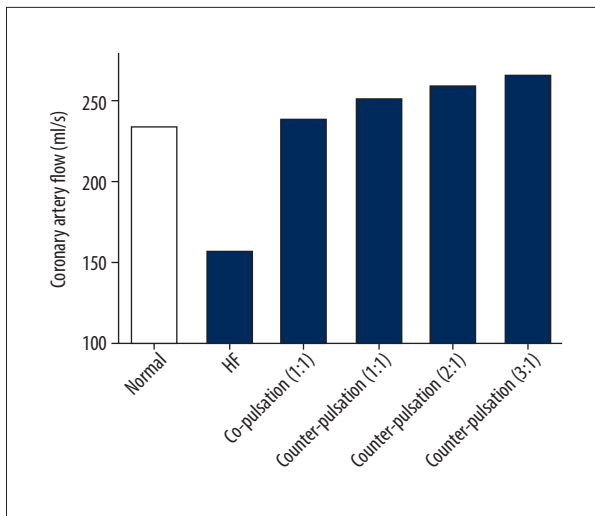| Parameters | Units | Normal | HF | LVAD support | | | |
				Co-pulsation (1: 1)	Counter-pulsation (1: 1)	Counter-pulsation (2: 1)	Counter-pulsation (3: 1)
Pump speed	rpm	0	0	60	60	120	180
Cardiac output	L/min	5.4	3.5	0	0	0	0
LVAD flow	L/min	0	0	5.4	5.4	5.4	5.4
Pump stroke volume	ml	0	0	90	90	45	30
Heart rate	bpm	60	60	60	60	60	60
Mean LV pressure	mmHg	59.6	38.9	37.1	21.5	15.4	10.9
Peak LV pressure	mmHg	124.5	82.8	120.9	58.9	32.4	23.4
Mean aortic pressure	mmHg	100	64.9	100	100	100	100
Peak aortic pressure	mmHg	123.7	82.1	122.0	122.4	113.8	111.5
Coronary artery TIW	J/s	0.0518	0.0228	0.053	0.0570	0.0573	0.0583
Coronary artery EEP	mmHg	100.5	65.9	100.4	102.4	100.7	99.8
Mean coronary flow	ml/min	234	157	239	252	260	266
Mean coronary flow%	%	100	67.1	102.1	107.7	111.1	113.7

Hemodynamic effects under various pulsatile frequencies of LVAD

Four different operation modes of LVAD were simulated: co-pulsation mode, counter-pulsation mode, and counter-pulsation modes in synchronization ratios of 2: 1 and 3: 1. The hemodynamic waveforms of the various operation modes are shown in Figure 5. The cardiac cycle starting point was set to the start of systole. To compare the effects of pulsatile frequency of LVAD on coronary perfusion, the LVAD flow was set as 5.4 L/min and the mean aortic pressure was maintained at 100 mmHg in all operation modes of LVAD. The arterial pressure exceeded the peak LV pressure, as shown in Figure 5D, 5G, and 5J, respectively. Therefore, the aortic valve was not open and the native cardiac output did not generate any flow in the counter-pulsation modes. We also found that the peak LV pressure gradually decreased with increasing pulsatile frequency, which suggests that elevated pulsatile frequency can result in lower LV pressure.
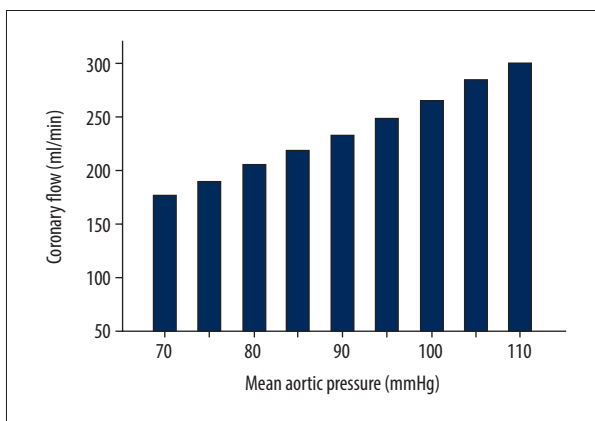
The changes in the aortic flow for various LVAD operation modes are shown in Figure 5B, 5E, 5H, and 5K, respectively. With the increase of pulsatile frequency, several similar peaks were formed in the aortic flow. Similarly, the number of coronary flow wave peaks was consistent with frequency, as shown in Figure 5C, 5F, 5I, and 5L, respectively. The simulation results

are summarized in Table 3, showing that the pump stroke volume in a synchronization ratio of 3: 1 declined to 35.8% of that in the synchronization ratio of 1: 1. Therefore, this result suggests that the pump volume may be reduced with increasing pulsatile frequency.

Coronary perfusion was effectively improved with increasing pulsatile frequency because the magnitude of coronary impedance decreases with increasing pulsatile frequency, as shown in Table 3 and Figure 6. Under the same mean aortic pressure, the mean coronary flow was enhanced. The EEP of the coronary artery was almost constant under LVAD support, which can be attributed to unchanged mean aortic pressure. The TIW of the coronary artery under the HF condition was 0.0228 J/s, which is only 44% of that under the normal condition. However, under LVAD support, the maximum TIW of coronary artery increased to 0.0583 J/s. Moreover, the TIW of the coronary artery had the same trend as the coronary flow under various pulsatile frequencies. These results indicate that increasing LVAD pulsatile frequency can effectively improve coronary perfusion by reducing the coronary impedance. As shown in Figure 7, the coronary flow increased with increasing mean aortic pressure in the counter-pulsation mode with a synchronization ratio of 3: 1. Therefore, normal aortic pressure is also crucial for coronary perfusion.

closely related to the frequency in the circuit network. Similarly, the frequency characteristics of the coronary system can affect the coronary impedance, as shown in Figure 3. Hence, based on the counter-pulsation mode, the pulsatile frequency of LVAD is further changed to reduce coronary impedance. The simulation results show that the coronary flow increases by about 10% when the working mode changes from co-pulsation to counter-pulsation in a synchronization ratio of 3: 1. The proposed operating mode is partly similar to the IABP (intra-aortic balloon pump) [39]. The increased coronary flow can provide more myocardial oxygen supply and may be beneficial to the cardiac function. Therefore, similar to the IABP, the proposed method may potentially be used to alleviate ischemic myocardial dysfunction, acute coronary syndrome, low cardiac output syndrome, and cardiogenic shock after myocardial infarction.

Unloading the LV can also contribute to improving myocardial function. The simulation results indicated that the counter-pulsation mode in a synchronization ratio of 3: 1 results in the lowest peak aortic pressure and LV pressure. Unloading the LV is related to the lack of fluid during counter-pulsation and high synchronization ratios. Moreover, as shown in Table 3, the pump stroke volume declined from 90 ml to 32 ml with increasing pulsatile frequency. This suggests that the proposed method has the potential to reduce LVAD volume.

For several reasons, the synchronization ratio of LVAD was limited to a maximum of 3: 1 in the present study. Firstly, it is because the pulsatility of aortic flow gradually decreases with increasing pulsatile frequency. Sufficient pulsatility is essential for inducing myocardial recovery and energy transmission in the cardiovascular system [15,40]. Moreover, the high pulsatile frequency requires more reliability and accuracy control of LVAD, which are difficult to realize in practical clinical applications. Therefore, our study focused on the counter-pulsation modes in synchronization ratios from 1: 1 to 3: 1, which can verify the effects of pulsatile frequency on coronary perfusion and are easy to achieve in practical applications.

Figure 6. Coronary perfusion in the normal, HF, co-pulsation mode, and counter-pulsation mode in synchronization ratios of 1: 1, 2: 1, and 3: 1.

Figure 7. The effects of aortic pressure on coronary perfusion in counter-pulsation mode with a synchronization ratio of 3: 1.

Discussion

We simulated the hemodynamic effects of 4 different operation modes of LVAD, which all increased coronary perfusion and aortic flow to a healthy level. The restorations of cardiac output and aortic pressure are beneficial to alleviate end-organ failure and cardiogenic shock [37]. Moreover, the increased coronary flow could be considered as an indicator of improving myocardial function [38]. As shown in Figure 6, the counter-pulsation mode was obviously superior to the co-pulsation mode in terms of myocardial perfusion and reducing ventricular pressure, which is consistent with previous reports [11,12].

The human cardiovascular system is a sophisticated impedance network that can be characterized by the LP electric analog model. It is well known that the magnitude of impedance is

Study limitations

The cardiovascular system model used in this study has some limitations, similar to other zero-dimensional LP models. Some researchers have shown that pulsatile flow is directly related to endothelial production of nitric oxide, which can increase bradykinin-dependent vascular relaxation and decrease vascular oxidative stress [41,42]. Therefore, the corresponding nervous and hormonal regulation system should be considered in clinical applications. In addition, some peripheral organs, such as pulmonary and kidney tissue, should also be considered. The aortic valve is assumed to be closed during the cardiac cycle, which may result in aortic insufficiency [43]. Therefore, the LVAD operating mode still needs to be improved to protect

the aortic valve in clinical applications. Moreover, further *in vivo* experiments are needed to evaluate the effects of LVAD pulsatile frequency on coronary perfusion.

Conclusions

We investigated the effects of pulsatile frequency of LVAD on coronary perfusion. First, we simulated the cardiovascular system using the LP model, which incorporates left heart, LVAD, coronary circulation, and systemic circulation. Then, the effects of pulsatile frequency on the coronary impedance were analyzed. The present theoretical analysis suggests that increased pulsatile frequency can effectively decrease the coronary impedance when the pulsatile frequency is not higher than the resonance frequency. Therefore, the 4 different operation modes of LVAD (co-pulsation and counter-pulsation modes in synchronization ratio of 1: 1, 2: 1, and 3: 1) were simulated to compare the hemodynamic effects. The simulation results show that the counter-pulsation mode with high pulsatile frequency not only effectively improves the coronary flow, but also helps unload the LV. Although the pulsatile LVAD was used in the study, changing the pulsatile frequency of CFLVADs by the speed control algorithms to improve myocardial function in patients with ICM appears to be promising.

Conflicts of interest

None.

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