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The influence of rotary blood pump speed modulation on the risk of intraventricular thrombosis

Sam Liao, Eric L. Wu, Michael Neidlin, Zhiyong Lia, Benjamin Simpson, Shaun D. Gregory

1 Abstract

Rotary left ventricular assist devices (LVADs) are commonly operated at a constant speed, attenuating blood flow pulsatility. Speed modulation of rotary LVADs have been demonstrate to improve vascular pulsatility and pump washout. The effect of LVAD speed modulation on intraventricular flow dynamics is not well understood, which may have an influence on thromboembolic events. This study aimed to numerically evaluate intraventricular flow characteristics with a speed modulated LVAD. A severely dilated anatomical left ventricle was supported by a HeartWare HVAD in a three-dimensional multiscale computational fluid dynamics model. Three LVAD operating scenarios were evaluated: constant speed and sinusoidal co- and counter-pulsation. In all operating scenarios, the mean pump speed was set to restore the cardiac output to 5.0 l/min. Co- and counter-pulsation was speed modulated with an amplitude of 750 rpm. The risk of thrombosis was evaluated based on blood residence time, ventricular washout, kinetic energy densities and a pulsatility index map. Blood residence time for co-pulsation was on average 1.8% and 3.7% lower than constant speed and counter-pulsation mode, respectively. After introducing fresh blood to displace pre-existing blood for 10 cardiac cycles, co-pulsation had 1.5% less old blood in comparison to counter-pulsation. Apical energy densities were 84% and 27% higher for co-pulsation in comparison to counter-pulsation and constant speed mode, respectively. Co-pulsation had an increased pulsatility index around the left ventricular outflow tract and mid-ventricle. Improved flow dynamics with co-pulsation was caused by increased E-wave velocities which minimised blood stasis. In the studied scenario and from the perspective of intraventricular flow dynamics, co-pulsation of rotary LVADs could minimise the risk of intraventricular thrombosis.

Key words

Heart failure; pulsation; computational model; ventricular assist device; ventricular flow; cannula

2 Introduction

Treatment for heart failure patients with left ventricular assist devices (LVADs), in particular with rotary blood pumps, has been on the rise [1]. Despite improved survival with LVADs compared to optimal medical management, patients with LVADs are still exposed to high complication rates [1,2]. The major cause of

death for continuous flow LVAD patients are neurological events [1]. Many factors can be attributed to this adverse event: one potential reason could be intraventricular thrombosis, stemming from unfavourable flow patterns caused by, but not limited to, the LVAD inflow cannula design, length and position [3–10].

Rotary LVADs are commonly operated at a constant speed, attenuating blood flow pulsatility, which has been associated with vascular and valvular dysfunction and inadequate pump washout [11]. The benefits of increasing pulsatility with rotary blood pumps is still open to debate. Due to the lack of understanding on the effects of speed modulation, some researchers argue that a rotary LVAD should be operated at a constant speed or it could cause more harm than good [12,13].

Studies have shown that rotary LVAD speed modulation can affect various haemodynamic parameters [14–19]; however, localised blood flow effects in the left ventricle (LV) are not well understood. From a haemodynamic perspective, speed modulation of a rotary LVAD in counter-pulsation (i.e. highest LVAD speed corresponding to ventricular diastole) decreases LV stroke volume (SV), potentially causing blood stasis and increasing the risk of thrombosis based on Virchow's triad [20]. However, Pirbodaghi et al. [21] reported that counter-pulsation may be conducive to LV unloading, thus myocardial recovery.

Intraventricular flow assessment and optimisation of LVAD operating conditions in-vivo is non-trivial, thus alternatives are required. Zimpfer et al. [22] experimentally assessed the Lavare™ cycle, an asynchronous HeartWare HVAD (Medtronic, Framingham, MN, USA) speed modulation feature, with particle image velocimetry. The Lavare™ cycle activates every 60 s which reduces pump speed by 200 rpm for 2 s and increases by 400 rpm for 1 s before returning to baseline. In a non-pulsatile heart model, speed modulation in itself improved LV washout based on increased deviations in fluid velocities, angular dispersion and decreased stagnation indices.

A notable study by McCormick et al. [23], overcoming the non-pulsatile limitation, evaluated the effects of flow synchrony in a self-developed numerical model [24]. A generic LVAD was compared in constant flow and sinusoidal co- and counter-pulsatile flow; however, a limitation was that a constant/prescribed flow rate is not particularly physiological in a LVAD scenario as there would be variations in pump flow due to the contracting heart. This may have implications on the ventricular volume, but the influence is not clear. Furthermore, blood residence time was assessed using a Lagrangian approach. This method has the susceptibility to underestimate regions of stagnation: the injected particles may not enter these pre-existing recirculation regions.

This study aimed to address some prior limitations by assessing intraventricular flow in a commercial software and synchronously speed modulating a clinically relevant rotary LVAD, a HeartWare HVAD, in a pulsatile numerical model. It was hypothesised that co-pulsation could minimise the risk of thrombosis based on higher SVs. The risk of thrombosis was evaluated based on: an Eulerian blood residence time approach [23,25]; the rate of ventricular washout [10,26];

ventricular and apical energy densities [10]; a pulsatility index map [27], and instantaneous blood stagnation [9,10].

3 Materials and Methods

3.1 Lumped parameter network setup

The modelling setup undertaken for this study has been comprehensively described elsewhere [10]. In brief, the multiscale model consisted of a severely dilated three-dimensional anatomical LV, which was one-way coupled to lumped parameter network (LPN) to provide the boundary conditions. A fictitious heart wall was deformed with a pressure loading that was a function of time, obtained from the LPN. The initial geometry and meshing was identical to the 24 mm cannulation length case as presented by Liao et al. [10]. A HeartWare HVAD was modelled as the numerical LVAD which was based off head-flow curves from Larose et al. [28]. Only differences to the previously described methods will be presented. The novel variation to the previous work was the addition of a sinusoidal speed profile, which was operated in either synchronous co- or counter-pulse with respect to maximum LV pressure. The mean pump speed was set to maintain a cardiac output of 5.0 l/min. A constant speed (2600 rpm) LVAD operation mode was evaluated as a benchmark. The sinusoidal pulsatile profiles had an amplitude of 750 rpm, which was chosen to be within the manufactured designed speed of the HeartWare HVAD. The corresponding speeds of a HeartWare HVAD over a cardiac cycle can be seen in Figure 1. The SVs found from the LPN was implemented in the following section to determine the target LV geometries at end systole and diastole.

3.2 Geometry

The following section describes the steps taken to determine the starting LV geometry (end systole) for the CFD simulation and the required fictitious wall pressure loadings to pulse the LV to obtain the required SVs.

Briefly, this involved: 1) assuming the original patient data geometry [10] was the smallest end systolic LV volume (450.7 ml), which was related to the co-pulsation scenario; 2) determining the SVs of each operating scenario from an LPN; 3) determining the target end diastolic co-pulsation geometrical volume; 4) determining the difference in end diastolic volumes, from the LPN, for constant speed and counter-pulsation relative to co-pulsation; 5) subtracting the end diastolic volume differences from the co-pulsation end diastolic geometry, resulting in the target end diastolic geometrical volumes for constant speed and counter-pulsation; 6) determining the target end systolic geometrical volume by subtracting the corresponding SVs (determined in 2)) from the end diastolic geometrical volume; 7) artificially increasing the original patient LV geometry, in a balloon-like manner, to the determined target end diastolic volumes found in 6); and 8) determining the maximum wall loading pressure on the geometrical model to obtain the LPN calculated SV for each LVAD operating scenario.

The maximum wall loading pressure to achieve the required SV of 62 ml, obtained the LPN simulation of a restored heart failure condition as described in Liao et al. [10], was found by performing a pressure sweep on the fictitious LV wall. A fluid-structure interaction (FSI) simulation was performed whereby the only variable of interest was the relationship between the LV volume and the pressure loading.

From the assumption that the original patient LV geometry of 450.7 ml was for co-pulsation and the SV determined from the LPN was 62 ml, a wall pressure of 3337.9 Pa resulted in an end diastolic volume of 512.8 ml. The co-pulsation mode was the reference in determining the LV end systolic and diastolic volumes for the other modes.

In reference to the co-pulsation mode, differences between end diastolic volumes were 10.75 and 4.66 ml lower for counter-pulsation and constant speed mode, respectively, determined by the LPN. Therefore, the end diastolic volume target for the LV computational fluid dynamics (CFD) geometry was 502.05 and 508.14 ml for counter-pulsation and constant speed mode, respectively.

For counter-pulsation and constant speed modes, the LPN SVs were 29.83 and 45.67 ml, respectively. The target end systolic volume for the counter-pulse and constant speed modes were found by taking the difference between the end diastolic volume and SV. Therefore, the end systolic volumes for the CFD models were 472.22 and 462.47 ml for counter-pulsation and constant mode, respectively.

From the pressure sweep from the co-pulsation case, linear interpolation was used to find the required pressure wall loading to obtain the desired LV volume. A loading pressure of 1112.8 and 547 Pa resulted in a volume of 472.26 ml and 462.09 ml for counter-pulsation and constant mode, respectively, providing all starting geometries for the CFD simulation.

Since the starting geometries were no longer the same, another FSI simulation with a pressure sweep was performed to determine the maximum wall pressure loading to achieve the corresponding end diastolic volumes.

For counter-pulsation, a maximum wall loading pressure of 1728 Pa resulted in an end diastolic LV volume of 505.16 ml starting from 472.26 ml, an SV of 32.9 ml. For the constant speed mode, a maximum wall loading pressure of 2604 Pa resulted in an end diastolic LV volume of 507.68 ml starting from 462.09 ml, an SV of 45.6 ml. The resultant LV volume and relative LV unloading differences compared with a shifted LPN SV profile can be seen in Figure 2.

3.3 Simulation

All simulations were performed with commercial codes, ANSYS 18 (Pennsylvania, USA). The flow was assumed to be laminar, due to limited computational resources, with awareness that turbulence could exist in the LV [29]. The non-Newtonian blood behaviour was described with a Carreau model [10,30]. The convergence criteria were set to 10^{-4} for continuity and $x/y/z$

velocities. No aortic valve opening occurred in all cases. The simulation was initialised for 30 s followed by another 10 s of result collection with a time step size of 0.0002 s. Each time step had a maximum of ~25 iterations per coupling iteration with a maximum of 5 coupling iterations. The heart rate was set at 60 bpm. A total CPU time of ~20 days were used for initialisation with a further ~130 days of CPU time for the result collection per scenario with an Intel Xeon 2.5 GHz processor.

3.4 Analysis methods

A broad intraventricular flow velocity visualisation of the last cardiac was evaluated on a plane which intersected the mid-points of the cannula, mitral and aortic valve. Early diastolic vortex development and dissipation was visualised at the last cardiac cycle with an isosurface using the Q-criterion with a threshold at 60000 s^{-2} [10].

As there is currently no gold standard to predict the risk of thrombosis, several approaches were implemented. The risk of thrombosis was evaluated with: blood residence time, LV washout, energy densities in the LV and at the apex, pulsatility index, instantaneous stagnation volume [10]. Local distribution of blood residence time was visualised throughout the last cardiac cycle: at early diastole, mid diastole, mid systole and end systole. The rate of LV washout was monitored for 10 cardiac cycles, presented as a normalised LV volume percentage. The ink flow path was assessed during early diastole. The volume-averaged kinetic energy at the apex and LV was evaluated on the last two cardiac cycles sampled at 0.02 s intervals with mean values analysed. Likewise, the instantaneous blood stagnation and pulsatility index was evaluated based on the last two cardiac cycles with a sample rate of 0.02 s.

4 Results

The generally accepted diastolic vortex in the clockwise rotation was found in all LVAD operating scenarios, Figure 3. Due to higher E-wave flow rates for co-pulsation, as seen in Figure 4, the velocity at the septum was higher than the constant and counter-pulsation modes. Changes in LVAD flow rates due to the operating scenario can be observed with velocity changes in the inflow cannula throughout the cardiac cycle.

A distinct asymmetrical diastolic vortex annulus in all LVAD operating scenarios was observed (Figure 5). The annulus rotational velocity was lower with counter-pulsation. Throughout early diastole, vortical structures appeared to be more persistent with co-pulsation compared to constant and counter-pulsation modes. At 0.08 s in Figure 5, the vortices in co-pulsation can be seen to have travelled towards the medial aspect of the inflow cannula. Qualitatively, at the end of the E-wave, more vortical structures appeared to deviate towards the inflow cannula in comparison to the vortices travelling up the septum with co-pulsation.

The average blood residence time in the LV was consistently longer with counter-pulsation in comparison to constant speed and co-pulsation scenarios. Over 10 cardiac cycles, the average blood residence time in the LV was 6.60 ± 0.16 , 6.72 ± 0.13 and 6.85 ± 0.14 s for co-pulsation, constant speed and counter-pulsation, respectively. Using a one-way ANOVA (MATLAB, MathWorks, Natick, USA), the average blood residence time for all LVAD operating scenarios were found to be statistically different ($p < 0.0001$). In reference to co-pulsation, residence times for constant speed LVAD operation and counter-pulsation was on average 1.8% and 3.7% longer, respectively. The LVOT and basal regions tended to have higher localised blood residence times than the apex, as seen in Figure 6.

In Figure 7, the rate of ventricular washout indicated that after 10 cardiac cycles, counter-pulsation had the slowest rate of washout in comparison to constant speed and co-pulsation scenarios. At the end of 10 cardiac cycles, 21.80%, 22.36% and 23.30% of pre-existing blood remained for co-pulsation, constant speed and counter-pulsation, respectively. The difference between co- and counter-pulsation was 1.5%. At early diastole, Figure 8 showed that incoming blood tended to travel further up the septum with co-pulsation in comparison to constant speed and counter-pulsation. The pulsatility index contour plot, Figure 8, showed that co-pulsation had markedly increased velocity fluctuations up the septum, LVOT and in the mid-LV regions in comparison to counter-pulsation.

In Figure 9a and b, it was found that co-pulsation had a higher energy density than the other LVAD operating scenarios. At the apex, counter-pulsation, constant speed and co-pulsation modes had a maximum energy density of 2351, 1795 and 955 J/m³, respectively, where the peak occurred shortly after the E-wave. The median apical energy density was 25, 13 and 10 J/m³, for co-pulsation, constant speed and counter-pulsation, respectively. This trend was similarly observed when assessing the entire LV: the LV median energy density was 36, 29 and 25 J/m³, for co-pulsation, constant speed and counter-pulsation, respectively. There was consistently a period of no instantaneous blood stagnation at the apex for all LVAD operating scenarios (Figure 9c). Co-pulsation generally had lower volumes of instantaneous stagnation throughout the entire cardiac cycle. The median stagnation volume for co-pulsation, constant speed and counter-pulsation was 107, 144 and 301 μ l, respectively.

5 Discussion

LVAD speed modulation has been of interest to address vascular, baroreceptor, and sympathetic nervous system function adaptations, ascribed to attenuated pulsatility [13]. The aim of this study was to provide further insights on intraventricular flow dynamics with different speed modulation approaches, potentially associated with the risk of thrombosis. A previous study has reported that blood residence time can be reduced by having low and high LVAD flows during diastole and systole, respectively [23]. Results from this study similarly reflected this notion. In particular, this study provided further understanding of

intraventricular flow dynamics with a speed modulated HeartWare HVAD, in contrast to the prescribed sinusoidal LVAD flow rates by McCormick et al. [23].

The most significant finding, in alignment with McCormick et al. [23] and despite large differences in the patient-specific LV volumes, was that synchronous co-pulsation resulted in the lowest blood residence times. This agreement can be attributed to several interconnecting factors, including increased SV, higher E-wave velocities and kinetic energy. Even though this study provided a more physiological LVAD flow, the outcomes were similar. The significance of this may indicate that the effect of co-/counter-pulsation may have a more prominent effect than the actual LVAD flow profile: the influence of speed modulation profiles, square/sinusoidal, on ventricular washout could play a smaller role than phase synchronisations. Furthermore, previous in-vitro haemodynamic assessments with co-pulsation has shown to increase the LV ejection fraction over counter-pulsation, which has been speculated to increase ventricular washout [31].

Apical velocity was lower during early diastole with counter-pulsation, potentially attributed to lower E-wave flow rates. Minor differences in E-wave flow rates between the co-pulse and counter-pulse scenarios highlighted the inflow boundary sensitivity. This may suggest the significance of E-wave propagation velocities on the risk of thrombosis, potentially correlating with the degree of LV blood mixing. The dependence of blood mixing on the E- and A-waves have been previously suggested by Seo et al. [32].

The higher LV energy density with co-pulsation could explain the lower levels of instantaneous apical blood stagnation. Greater E-wave flow rates with co-pulsation appeared to enhance blood mixing, especially around the LVOT. Co-pulsation created stronger diastolic vortex structures which promoted longer flow paths to be traced before being cleared by the inflow cannula, in close agreement with findings by McCormick et al. [23]. It could be hypothesised that the most optimal LVAD support strategy is to promote the healthy and natural characteristic clockwise vortex [33].

The major displacement of pre-existing blood appeared to occur during diastole. That is, the clearance of old blood was greater during diastole for co-pulsation in comparison to counter-pulsation. It was suspected that the rate of washout had a greater influence on the LVAD flow rate during the diastolic phase than systole.

The tendency of high blood residence times around the LVOT and basal regions, corroborating with previous studies, may increase susceptibility to thrombosis [10,27]. Over the cardiac cycle, co-pulsation tended to have lower volumes of instantaneous stagnation. The small difference in the rate of washout (1.5%) between co- and counter-pulsation appears to be minor but could be significant in regard to the risk of thrombosis: especially when small thrombi have the potential to initiate a positive feedback loop for larger thrombi formation [6].

The ideal speed modulation strategy could depend on the optimisation criteria. From the perspective of myocardial recovery, Pirbodaghi et al. [34,35] showed that counter-pulsation was the most beneficial. However, from the perspective of

left intraventricular flow dynamics, counter-pulsation with no aortic valve opening could increase the risk of intraventricular thrombosis.

Limitations of this study included the assumption of a smooth endocardial surface. Ventricular wall motion was modelled in a balloon-like manner, whereby the twisting motion is significantly reduced in severely dilated LVs [36]. Transient pump characteristics were not modelled, thus may not provide an absolute representation of the physical HeartWare HVAD. However, it is hypothesised that the dynamic pump characteristics would have minimal effects on intraventricular flow dynamics in comparison to pump speed synchrony. This was based on suggestions by Pirbodaghi et al. [34] that the effect of pump speed wave forms on LV unloading and haemodynamics were minimal. Only one characteristic pump profile was investigated and the results would be expected to differ slightly with different LVADs [37]. It can be hypothesised that a pump with a flatter HQ curve could increase the volume loading and potentially improving ventricular washout while a steeper HQ curve may result in decreased ventricular washout due to smaller variations in flow. Nevertheless, the concept of flow timing relative to the cardiac cycle may prove to be more influential on the risk of thrombosis. The LPN compartments that were modelled did not consider the inertial characteristics due to pulsing, which can be addressed in future work.

The degree of clinical significance is hard to predict; however, an appreciation of differences that may affect the risk of thrombosis contributes to the debate on whether co- or counter-pulsation would be more advantageous. Benefits of co-pulsation compared to continuous/constant speed must be weighed against the potentially increased LVAD power consumption, pump induced haemolysis, heat generation and rotor instabilities [38].

Since no current clinical LVADs are triggered by electrocardiographs or LV pressure, it is difficult to relate current findings with clinical observations. There are LVADs where asynchronous speed modulation is implemented, including the Jarvik 2000 Flowmaker and HeartMate III [39,40]. Since one of the motivations of speed modulated LVADs is to maximise vascular pulsatility, Ising et al. [16] reported that an asynchronous operating strategy resulted in the highest vascular pulsatility; therefore, future studies should consider the effects of asynchronous LVAD speed modulation on intraventricular flow. This study only evaluated a single amplitude. Lower amplitudes may result in reduced SVs and therefore washout; however, this would need to be validated and is an avenue for further investigation.

Conclusions drawn from this study may only be applicable to the simulated case. This study showed that longer localised blood residence times at the LVOT with counter-pulsation may increase the probability for thrombosis; however, counter-pulsation can aid in aortic valve opening which may address the higher blood residence times around the LVOT. It could be speculated that the most unfavourable LVAD operating approach is counter-pulsation with no aortic valve opening, but it is hypothesised that counter-pulsation with aortic valve opening could be the most desirable, potentially superior to co-pulsation with no aortic

valve opening. A comparison between counter-pulsation with aortic valve opening and co-pulsation would be of interest for future work.

6 Conclusion

The significance of this study was to understand and compare three operating strategies with a HeartWare HVAD from the perspective of intraventricular flow. It was found that co-pulsation may be beneficial to reduce the risk of thrombosis by exhibiting a relatively lower LV blood residence time and faster ventricular washout in comparison to operating the LVAD in constant speed or counter-pulsation mode. While the clinical benefits and feasibility of co-pulsation are difficult to predict, and require further evaluation, the presented model demonstrated that co-pulsation was the most favourable LVAD operating method to reduce the risk of thrombosis.

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9 Figure legends

Figure 1: Speed modulation of the HeartWare HVAD. Solid line represents co-pulsation, dashed line represents counter-pulsation and the dotted line represents constant speed operation. The orange lines represent pump speed while the blue lines indicate left ventricular pressure.

Figure 2: Comparison of the different starting left ventricular volumes and stroke volume between the 3 LVAD operating scenarios.

Figure 3: Intraventricular velocity contours and directional arrows with different LVAD operating scenarios of the last cardiac cycle. During diastole, co-pulsation has a higher velocity along the septum in comparison to constant and counter-pulsation modes. The LVAD operating scenarios throughout the cardiac cycle can be related with the velocity within the inflow cannula.

Figure 4: Transmitral and LVAD flow rates with different LVAD operating scenarios.

Figure 5: Diastolic vortex annulus with different LVAD operating scenarios. The annulus rotational intensity was lower with counter-pulsation in comparison to co-pulsation as seen at 0.04 s. Disordered vortical structures at the end of the E-wave travelled further up the septal wall with co-pulsation than counter-pulsation.

Figure 6: Localised intraventricular blood residence time distribution with varying LVAD operating scenarios. Counter-pulsation was observed to have longer blood residence time at the left ventricular outflow tract, especially evident at end systole.

Figure 7: Rate of ventricular washout with LVAD operating scenarios. The first couple of cardiac cycles appears to show minimal difference in the rate of washout but in the proceeding cardiac cycles, these differences increased. Counter-pulsation had the slowest rate of washout, followed by constant speed and co-pulsation. Increases in the normalised old blood percentage for each cardiac cycle is due to systole: the contraction reduces left ventricular volume with the lack of incoming blood.

Figure 8: Top row: flow path visualisation of incoming blood for different LVAD operating scenarios at early diastole. New incoming blood travelled further up the septal wall with co-pulsation in comparison to counter-pulsation. Bottom row: pulsatility index contour plot with different LVAD operating scenarios. Lower pulsatility index was observed with counter-pulsation around the LVOT and central regions in comparison to constant and co-pulse operation.

Figure 9: Comparison of energy densities at the left ventricular apex (a) and entire left ventricle (b) with different LVAD operating scenarios. The highest energy density can be seen with co-pulsation, followed by constant speed and counter-pulsation. Throughout the cardiac cycle, co-pulsation consistently harnessed greater energy in comparison to the other LVAD operating scenarios. Instantaneous stagnation (c) at the apex with different LVAD operating scenarios showed a period of no blood stagnation directly after the E-wave. Results were based on the mean of 2 cardiac cycles. The purple, blue, green and orange shaded areas corresponds to the E-wave, mid-diastole, A-wave and systole, respectively.