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Title:

IN-VITRO EVALUATION OF AORTIC INSUFFICIENCY WITH A ROTARY LEFT VENTRICULAR ASSIST DEVICE

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Running Title

Aortic insufficiency with a rotary LVAD

Abstract

Aortic insufficiency (AI) is usually repaired prior to rotary blood pump (RBP) implantation, but can develop during support due, in part, to the sustained RBP-induced high pressure gradient across the aortic valve. Repair of the aortic valve before or during RBP support predisposes these critically ill patients to even higher risks. This study used an in-vitro mock circulation loop to identify the severity of AI and/or left heart failure (LHF) that might benefit from valve repair, while investigating RBP operating strategies to reduce the haemodynamic influence of AI. Reproduction of AI with RBP supported LHF reduced device efficiency, particularly in the more severe cases of AI and LHF. The requirement for repair or closure of the aortic valve was demonstrated in all conditions other than those with only mild AI. When a sinusoidal RBP speed pulse was induced, small changes in systemic flow rate and regurgitant volume were observed with all degrees of AI. Variation of the pulse phase delay only resulted in minor changes to systemic flow rate, with a maximum difference of 0.17 L/min. While the clinical implications of these small changes may be insignificant, changes in systemic flow rate and transvalvular pressure were shown when the sinusoidal RBP speed pulse was applied with no AI. In these cases, transvalvular pressure was reduced by up to 8% through sinusoidal co-pulsation of the RBP, which may prevent or delay the onset of AI. This in-vitro study suggests that surgical intervention is required with moderate or worse AI and that RBP operating strategies should be further explored to delay the onset and reduce the harmful effects of AI.

Keywords

Aortic insufficiency, ventricular assist device, rotary blood pump, mock circulation loop.

Introduction

The ever increasing epidemic of end stage heart failure combined with the worldwide shortage of donor hearts necessitates the use of mechanical solutions to provide circulatory support. Ventricular assist devices (VADs) are used in the more critically ill patient population and in most cases provide mechanical circulatory support in parallel with the native ventricles. The left ventricle constitutes the greater mass of myocardial tissue and it is here that the majority of ventricular dysfunction is seen [1]. Therefore, the most common motivation for VAD implantation is for left ventricular support as a left VAD (LVAD).

The development of magnetically driven rotary blood pumps (RBPs) has lead to an increase in potential support duration and a decrease in postoperative complications [2]. These rotary devices are usually set at a constant rotational speed which results in a relatively and consistently high aortic pressure with minimal or no ejection through the aortic valve [3]. The structural and haemodynamic changes induced by RBPs have been reported to cause severe aortic insufficiency (AI). Cowger et al. [4] reported that 51% of patients developed moderate to severe AI in the first 18 months after LVAD implantation. Separating this patient population into device type demonstrated marked differences in AI development after 18 months of support. Of the patients still on VAD support at the time, only 20% of those with a positive displacement HeartMate XVE (Thoratec Corporation, Pleasanton, CA, USA) had moderate to severe AI, compared with 64% of patients supported by a rotary HeartMate II (Thoratec Corporation, Pleasanton, CA, USA). Others have also reported AI following rotary LVAD implantation [5-8].

The combination of AI with RBP implantation creates a circulatory shunt which ultimately decreases pump efficiency and subsequently reduces cardiac output and organ perfusion [3, 4, 9, 10]. Increased pump speed to compensate for AI may result in higher power consumption and long term negative effects on RBP durability [4]. Therefore, incompetent aortic valves are usually repaired or closed during LVAD implantation. This can be achieved through a variety of techniques such as a single stitch to approximate the valve leaflets or by suturing felt strips along the leaflets and anchoring to the aortic wall [9, 11].

If AI develops during LVAD support then a reoperation may be necessary, thus creating an additional risk to the patient. Successful sutured aortic valve repair to compensate for LVAD induced AI has been reported previously [10, 11], yet may still be associated with recurrent AI if the valve leaflets are thin or fragile. Prosthetic valve implantation has also been reported to overcome LVAD induced AI [6], however the valve placement may result in abnormal washing of the prosthesis and predispose to

thrombus formation and embolic complications [12]. Therefore, the conditions where aortic valve repair or closure is necessary must be categorized.

The complex interaction between aortic flow and aortic valve function with a RBP was evaluated by Tuzun et al. [13] using a mock circulation loop (MCL). When LVAD speed was increased there was a rise in mean aortic transvalvular pressure (TVP) and a drop in aortic valve flow rate and aortic valve opening time. It was concluded that RBPs increase the average pressure load on the aortic valve due to an increased aortic pressure during diastole and an increase in valve closure time. It is hypothesized that the combination of these two features, combined with reduced forward flow through the aortic valve, influence the progression of AI with RBP support.

Zamarripa et al. [14] also concluded that TVP increased with higher RBP speeds when evaluating AI in a mock circulation loop. As expected, aortic pressure, systemic perfusion and TVP all dropped when AI was simulated while significant recirculation due to the AI shunt was noted through an increase in RBP flow. However, decreased RBP speed combined with increased ventricular function resulted in forward aortic valve flow, suggesting that the effects of AI depend on pump speed and the degree of remnant ventricular contractility. This study concluded that the level of VAD support, and thus ventricular unloading, needs to be controlled to maintain some forward flow and reduce the risk of long term aortic valve complications.

There are some reports of temporarily reducing RBP speed to promote intermittent ventricular ejection through the aortic valve [15, 16]. Meanwhile, repetitive RBP speed pulsing in sync with the cardiac cycle has demonstrated a reduction in ventricular stroke work [17], and may influence the effects of AI. However, the haemodynamic effects of synced RBP speed pulsing on AI have not been investigated. Therefore, the aims of this study were to investigate the combined influence of AI and LHF severity on circulatory haemodynamics with RBP support, and to evaluate the potential for RBP speed and pulsing strategies to either accommodate for, or reduce the potential for AI development. Ultimately, in the event of RBP induced AI, the severity at which repair of the aortic valve is required may be determined.

Methods

Mock Circulation Loop

A physical five element Windkessel MCL (Figure 1) including systemic and pulmonary circulations was used for this study [18, 19]. Atrial and ventricular chambers were represented by 40 and 50 mm clear, vertical polyvinyl chloride pipes with tee sections connecting the inflow, outflow and heart chamber. In brief, ventricular systole was controlled through a series of electropneumatic regulators (ITV2030-012BS5, SMC Pneumatics, Brisbane, AUS) and 3/2 way solenoid valves (VT325-035DLS, SMC Pneumatics, Brisbane, AUS) to provide passively filled heart chambers and variable contractility, heart rate and systolic time. Heart rate and systolic time were maintained at 60 beats per minute and 38.86% respectively throughout this study, based on values from the literature [20]. A Starling response was implemented in both left and right ventricles which actively controlled ventricular contractility (through electropneumatic regulator supply current) based on ventricular end diastolic volume [21]. Mechanical check valves were used to simulate the mitral, aortic, tricuspid and pulmonary valves to ensure unidirectional flow throughout the circuit. AI was simulated through a circuit parallel to the aortic valve between the aortic compliance chamber and left ventricle. The degree of regurgitation was controlled via a pneumatically actuated socket valve (VMP025.03X.71, Convair Engineering, Epping, Australia) and electropneumatic regulator (ITV2030-012BS5, SMC Pneumatics, Brisbane, AUS). The same socket valve and electropneumatic regulator arrangement was used for manipulation of systemic and pulmonary vascular resistance. Four independent Windkessel chambers were employed to simulate lumped systemic and pulmonary arterial and venous compliance. The working fluid throughout this study was a water/glycerol mixture (60/40% by mass) which, at a room temperature of 22°C, demonstrated similar viscosity (3.5 mPa.s) and density (1100 $kg.m^{-3}$) to that of blood at 37°C.

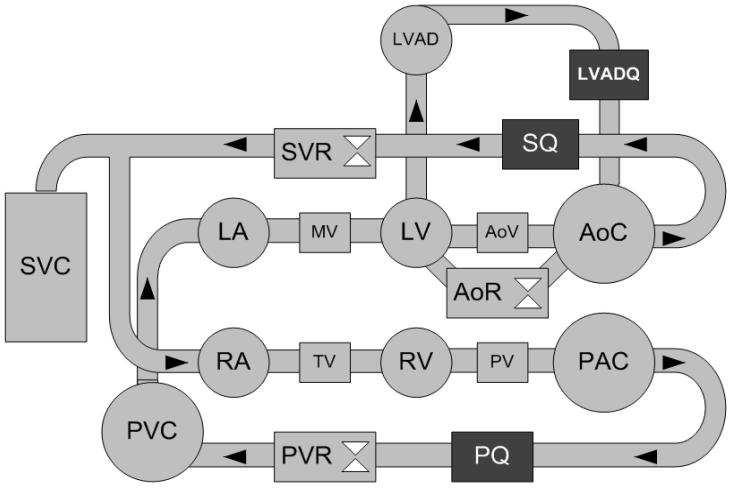

Figure 1 - Schematic of the MCL setup for evaluation of aortic valve regurgitation with rotary LVAD support. LA - left atrium, MV - mitral valve, LV - left ventricle, AoV - aortic valve, AoR - aortic valve regurgitation port, AoC - aortic compliance chamber, SQ - systemic flow meter, SVR - systemic vascular resistance valve, SVC - systemic venous compliance chamber, RA - right atrium, TV - tricuspid valve, RV - right ventricle, PV - pulmonary valve, PAC - pulmonary arterial compliance chamber, PQ - pulmonary flow meter, PVR - pulmonary vascular resistance valve, PVC - pulmonary venous compliance chamber, LVAD - left ventricular assist device, LVADQ - left ventricular assist device flow meter.

Aortic Valve Regurgitation

The MCL was initially configured to represent a healthy condition with no AI. The resistance of the aortic valve regurgitation port (AoR) was then manipulated to simulate a mild AI condition, based on haemodynamic data from the literature [22]. The AoR resistance in this condition was recorded and used for all mild AI simulations throughout this study. This process was repeated for moderate and severe AI conditions, with the classification of AI severity and the resultant MCL AoR resistance shown in Table I. Systemic vascular resistance was maintained at 1500 dynes.s.cm^{-5} throughout all tests.

AI Severity	Regurgitant Volume (mL)	Regurgitant Fraction (%)	MCL AoR Resistance (Dyne.s.cm^{-5})
Mild	<30	<30	2530
Moderate	31-59	31-49	1200
Severe	≥60	≥50	640

Table I - Classification of aortic insufficiency (AI) severity based on data from the literature [22]. Data is shown per beat. MCL - mock circulation loop, AoR - aortic valve regurgitation port.

A VentrAssist (Ventracor Ltd., Sydney, Australia) rotary LVAD was then connected to the MCL via the left ventricle and aorta for inflow and outflow cannulation respectively. A mild left heart failure (LHF) condition was simulated in the MCL before LVAD speed was manipulated to achieve a haemodynamically restored condition (Table II). Mild AI severity was then induced through manipulation of the AoR resistance before the LVAD speed was increased to again reach the defined restored condition. This process was repeated for moderate and severe AI before the experiment was repeated with a severe LHF condition. Results were recorded to determine if increasing the LVAD speed, within the maximum speed range of the pump (1800 - 3000 RPM), could overcome the regurgitant flow created by AI simulation.

Condition	LAP (mmHg)	MAP (mmHg)	MSQ (L/min)	LV_{EDV} (mL)
Mild LHF	10	75	3.5	190
Severe LHF	12	50	2.1	200
Restored	8	100	5.0	100

Table II - Mock circulation loop haemodynamic parameters used to simulate mild and severe left heart failure (LHF) and restored conditions. LAP - left atrial pressure, MAP - mean aortic pressure, MSQ - mean systemic flow rate, LV_{EDV} - left ventricular end diastolic volume.

To investigate the capacity of LVAD operational strategies to reduce the influence of AI, each combination of AI and LHF severity was then repeated with a pulsed LVAD speed. For each test, mean LVAD speed was set at 2600 RPM with a sinusoidal pulse amplitude of 200 and 400 RPM (chosen to not exceed the maximum pump speed of 3000 RPM). The phase delay of each pulse was then varied throughout the cardiac cycle from 0% to 90% (in 10% increments) to assess LVAD pulse timing with respect to ventricular systole. Finally, the LVAD pulsing study was repeated in both mild

and severe LHF conditions with no AI simulation to determine if LVAD pulsing strategies can induce hemodynamic changes that may prevent or delay the onset of AI with rotary LVAD support.

Data Acquisition

Haemodynamic and VAD parameters were captured at 100 Hz using a dSPACE acquisition system (DS1103, dSPACE, MI, USA). Systemic and pulmonary flow rates were recorded using magnetic flow meters (IFC010, KROHNE, Sweden) while LVAD and aortic valve regurgitant flow rates were recorded with clamp on ultrasonic flow meters (TS410-10PXL, Transonic Systems, NY, USA). Circulatory and VAD pressures were recorded using silicon-based transducers (PX181B-015C5V, Omega Engineering, Connecticut, USA) while left and right ventricular volumes were recorded using a magnetostrictive level sensor (IK4-A-B-0200-E-1, GEFRAN, Italy).

Results

Results were compared between conditions of LHF and AI severity to determine if increasing LVAD speed can compensate for the regurgitant flow (Table III). As expected, the mean systemic flow rate (MSQ) decreased as AI or LHF severity increased. In the mild AI severity condition, restored haemodynamics were achieved with LVAD speeds of 2700 and 2800 RPM respectively for mild and severe LHF conditions. With only mild AI, regurgitant flow rates (ie. retrograde flow through the aortic valve) were 2.3 and 2.6 L/min in the mild and severe LHF conditions respectively. However with LVAD speeds reaching the maximum 3000 RPM, the restored haemodynamics could not be achieved in any of the moderate or severe AI conditions. In fact, the MSQ in the severe LHF and AI case was only 3.1 L/min with the maximum LVAD speed. With a LVAD flow rate of 10.4 L/min, the regurgitant flow rate through the aortic valve was 7.3 L/min in this most severe case. While MSQ was close to the restored conditions in the moderate AI and mild LHF condition with maximum LVAD speed, the clear reduction in circulatory support capacity with severe AI demonstrated the necessity of valvular repair.

AI Severity	Parameter	Mild LHF	Severe LHF
Mild	VADS (RPM)	2700	2800
	MSQ (L/min)	5.0	5.0
	LVADQ (L/min)	7.3	7.6
	AVR (mL)	38.1	48.3
Moderate	VADS (RPM)	3000	3000
	MSQ (L/min)	4.8	4.2
	LVADQ (L/min)	9.6	9.3
	AVR (mL)	79.2	84.7
Severe	VADS (RPM)	3000	3000
	MSQ (L/min)	3.9	3.1
	LVADQ (L/min)	10.4	10.4
	AVR (mL)	108.0	121.9

Table III - Combinations of left heart failure (LHF) and aortic insufficiency (AI) severity. The shaded sections indicate that the restored conditions of 5L/min (mean systemic flow rate) and 100 mmHg (mean aortic pressure) were not met at maximum LVAD speed. VADS - LVAD speed, MSQ - mean systemic flow rate, LVADQ - LVAD flow rate, AVR - aortic valve regurgitant volume per beat at 60 BPM.

Sinusoidally pulsing RBP speed resulted in haemodynamic changes for all conditions. An example of the aortic valve regurgitant volume per beat (AVR) and MSQ traces when varying the pulse phase delay is shown in Figure 2. Numerical results are presented for all conditions in Table IV. For all AI and LHF conditions, the minimum AVR occurred when the RBP speed pulse phase delay was set to either 0 or 10% after the start of ventricular systole. Essentially, this pulse phase delay can be defined as co-pulsation with the inertial effects of the cannulae causing up to a 10% delay. Maximum AVR occurred when the RBP speed pulse phase delay was set to 50 or 60%, essentially providing counter-pulsation. Minimum and maximum MSQ also occurred at 0-10% and 50-60% phase delays respectively.

The difference between maxima and minima AVR and MSQ was relatively small. The largest difference between maximum and minimum AVR induced by altering the pulse phase delay was 4.15 mL (mild LHF and moderate AI condition with 400 RPM pulse). The minimum difference between maximum and minimum AVR was only 0.23 mL (severe LHF and mild AI condition with 200 RPM pulse). Similarly small differences existed between maximum and minimum MSQ, with the largest difference (0.17 L/min) occurring in the mild LHF and mild AI condition with a 400 RPM pulse. The smallest difference between maximum and minimum MSQ occurred in the severe LHF and severe AI condition with a 200 RPM pulse (0.03 L/min). It can, however, be observed through these trends that a higher amplitude speed pulse induced larger changes in AVR and MSQ, yet the magnitude of these changes may lack clinical significance.

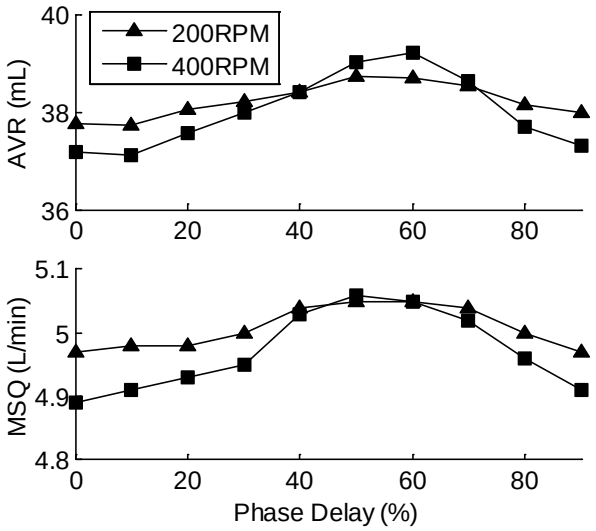

Figure 2 - Example aortic valve regurgitant volume per beat (AVR) (top) at 60 BPM and mean systemic flow rate (MSQ) (bottom) for a RBP pulsed sinusoidally in the mild left heart failure and mild aortic insufficiency condition. The speed pulse was time shifted at 10% intervals relative to the start of ventricular systole.

LHF Condition	AI Severity	Pulse Amplitude (±RPM)	AVR_{max} (mL)	AVR_{min} (mL)	MSQ_{max} (L/min)	MSQ_{min} (L/min)
Mild	Mild	200	38.7	37.7	5.05	4.97
		400	39.2	37.1	5.06	4.89
	Moderate	200	57.9	55.8	4.53	4.46
		400	58.7	54.6	4.51	4.41
	Severe	200	82.8	80.8	3.72	3.68
		400	81.3	79.1	3.76	3.71
Severe	Mild	200	38.8	38.6	4.58	4.51
		400	38.3	38.0	4.58	4.45
	Moderate	200	70.0	68.4	3.79	3.73
		400	70.5	68.7	3.78	3.68
	Severe	200	97.9	97.3	2.82	2.79
		400	98.8	97.6	2.83	2.79

Table IV - Minimum and maximum mean systemic flow rate (MSQ) and aortic valve regurgitant volume per beat (AVR) at 60 BPM for all left heart failure (LHF) and aortic insufficiency (AI) combinations with a RBP pulsed sinusoidally at ± 200 RPM and ± 400 RPM.

Altering the phase shift of a sinusoidally pulsed RBP with no AI resulted in changes to the TVP, MAP and MSQ. TVP is expressed as a mean value across five cardiac cycles. In the mild (Figure 3) and severe LHF conditions, TVP, MAP and MSQ all peaked at a phase delay of 50%, with minimum values occurring at 0-10% (ie. co-pulsation). Maximum and minimum values for pulsing and constant speed simulations are shown in Table V for all conditions. Pulsing RBP speed in the co-pulsation mode reduced TVP compared to the constant speed condition. This was particularly noticeable with the larger pulse magnitude, with a reduction in TVP of 6.1 and 3.0 mmHg for mild and severe LHF conditions respectively. However, slight reductions in MAP and MSQ were observed in the co-pulsation mode, particularly with increased RBP speed pulse amplitude.

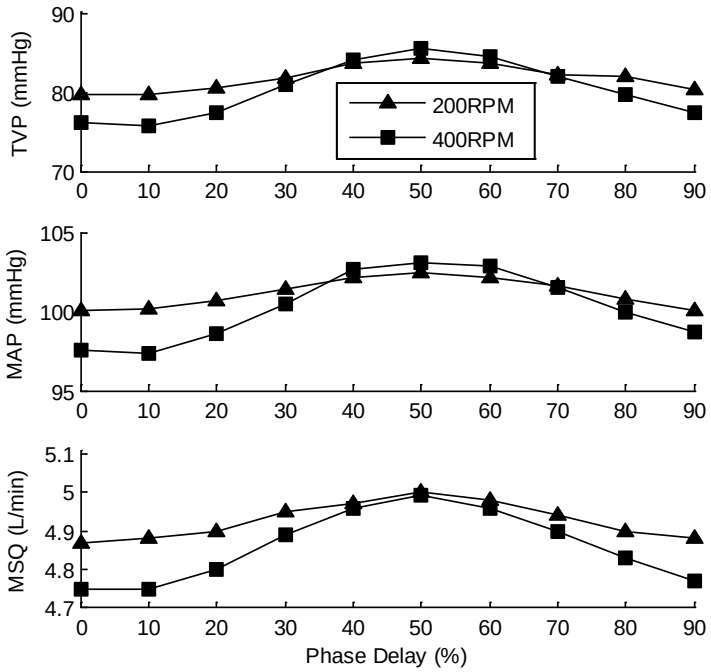

Figure 3 - Resultant haemodynamics in the mild left heart failure condition with no aortic insufficiency and a RBP pulsed sinusoidally at ± 200 RPM and ± 400 RPM and time shifted at 10% intervals relative to the start of ventricular systole. TVP - Aortic transvalvular pressure, MAP - mean aortic pressure, MSQ - mean systemic flow rate.

Condition	TVP_{max}	TVP_{min}	MAP_{max}	MAP_{min}	MSQ_{max}	MSQ_{min}
Pulse - 200 RPM						
MLHF	84.2	79.6	102.4	100.1	5.00	4.87
SLHF	94.1	92.3	103.3	101.8	5.09	5.00
Pulse - 400 RPM						
MLHF	85.5	76.1	103.1	97.3	5.00	4.75
SLHF	93.4	90.2	103.6	100.1	5.09	4.91
No Pulse						
MLHF	82.2		101.7		5.0	
SLHF	93.2		103.2		5.0	

Table V - Maximum and minimum transvalvular pressure (TVP), mean arterial pressure (MAP) and mean systemic flow rate (MSQ) without AI and with a RBP pulsed sinusoidally at ± 200 RPM and ± 400 RPM. All mild and severe LHF conditions were supported at mean LVAD speeds of 2400 and 2500 RPM respectively. Results with no pulse are expressed as a single value. Transvalvular pressure is expressed as a mean value over 5 cardiac cycles. $LVADS_m$ – mean LVAD speed, MLHF - mild left heart failure, SLHF - severe left heart failure.

Discussion

As the recent INTERMACS data has summarized, first generation LVADs are rapidly being phased out of use in favor of the smaller and more durable RBPs [23]. LVAD intervention has been attributed with causing AI, even in patients where little or no AI is present before institution of mechanical circulatory support. Various theories exist on the causes of LVAD induced AI including a constant and increased afterload [3, 24, 25], decreased left ventricular end-diastolic pressure [12, 24], dilation of the aortic root and annulus [11], changes in aortic blood flow dynamics [4], commissural fusion associated with myxoid thickening [5] and radial lengthening of the aortic leaflets leading to regurgitation and annular deformation [13].

Whether AI is caused by one or a combination of these factors, the resultant effect on patient haemodynamics can be significant. A reduction in systemic flow rate is to be expected, along with associated pulmonary congestion and potentially reduced RBP device lifetime as the pump is required to constantly run at higher speeds. Re-circulated flow may lead to hemolysis, while the reduced cardiac output could potentially result in multi-organ failure and death [14]. Clearly aortic valve repair would be recommended before these catastrophic consequences, however valve correction during LVAD support is associated with increased mortality [12]. There is, therefore, a need to characterize the conditions where aortic valve repair or closure is necessary, and determine if RBP operating strategies can be altered to reduce the likelihood of AI development.

Slaughter et al. [15] recommended that AI severity at moderate or higher levels should be corrected, while Morgan et al. [10] suggested even earlier repair when AI is mild or greater. Meanwhile, Bryant et al. [11] recommended anything greater than trivial AI at the time of implant should be treated. Our results concur with the recommendation by Slaughter et al., with suitable haemodynamics achieved by increasing pump speed in cases with mild AI. However, our results showed that with mild LHF and moderate AI, cardiac output can still be maintained at 4.8 L/min with maximum pump speed which may provide a suitable quality of life for most patients. With the more severe AI and LHF conditions, cardiac output was greatly depressed due to high regurgitant flow rates retrograde through the aortic valve. These results agreed with those found by Zamarripa et al. [14] who recorded similar reductions in cardiac output and high regurgitant flow rates with a damaged aortic valve in a MCL. Therefore, our results have demonstrated that repair of the aortic valve is required for sufficient circulatory support in cases with severe AI or moderate AI with severe LHF. However, AI repair should be based on a patient-by-patient case where the risks and haemodynamic benefits of corrective surgery are assessed, particularly if short term support is anticipated.

The concept of pulsing RBP speed has been investigated previously, with particular focus on unloading the left ventricle to promote myocardial recovery [17, 26]. However the effects of RBP

speed pulsing on aortic valve function has been relatively overlooked. As expected, our results showed that increasing the pulse amplitude resulted in larger changes to MSQ, which has been shown previously [17]. The changes to AVR and MSQ when pulsing a RBP at different phases can be primarily attributed to the change in preload and afterload, which demonstrates the dynamic nature of this system. Co-pulsation, where the ventricle and RBP essentially 'eject' at the same time, resulted in lower aortic pressure during diastole and thus reduced TVP and consequently reduced AVR. Counter-pulsation, however, increased the diastolic aortic pressure and thus resulted in consistently high afterload (and thus increased MSQ) yet minimal preload, thus increasing the TVP and promoting retrograde flow through an insufficient aortic valve. However, the magnitude of the AVR and MSQ differences between various pulse phase delays was minimal in our study. In fact, the highest change to AVR and MSQ during simulation of AI was 4.15 mL and 0.17 L/min respectively, while the smallest change to MSQ (0.03 L/min) approached the inherent error of our flow sensor. It is, therefore, doubtful that such small haemodynamic differences will be clinically relevant to this patient population who may be better served through improved clinical management of the systemic vascular resistance. However, this study only evaluated sinusoidal-pulsed RBP speed and further research should be completed to determine if alternative speed pulse waveforms are more influential.

Haemodynamic changes were also observed when RBP speed pulses were induced with no AI. As expected, larger amplitude speed pulses again resulted in increased changes to TVP, MAP and MSQ. Increased haemodynamic changes were also noted in the mild LHF condition and can be attributed with higher ventricular pressures resulting in greater variance in TVP when the RBP pulse phase was shifted throughout the cardiac cycle. TVP decreased by up to 12% when the RBP pulse phase was shifted from counter-pulsation to co-pulsation in the mild LHF condition, and up to 8% from the continuous flow, control condition to the co-pulsation mode. Although smaller reductions in TVP were noted when transitioning from counter-pulsation or continuous flow modes to the co-pulsation mode (4% and 3% respectively) in the severe LHF condition, the clinical influence of such changes should be investigated. The effects of reducing TVP in the mild LHF condition are of particular interest, as reduced retrograde flow and backwards pressure on the aortic valve may prevent valve deterioration and thus prove advantageous in the event of myocardial recovery. However, reduced forward flow with a co-pulsation strategy may also result in fusion of the valve leaflets, possibly eliminating the potential for RBP removal.

While this study has shown that implementation of such control strategies may reduce the potential for AI development with RBP support, in-vivo trials are required to further support this claim and validate the conclusions. The influence of speed pulsing a RBP on hemolysis and thrombosis must also be assessed before such strategies can be recommended for clinical implementation.

Conclusion

This in-vitro investigation revealed reduced RBP support efficiency with AI which may lead to worsened patient outcomes, particularly in the more severe cases. Simulation of AI with a RBP demonstrated the benefit, in most circumstances, of aortic valve closure or repair. The only conditions which may not require surgical intervention are conditions of mild AI or, potentially, moderate AI with mild LHF. Pulsing RBP speed resulted in small haemodynamic changes with all degrees of AI, with the highest MSQ produced in a counter-pulsation mode. However, the clinical significance of these small changes was questionable. When RBP speed was pulsed without AI, TVP was reduced by up to 8% in the co-pulsation mode (compared to continuous speed mode) which may prevent or delay the onset of AI. In conclusion, the RBP operating strategies employed in this study partially compensated for the deleterious effects of AI and should be explored further.

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