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Title:

In-vivo evaluation of active and passive physiological control systems for rotary left and right ventricular assist devices

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Running Title

In-vivo evaluation of physiological control systems for biventricular assistance

Abstract

Preventing ventricular suction and venous congestion through balancing flow rates and circulatory volumes with dual rotary ventricular assist devices (VADs) configured for biventricular support is clinically challenging due to their low preload and high afterload sensitivities relative to the natural heart. This study presents the in-vivo evaluation of several physiological control systems which aim to prevent ventricular suction and venous congestion. The control systems included a sensor-based, master/slave (MS) controller which altered left and right VAD speed based on pressure and flow; a sensor-less compliant inflow cannula (IC) which altered inlet resistance and, therefore, pump flow based on preload; a sensor-less compliant outflow cannula (OC) on the right VAD which altered outlet resistance and thus pump flow based on afterload; and a combined controller which incorporated the MS controller, compliant IC and compliant OC. Each control system was evaluated in-vivo under step increases in systemic (SVR ~ 1400 to 2400 dyne.s.cm^{-5}) and pulmonary (PVR ~ 200 to 1000 dyne.s.cm^{-5}) vascular resistances in four sheep supported by dual rotary VADs in a biventricular assist configuration. Constant speed support was also evaluated for comparison and resulted in suction events during all resistance increases and pulmonary congestion during SVR increases. The MS controller reduced suction events and prevented congestion through an initial sharp reduction in pump flow followed by a gradual return to baseline (5.0 L/min). The compliant IC prevented suction events; however reduced pump flows and pulmonary congestion were noted during the SVR increase. The compliant OC maintained pump flow close to baseline (5.0 L/min) and prevented suction and congestion during PVR increases. The combined controller responded similarly to the MS controller to prevent suction and congestion events in all cases while providing a backup system in the event of single controller failure.

Keywords

Physiological control, active control, passive control, ventricular assist device, heart failure.

Introduction

Ventricular assist devices (VADs) are used to provide mechanical circulatory support for end stage heart failure patients. The left ventricle is more susceptible to failure and, therefore, left VAD (LVAD) implantation is more common. However, right heart failure is a frequent and potentially fatal complication reported to occur in 10-44% of cases following initiation of LVAD support [1, 2] and is associated with worsened outcomes [3].

Although many devices are clinically available for left ventricular support [4], there are limited options to assist the failed right ventricle [5]. First generation, pulsatile blood pumps have been used as right VADs (RVADs) in patients, although efficacy is diminished through their poor durability, thrombus formation and patient discomfort [6, 7]. Some institutions have adapted clinically available rotary LVADs to function as RVADs using the HeartWare HVAD (HeartWare Inc, Framingham, MA, USA) or Jarvik 2000 (Jarvik Heart Inc., New York, NY, USA) systems [8-10]. Such dual rotary LVAD arrangements require either a reduction in right pump speed [9], which may promote pump thrombus and impeller instability for hydrodynamically suspended devices [8], or a restriction of the right outflow cannula to sufficiently reduce the pump outlet pressure to match the pulmonary circulation [8].

Although rotary VADs provide several advantages over the earlier first generation devices [5], their low preload and high afterload sensitivities in comparison to the native, healthy heart makes them susceptible to causing flow imbalances and thus venous congestion and ventricular suction events [11]. With only rotary LVAD support, the right ventricle may assist in maintaining flow balance through changes in contractility (via the Starling response). However with rotary BiVAD support, both ventricles may lack sufficient pumping capacity to balance circuit flow rates. Many investigators have reported the complexities of balancing systemic and pulmonary flow rates with rotary BiVAD support, particularly in the early postoperative phase [8, 9, 12, 13]. Therefore rotary VADs, and in particular rotary BiVAD systems, may benefit from physiological control systems which automatically adjust device flow to match patient demand and balance systemic and pulmonary flow rates.

Many reports have highlighted the importance of physiological controller development to prevent venous congestion and ventricular suction events [12, 14]. While some describe

accurate control systems with rapid response times, most rely on sensor-based systems, which are prone to sensor drift or failure [15-17], or on sensor-less systems, which rely on potentially inaccurate inferred data [18]. Passive control systems have also been reported which are hypersensitive to afterload [19] or specific to a single device [20].

Our group has previously reported the development of both active and passive control systems for rotary BiVAD support [21-24]. The active controller adjusts rotary LVAD and RVAD speed based on left and right end-diastolic ventricular pressures (EDP) respectively [21], while the passive control systems use compliant inflow and outflow cannulae to alter pump flow based on preload and afterload respectively [22-24]. Each control system, and a combined active/passive controller, has been evaluated extensively in-vitro [25], however the in-vivo response of each system has not been reported. Therefore, the aim of this study was to evaluate, in-vivo, the individual and combined active and passive BiVAD physiological control systems to improve flow balancing and, therefore, prevent ventricular suction and venous congestion.

Methods

Physiological Control System Development

A total of four physiological control systems were evaluated in this study:

1. Active master/slave controller (MS)
2. Passive compliant inflow cannulae on the LVAD and RVAD (Compliant IC)
3. Passive compliant outflow cannula on the RVAD (Compliant OC)
4. Active/passive combination (Combined).

The MS controller uses a Starling-like master/slave approach, with the master controller adjusting LVAD pump speed to achieve a set flow rate as a function of left EDP, while the slave controller adjusts RVAD speed to maintain a linear relationship between right and left EDP. This controller is described in full in [21], however it was modified for use in-vivo. Controller parameters were adjusted for each animal to ensure a resting flow rate of 5 L/min and suitable left and right ventricular pressures. As the initial system was very aggressive in-vitro, concerns were raised prior to the trial about the effect of this on the animal as well as interactions with the passive controllers in the combined system. As such, the proportional-integral gains (KP and KI) and the sensitivity of the master and slave controller (θ and α respectively) were reduced to produce a less responsive but otherwise stable system (Table 1). Additionally, a 2nd-order Butterworth low pass filter with a cut-off frequency of 0.1 Hz was used for smoothing the pressure and flow signals.

Master Control (LVAD)			
KP (RPM.min.L^{-1})	KI (RPM.L^{-1})	θ (degrees)	a (mmHg)
35	5	15	25.36
Slave Control (RVAD)			
KP (RPM.mmHg^{-1})	KI (RPM.mmHg^{-2})	α (degrees)	c (mmHg)
25	5	45	-3.5

Table 1 – Master/slave controller settings. KP – proportional gain; KI – integral gain; θ – sensitivity of master controller; a – patient-specific offset of master controller; α – sensitivity of the slave controller; c – patient-specific offset of the slave controller.

Compliant IC on the LVAD and RVAD and a compliant OC on the RVAD (Figure 1) were evaluated as passive physiological control systems. The compliant IC were a flexible section of tubing placed at the pump inlet which passively restricted the internal diameter as preload decreased, thus increasing VAD circuit resistance and reducing VAD flow rate [22, 24]. The

compliant OC was a flexible section placed at the RVAD outlet which, under normal afterload conditions, was restricted to approximately 4 mm in diameter. When afterload increases due to increased vascular resistance, the compliant OC expands in diameter (up to a maximum dictated by the outer casing), thus reducing VAD circuit resistance and maintaining pump flow [23]. The compliant IC and OC were made of silicone rubber (Soft Translucent RTV, Barnes Pty Ltd, Australia) enclosed in a custom rapid prototyped casing (Objet24, Objet, Rehovot, Israel). Cannula compliance was altered using a silicone-diluent (Silicone diluent, Barnes Pty Ltd., Australia) to lower Shore hardness which, along with device geometry, was optimised using a mock circulation loop [26]. The LVAD and RVAD compliant IC casings were made with an outer diameter of 20.6 mm, with a small O-ring groove to interface with a HeartWare (HeartWare Inc., Massachusetts, USA) inflow cannula sewing ring. The RVAD inflow cannula was shortened by 15 mm to prevent septal occlusion after being placed in the right ventricular free wall. The combined control system utilised the compliant IC, compliant OC and MS controller. The physiological control systems were compared with the performance of a fixed-speed LVAD and RVAD with rigid cannulae (constant speed). The RVAD outflow cannula was banded to a 5 mm diameter using a rapid prototyped section to allow the LVAD and RVAD to operate at similar speeds during evaluation of the MS controller and compliant IC.

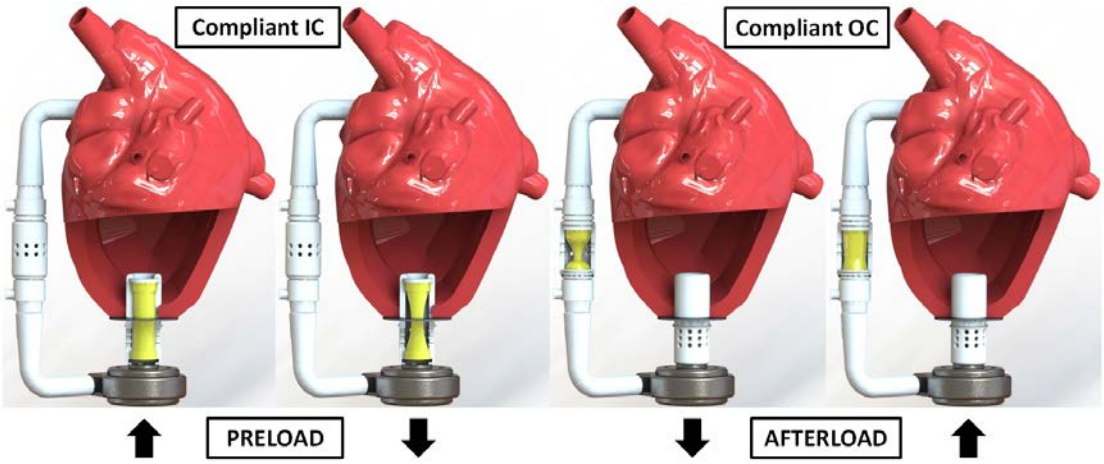

Figure 1 - Compliant inflow cannula (left) with decreasing preload and compliant outflow cannula (right) with increasing afterload. Compliant IC – compliant inflow cannula, Compliant OC – compliant outflow cannula.

In-vivo Evaluation

Ethics approval was obtained from the Queensland University of Technology Animal Ethics Committee prior to experimentation (Approval Number 1300000280). Four female sheep

weighing 62, 67, 76 and 81 kg were used. After induction of general anaesthesia, the animal was intubated and remained ventilated and anaesthetized throughout the entire study period. Ventilation was titrated to maintain normal gas exchange and pH. The experimental animal was instrumented and invasive monitoring was commenced and continuously recorded. Animals were heparinized until an activated clotting time of > 480 seconds was achieved and maintained at > 200 seconds after cardiopulmonary bypass. Prior to implantation, all pumps, cannulae and connectors were soaked in a heparinized saline solution for at least one hour to prevent thrombus formation.

Two VentrAssist (Ventracor Ltd., Sydney, New South Wales, Australia) rotary VADs were implanted with cardiopulmonary bypass via a median sternotomy. Following initiation of cardiopulmonary bypass, the LVAD inflow cannula was inserted through the left ventricular apex and secured using a HeartWare sewing ring while the outflow graft was connected to the ascending aorta via an end-to-side anastomosis. The RVAD inflow cannula was inserted through the right ventricular free wall and secured with a HeartWare sewing ring while the outflow graft was connected to the main pulmonary artery via an end-to-side anastomosis. Both LVAD and RVAD outflow grafts (Gelweave, Terumo Cardiovascular Systems, AnnArbor, MI) were approximately 30 cm long and 12 mm diameter. To eliminate the healthy Starling response of the left and right ventricles, the heart was fibrillated using a purpose built fibrillator, resulting in global akinesis. This was completed to observe each physiological controller's performance in the worst-case clinical scenario of having no flow-balancing ventricular Starling response. An in-vitro comparison of each physiological control system with a beating heart is presented in [25]. Left and right pump speeds were slowly increased while weaning from bypass before being individually manipulated to maintain suitable systemic and pulmonary haemodynamics (mean aortic pressure, MAP ~ 85 mmHg, mean pulmonary arterial pressure, MPAP ~ 20 mmHg, LVADQ and RVADQ > 4 L/min).

After a period of haemodynamic stabilization (~1 hour), the system response to flow imbalances was assessed through changes in systemic (SVR) and pulmonary (PVR) vascular resistances, initially in the constant speed mode. Vascular resistance increases were simulated through placement of rapid prototyped (Objet24, Objet, Rehovot, Israel) restrictions on the corresponding outflow graft near the arterial anastomosis which resulted in large increases in SVR (~1400 to 2400 dyne.s.cm^{-5}) and PVR (~200 to 1000 dyne.s.cm^{-5}). These vascular resistance changes were chosen to represent the most extreme cases caused by severe

hypertension and coughing [27, 28]. Results were recorded for 120 seconds after the resistance increase while at least 120 seconds were allowed between tests (after restriction removal) to allow haemodynamics to equilibrate. LVAD and RVAD speeds were manipulated between tests to restore haemodynamics to the baseline level with each control system. For each resistance change the suite of measurements were then completed with implementation of the MS controller, compliant IC, compliant OC and combined system.

Data Acquisition

Haemodynamic and VAD parameters were captured at 100 Hz using a dSPACE acquisition system (DS1104, dSPACE, Wixom, MI, USA). LVAD and RVAD outlet flow rates were recorded with clamp-on ultrasonic flow meters (TS410-10PXL, Transonic Systems, Ithaca, NY, USA) placed on small sections of Tygon tubing attached between the rotary VAD outlet and the arterial graft. A pulmonary artery catheter (Swan-GanzCCOmbo, Edwards Lifesciences, Irvine, California, USA) was inserted prior to RVAD placement via the external left jugular vein to monitor pulmonary arterial pressure. All other circulatory and VAD pressures were recorded using silicone-based transducers (PX181B-015C5V, Omega Engineering, Stamford, CT, USA). Systemic arterial pressure was monitored via cannulated facial artery. Central venous pressure was monitored via central venous catheter inserted in the jugular vein. Left and right atrial pressures were measured using indwelling catheters. VAD inlet and outlet pressures and ventricular pressures were measured using fluid-filled lines that were attached to catheters placed through the rapid prototyped sections of the compliant IC and OC. The pressure sensors on the compliant IC were used to demonstrate compliant IC activation by measuring the pressure upstream and downstream of the compliant IC, and calculating the resistance across the compliant IC. Large increases in resistance were indicative of the compliant IC activating.

Results

Results were obtained to evaluate each physiological control systems' capacity to balance flow rates during SVR and PVR changes, and compare with the clinical scenario of constant speed. Steady state results for the SVR increase (~1400 to 2400 dyne.s.cm^{-5}) from all trials are summarised in Table 2, while transient results from the third trial are shown in Figure 2 to demonstrate controller performance. Rapid right ventricular suction occurred shortly after SVR was increased in the constant speed mode, demonstrated by sharp oscillations in RVAD flow (RVADQ – Figure 2) and a reduction in right ventricular pressure (RVP) of 11.8 ± 11.9 mmHg. Pulmonary congestion was also evident with left atrial pressures (LAP) often exceeding 25 mmHg, even after the haemodynamics had settled.

Addition of the MS controller decreased right ventricular suction and eliminated pulmonary congestion (LAP < 25 mmHg) after SVR was increased by rapidly increasing LVAD speed by 663 ± 246 RPM and decreasing RVAD speed by 331 ± 244 RPM. The LVAD and RVAD speed changes balanced systemic and pulmonary flow rates and resulted in only a 0.5 ± 0.4 L/min reduction in mean RVAD flow rate (RVADQm), compared to 0.8 ± 0.9 L/min RVADQm reduction in the constant speed mode. The increase in LVAD speed resulted in a mean aortic pressure (MAP) rise of 55.0 ± 6.5 mmHg with the MS controller, compared to an increase of only 32.0 ± 8.5 mmHg in the constant speed mode after the SVR increase.

Although pump speeds were constant during the SVR increase with the compliant IC, right ventricular suction was prevented as mean RVAD inflow cannula resistance increased from 87 ± 47 to 972 ± 818 dyne.s.cm^{-5} which decreased RVADQm by 1.4 ± 0.9 L/min and subsequently resulted in a small reduction in RVP of 2.5 ± 0.5 mmHg. MAP increased by 14.0 ± 8.0 mmHg during the SVR increase. However, the risk of pulmonary congestion was observed with LAP increasing above 25 mmHg after SVR was increased. Sharp oscillations in RVADQ are shown in Figure 2 and can be attributed to the fluttering nature of the RVAD compliant IC rather than right ventricular suction, determined through calculation of RVAD inlet resistance.

The best performing control system during SVR changes was the combined controller, which prevented both pulmonary congestion and right ventricular suction. This was achieved through an automatic increase in LVAD speed (592 ± 229 RPM) and decrease in RVAD

speed (142 ± 97 RPM) which balanced circulatory flow rates with a minor reduction in RVADQm of 0.3 ± 0.1 L/min. Similar to the MS controller, a large increase in MAP of 57.0 ± 22.2 mmHg was observed. However, this system had a longer settling time compared to all other controllers. Interestingly, the RVAD speed initially decreased significantly which resulted in reduced RVAD outlet pressures and, therefore, a rapid decrease in the RVAD compliant OC resistance (1115 ± 245 to 845 ± 195 dyne.s.cm^{-5}) which may have contributed to the larger initial drop in RVAD speed to prevent right ventricular suction. The RVAD compliant IC did not restrict throughout the test, indicating the majority of flow balancing was achieved through the MS controller and compliant OC in this case.

Similar trends were observed for the PVR increase (~200 to 1000 dyne.s.cm^{-5}), with results summarized from all trials shown in Table 3 and transient results from the third trial in Figures 3 and 4. Rapid left ventricular suction occurred in the constant speed mode, evident by the sharp oscillations in LVAD flow (LVADQ), shown in Figure3, and reduction of left ventricular pressure by 16.3 ± 11.8 mmHg. As with almost all of the control systems evaluated in our study, only minor changes in right atrial pressure (RAP) were recorded (-0.8 ± 1.8 mmHg) due to the large systemic venous compliance compensating for the flow imbalance and thus preventing significant venous congestion.

Near suction events were observed with the MS controller after the large PVR increase, signified by the occasional downwards spike in LVADQ and LVP. However, these events were far less frequent than those observed in the constant speed mode as the MS controller increased RVAD speed by 358 ± 183 RPM and maintained LVAD speed (change of -8 ± 43 RPM) to balance systemic and pulmonary flow rates. This resulted in only minor reductions to LVAD flow (LVADQm) of 0.2 ± 0.1 L/min, compared with 1.0 ± 0.6 L/min in the constant speed mode. The increase in RVAD speed resulted in a rise of mean pulmonary arterial pressure (MPAP) of 45.7 ± 11.9 mmHg compared to 27.8 ± 13.0 mmHg in the constant speed mode.

Rapid oscillations in LVADQ were also observed with the compliant IC, however this was attributed to the compliant section on the LVAD fluttering (and restricting) as LVAD preload dropped due to the PVR increase. Restriction of the compliant IC increased mean LVAD inflow resistance from 256 ± 131 to 1027 ± 281 dyne.s.cm^{-5} which subsequently reduced LVADQm by 1.0 ± 0.3 L/min and prevented left ventricular suction while maintaining

constant LVAD and RVAD speeds. MPAP increased by 26.8 ± 7.4 mmHg after the PVR increase with the compliant IC.

The RVAD compliant OC also maintained constant pump speeds and prevented left ventricular suction through a rapid decrease in RVAD outflow cannula resistance from 1228 ± 249 to 675 ± 34 dyne.s.cm^{-5} which maintained RVAD flow at 4.8 ± 0.4 L/min and increased MPAP by 43.3 ± 11.3 mmHg. The decrease in cannula resistance compensated for the increased PVR and maintained total circuit resistance relatively constant (increase of 30 ± 29 dyne.s.cm^{-5}). This is contrary to the results seen with the rigid cannulae in constant speed mode where cannula resistance remained relatively constant during the PVR increase, thus increasing total circuit resistance by 701 ± 109 dyne.s.cm^{-5}.

The RVAD compliant OC was also the main contributor to flow balancing in the combined controller, with a decrease in RVAD outflow cannula resistance from 1085 ± 255 to 660 ± 60 dyne.s.cm^{-5}, and a subsequent increase in MPAP of 51.3 ± 4.1 mmHg after PVR was increased. Therefore, the active MS controller only made minor changes to LVAD (decrease of 67 ± 62 RPM) and RVAD (increase of 133 ± 85 RPM) speeds to balance circulatory flow rates and prevent left ventricular suction. The LVAD compliant IC did not restrict during this test.

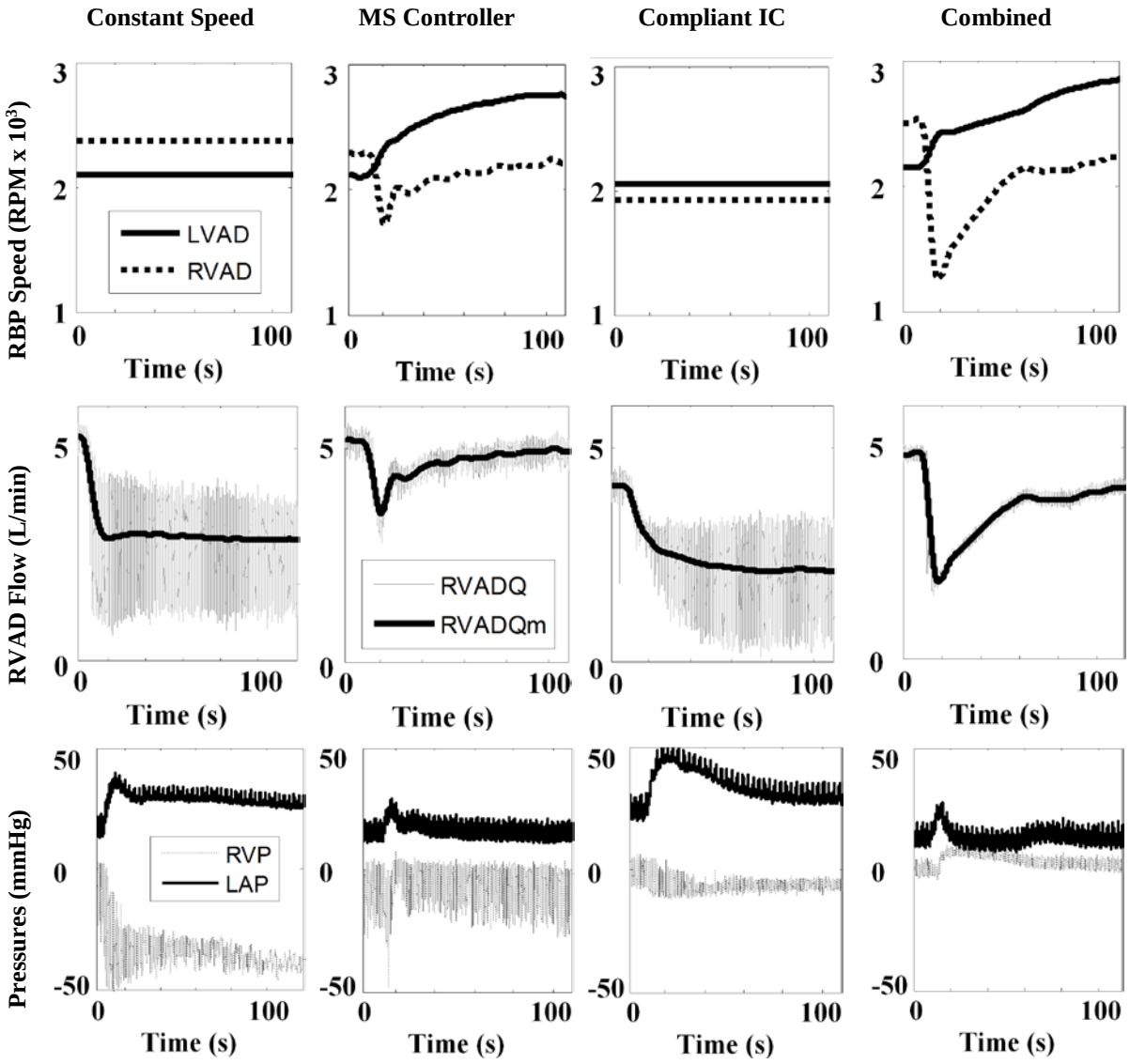

Figure 2 – Pump and haemodynamic results during a SVR increase (~1400 to 2400 dyne.s.cm^{-5}). MS – master/slave, IC – inflow cannula, OC – outflow cannula, RBP – rotary blood pump, RPM – revolutions per minute, LVAD – left ventricular assist device, RVAD – right ventricular assist device, RVADQ – RVAD flow rate, RVADQm – mean RVAD flow rate, RVP – right ventricular pressure, LAP – left atrial pressure.

	Units	Constant Speed (n=4)		MS Controller (n=4)		Compliant IC (n=2)		Combined (n=3)	
		Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
SVR	dyne.s.cm^{-5}	1375 ± 311	1005 ± 185	1344 ± 376	1086 ± 179	1400 ± 50	1135 ± 385	1490 ± 386	1293 ± 421
LVADS	RPM	2412 ± 201	0 ± 0	2381 ± 220	663 ± 246	2175 ± 125	0 ± 0	2233 ± 165	592 ± 229
RVADS	RPM	2519 ± 331	0 ± 0	2500 ± 341	-331 ± 244	1987 ± 62.5	0 ± 0	2592 ± 153.2	-142 ± 97
RVADQ	L/min	4.8 ± 0.7	-0.8 ± 0.9	4.9 ± 0.4	-0.5 ± 0.4	5.0 ± 0.8	-1.4 ± 0.9	4.5 ± 0.1	-0.3 ± 0.1
RVP	mmHg	3.5 ± 9.1	-11.8 ± 11.9	2.3 ± 8.9	-0.8 ± 0.8	3.0 ± 6.0	-2.5 ± 0.5	4.3 ± 2.9	-0.3 ± 1.2
LAP	mmHg	14.8 ± 5.1	11.5 ± 4.2	15.5 ± 2.7	0.0 ± 1.9	20.5 ± 2.5	10.0 ± 1.0	18.3 ± 5.3	-3.7 ± 2.9
MAP	mmHg	98.5 ± 11.8	32.0 ± 8.5	94.5 ± 16.2	55.0 ± 6.5	98.5 ± 6.5	14.0 ± 8.0	96.7 ± 19.6	57.0 ± 22.2

Table 2 – Results from all trials for the SVR increase (~1400 to 2400 dyne.s.cm^{-5}) with constant speed mode, the master/slave (MS) controller, compliant inflow cannula (IC), and combined controller. SVR – systemic vascular resistance, LVADS – left ventricular assist device speed, RVADS – right ventricular assist device speed, RVADQ – right ventricular assist device flow rate, RVP – right ventricular pressure, LAP – left atrial pressure, MAP – mean aortic pressure. Results presented as mean ± standard deviation. The combined controller was not evaluated in trial 2 and the RVAD compliant IC was not evaluated in trials 2 and 4 due to improper coring of the right ventricular free wall which resulted in continuous collapse of the compliant section.

	Units	Constant Speed (n=4)		MS Controller (n=3)		Compliant IC (n=4)		Compliant OC (n=3)		Combined (n=3)	
		Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
PVR	dyne.s.cm^{-5}	258 ± 98	868 ± 102	150 ± 81	773 ± 87	180 ± 102	816 ± 140	225 ± 101.6	768 ± 135.5	190 ± 94	1007 ± 42
LVADS	RPM	2425 ± 182	0 ± 0	2392 ± 372	-8 ± 43	2356 ± 72	0 ± 0	2575 ± 228	0 ± 0	2217 ± 229	-67 ± 62
RVADS	RPM	2519 ± 331	0 ± 0	2500 ± 245	358 ± 183	2419 ± 435	0 ± 0	2862 ± 263	0 ± 0	2583 ± 143	133 ± 85
LVADQ	L/min	5.0 ± 0.2	-1.0 ± 0.6	5.1 ± 0.8	-0.2 ± 0.1	4.8 ± 0.5	-1.0 ± 0.3	4.8 ± 0.2	-0.1 ± 0.1	4.2 ± 0.4	-0.1 ± 0.1
LVP	mmHg	14.0 ± 6.7	-16.3 ± 11.8	14.3 ± 5.2	-1.7 ± 1.2	17.0 ± 2.2	-9.7 ± 7.0	11.2 ± 4.8	-0.5 ± 0.4	5.3 ± 2.3	-0.3 ± 0.3
RAP	mmHg	18.3 ± 5.0	-0.8 ± 1.8	20.7 ± 4.5	-1.0 ± 0.8	18.8 ± 5.1	-0.3 ± 2.2	18.0 ± 5.6	-0.3 ± 0.4	17.8 ± 7.2	-0.3 ± 0.5
MPAP	mmHg	30.5 ± 8.3	27.8 ± 13.0	32.3 ± 11.3	45.7 ± 11.9	32.8 ± 4.9	26.8 ± 7.4	30.0 ± 4.6	43.3 ± 11.3	28.7 ± 11.6	51.3 ± 4.1

Table 3 – Results from all trials for the PVR increase (~200 to 1000 dyne.s.cm^{-5}) with constant speed mode, the master/slave (MS) controller, compliant inflow cannula (IC), compliant outflow cannula (OC) and combined controller. PVR – pulmonary vascular resistance, LVADS – left ventricular assist device speed, RVADS – right ventricular assist device speed, LVADQ – left ventricular assist device flow rate, LVP – left ventricular pressure, RAP – right atrial pressure, MPAP – mean pulmonary arterial pressure. Results presented as mean ± standard deviation. The MS controller was not evaluated in trial 4 due to data acquisition and control issues. The compliant OC and combined controller results from trial 4 not reported in this study due to a compliant OC design change.

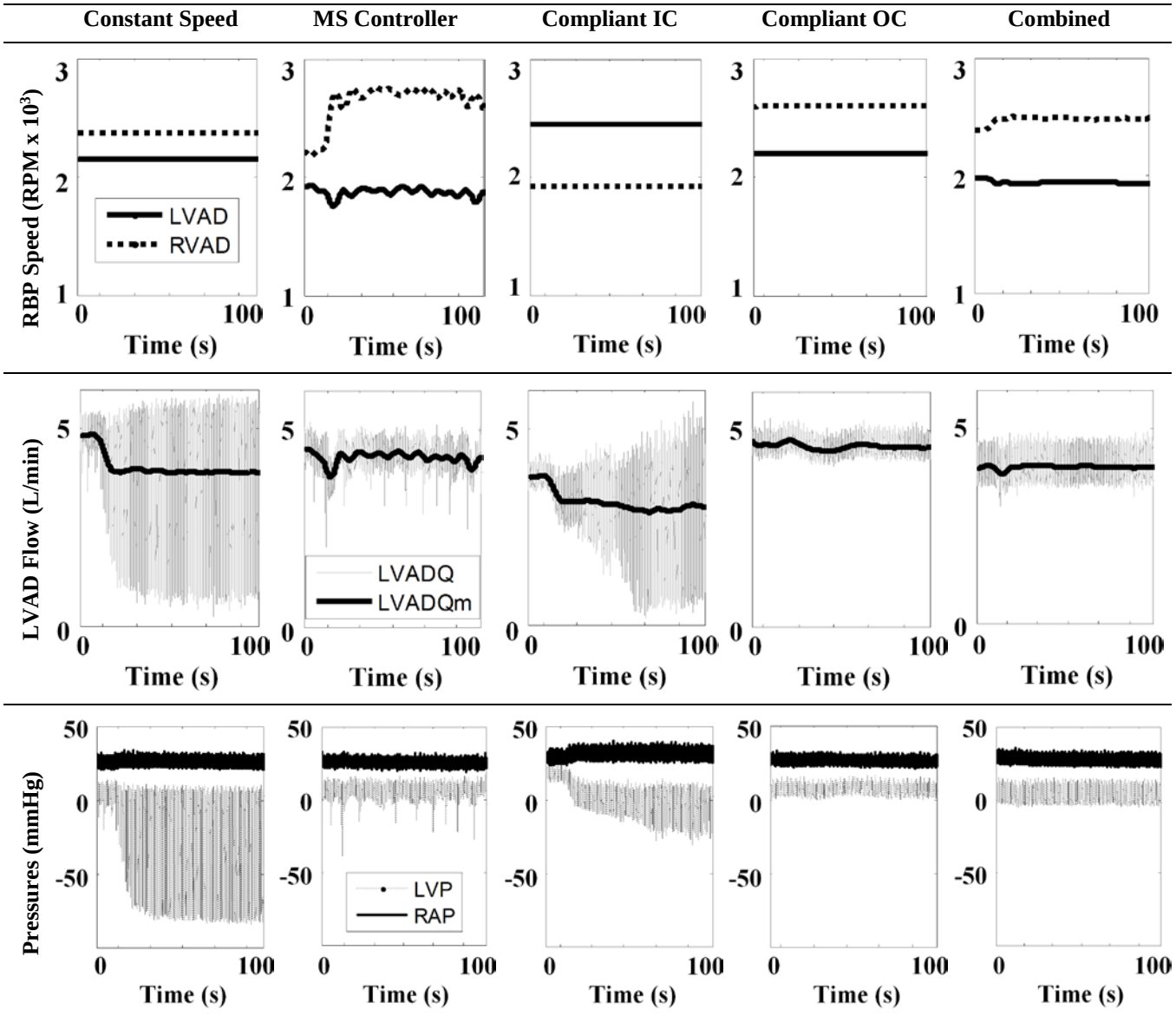

Figure 3 – Pump and haemodynamic results during a PVR increase (~200 to 1000 dyne.s.cm^{-5}). MS – master/slave, IC – inflow cannula, OC – outflow cannula, RBP – rotary blood pump, RPM – revolutions per minute, LVAD – left ventricular assist device, RVAD – right ventricular assist device, LVADQ – LVAD flow rate, LVADQm – mean LVAD flow rate, LVP – left ventricular pressure, RAP – right atrial pressure.

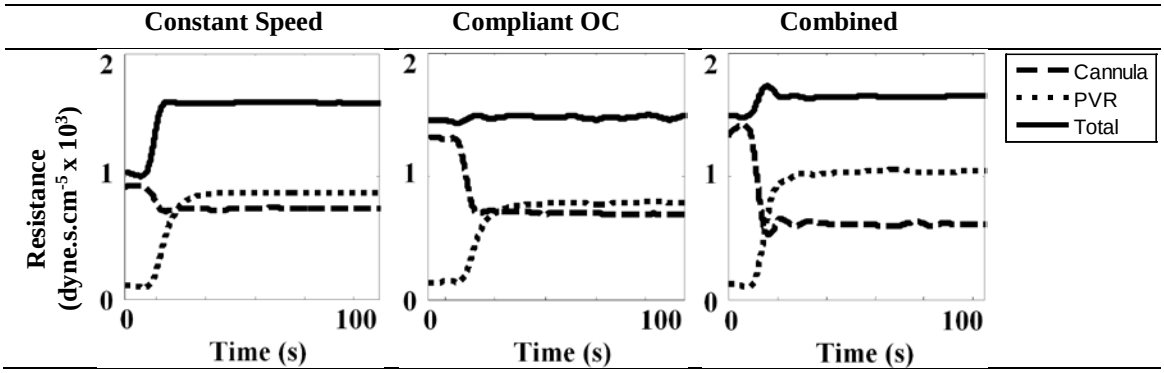

Figure 4 – Comparison of resistances (cannula, pulmonary vascular – PVR, and total) between the constant speed mode, compliant outflow cannula (OC) and combined controller during a PVR increase (~200 to 1000 dyne.s.cm^{-5}).

Discussion

Several clinical studies indicate the risk of haemodynamic instability associated with rotary LVADs [29, 30]. This is exacerbated with biventricular support as the flow-balancing Starling response of both failing ventricles is diminished. Meanwhile, the afterload sensitivity of rotary VADs is overly high compared to the native heart [11], which may result in reduced flow with increased vascular resistance downstream of the rotary VAD. This is particularly noteworthy for right heart support, as the right ventricle is more afterload-sensitive than the left and systolic pulmonary artery pressures may rise above 60 mmHg in patients with severe pulmonary hypertension [31].

Hetzer et al. [8], highlighted the importance of afterload sensitivity with rotary right ventricular support and reported manually adjusting the right-sided HeartWare HVAD outflow banding diameter to suit patients with different pulmonary vascular resistance (PVR). The afterload sensitivity of the rotary VADs in our study was clearly demonstrated by sharp reductions in VAD flow rate due to downstream increases in SVR and PVR. This decrease in left or right VAD flow rate ultimately reduced venous return to the right or left heart, respectively, and combined with the low preload sensitivity of the LVAD and RVAD resulted in ventricular suction or venous congestion. These results appear to agree with those reported in the literature, with Saito et al. [12] reporting suction during weaning from cardiopulmonary bypass and pulmonary congestion following extubation, where right sided afterload is reduced on conversion of positive pressure ventilation to the native negative pressure ventilation.

This study demonstrated the benefit of adding a physiological control system for rotary BiVAD support. With both SVR and PVR increases, the MS controller reduced ventricular suction events and eliminated venous congestion through rapid decreases in pump speed, followed by gradual increases in pump speed to restore left and right sided flow rates close to baseline. Near-suction events were recorded directly after the SVR increase (one sharp drop in RVP) and PVR increase (several small drops in LVP and LVADQ). These could be attributed to the use of the smoothing filter and slow proportional-integral gains, which prevented overly aggressive controller action. Despite this, the MS control system performed much better than the constant speed mode, even though vascular resistances were increased to the upper limits seen clinically. Other dual RBP control strategies have also been

implemented in-vivo with some success and, as with our MS controller, rely on flow and / or pressure sensors which are prone to drift and may require recalibration [16, 17]. In fact the MS controller here relies on pressure sensors at the LVAD and RVAD inlet and a flow sensor on the LVAD. Therefore, this system requires either reliable sensors which are not yet clinically available [32], a sensor-less estimation for pump inlet pressure and flow which may be associated with error [9, 33], or a backup control system in the event of sensor error or significant drift.

The passive control systems, in the form of the compliant IC and compliant OC, may provide a suitable backup control system to the MS controller. Evaluated independently, the compliant IC typically restricted as pump inlet pressure decreased to -5.5 ± 1.5 mmHg. The passive restriction of the pump inlet in response to reduced preload decreased pump flow during SVR or PVR increases and prevented ventricular suction. Although ventricular suction events were prevented, VAD flow rates decreased significantly and venous congestion occurred during SVR increases, which were potential limitations of this system. Throughout evaluation of the combined controller, the compliant IC had no negative effect on performance during SVR and PVR increases, which supports the argument for its use as a backup control system.

While the independently evaluated compliant right OC was not able to prevent suction events during SVR increases, it prevented suction and venous congestion during PVR increases through a reduction in right cannula resistance which maintained a relatively constant pulmonary circuit resistance. The rapid response of the compliant OC prevented any significant speed changes when the combined controller was evaluated and almost exclusively compensated for the increase in PVR through a decrease in RVAD cannula resistance. A similar device could be used to reduce LVAD afterload sensitivity; however the initial pump speed and thus pump power would need to be sufficiently high to overcome the restriction.

The combined active and passive system was able to avoid suction and pulmonary congestion for both SVR and PVR increases. However, during the SVR increase the master control system did not reach a stable LVAD speed after 120 seconds, despite being able to settle within that timeframe when only the active control system was used. This indicates that the inclusion of the passive system affected the frequency response of the combined system. This

could be compensated for by adjusting the proportional-integral gains, however this may require further investigation into the frequency response of the passive systems. Meanwhile, the baseline LVADQ was reduced (4.2 ± 0.4 L/min) with the combined controller during the large PVR increase. This can be attributed to the increased RVAD speed required to overcome the resistance of the compliant OC. The increased RVAD speed reduced RVAD inlet pressure and thus partially restricted the RVAD compliant IC which reduced RVADQ and subsequently reduced LVAD preload. Therefore, reduced LVAD speeds were required to prevent LVAD compliant IC collapse, which resulted in decreased LVADQ. This could be addressed in future studies by optimizing the compliance of the RVAD inflow cannula to enhance the performance of the active and passive components of the combined controller.

MAP is typically maintained around 65-80 mmHg using intravenous vasodilators in the immediate post-operative period and subsequently with diuretics, angiotensin-converting enzyme inhibitors, β-blockers and angiotensin receptor blockers after hospital discharge [33, 34]. The high arterial pressures in our study resulted after dramatic, step increases in SVR and PVR in an effort to evaluate each controller under the most severe circumstances. Such high arterial pressure increases, particularly with the MS controller, compliant OC and combined controller, may result in neurological complications (ie. haemorrhagic stroke) if blood pressures are not properly managed, particularly in the setting of systemic anticoagulation [33, 35]. Such hypertensive events could be managed through reduction of the maximum pump speed limit or implementation of an alarm which alerts the clinician or caregiver to high arterial pressures and recommends medical management with vasodilators.

There are also several potential limitations with both the compliant IC and compliant OC systems. Issues such as preventing tissue ingrowth, maintaining long term compliance and reducing blood damage (haemolysis) due to fluttering must be addressed before progressing to the clinical setting. Further investigation and validation of the flow dynamics within the compliant cannulae is required to prevent flow separation and regions of stasis which may promote thrombus formation [36, 37], although no thrombus was observed on the compliant IC or OC during our acute studies. A limitation of our study was the unphysiological instant step response in resistance, which should be interpreted with the knowledge that in clinical practice these changes would almost always occur over a longer duration. The small number of in-vivo trials (four) is another limitation with this study as there is significant variability and uncertainties, such as reproducibility issues, during animal experiments. The lack of a

clinically representative in-vivo congestive heart failure model is also a significant limitation of this study. Although our model eliminated the Starling response of both ventricles, it only represented patients with negligible contractility and, therefore, this study would benefit from using a congestive heart failure model.

Conclusion

This study demonstrated the ease with which ventricular suction and venous congestion events can occur with rotary BiVAD support in the clinically representative constant speed mode during SVR and PVR changes. Addition of the MS controller reduced suction events and prevented venous congestion through automatic pump speed changes. The compliant IC prevented suction events through an increase in pump inlet resistance and subsequent flow reduction; however pulmonary venous congestion was still noted after increased SVR. Pulmonary venous congestion and left ventricular suction events were prevented during PVR changes with the compliant right OC which reduced RVAD outlet resistance to maintain pulmonary circuit flow. The combined controller, which used the MS controller, compliant IC and compliant OC, prevented suction and congestion events in all cases while providing a backup suction prevention system in the event of sensor failure.

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References

1. Aissaoui, N., Morshuis, M., Schoenbrodt, M., et al., *Temporary right ventricular mechanical circulatory support for the management of right ventricular failure in critically ill patients.* The Journal of Thoracic and Cardiovascular Surgery, 2013. **146**(1): p. 186-191.
2. Drakos, S.G., Janicki, L., Horne, B.D., et al., *Risk Factors Predictive of Right Ventricular Failure After Left Ventricular Assist Device Implantation.* American Journal of Cardiology, 2010. **105**(7): p. 1030-5.
3. Kirklin, J.K., Naftel, D.C., Pagani, F.D., et al., *Sixth INTERMACS annual report: A 10,000-patient database.* The Journal of Heart and Lung Transplantation, 2014. **33**(6): p. 555-564.
4. Timms, D., *A review of clinical ventricular assist devices.* Med Eng Phys, 2011. **33**(9): p. 1041-7.
5. Gregory, S.D., Timms, D., Gaddum, N., Mason, D.G. and Fraser, J.F., *Biventricular assist devices: A technical review.* Annals of Biomedical Engineering, 2011. **39**(9): p. 2313-2328.
6. Saeed, D., Massiello, A.L., Shalli, S., et al., *Introduction of fixed-flow mode in the DexAide right ventricular assist device.* J Heart Lung Transplant, 2010. **29**: p. 32-36.
7. Slaughter, M.S., Rogers, J.G., Milano, C.A., et al., *Advanced heart failure treated with continuous-flow left ventricular assist device.* The New England Journal of Medicine, 2009. **361**(23): p. 2241-51.
8. Hetzer, R., Krabatsch, T., Stepanenko, A., Hennig, E. and Potapov, E.V., *Long-term biventricular support with the heartware implantable continuous flow pump.* The Journal of Heart and Lung Transplantation, 2010. **29**(7): p. 822-824.
9. Strueber, M., Meyer, A.L., Melehsa, D. and Haverich, A., *Successful use of the HeartWare HVAD rotary blood pump for biventricular support.* The Journal of Thoracic and Cardiovascular Surgery, 2010. **140**(4): p. 936-937.
10. Frazier, O.H., Myers, T.J. and Gregoric, I.D., *Biventricular assistance with the Jarvik FlowMaker: A case report.* The Journal of Thoracic and Cardiovascular Surgery, 2004. **128**: p. 625-626.
11. Salamonsen, R.F., Mason, D.G. and Ayre, P.J., *Response of rotary blood pumps to changes in preload and afterload at a fixed speed setting are unphysiological when compared with the natural heart.* Artificial Organs, 2011. **35**(3): p. E47-E53.
12. Saito, S., Sakagushi, T., Miyagawa, S., et al., *Biventricular support using implantable continuous-flow ventricular assist devices.* J Heart Lung Transplant, 2011. **30**: p. 475-8.
13. Krabatsch, T., Potapov, E., Stepanenko, A., et al., *Biventricular circulatory support with two miniaturized implantable assist devices.* Circulation, 2011. **124**: p. S179-186.
14. AlOmari, A.H.H., Savkin, A.V., Stevens, M., et al., *Developments in control systems for rotary left ventricular assist devices for heart failure patients: a review.* Physiol. Meas., 2013. **34**: p. R1-R27.
15. Giridharan, G.A. and Skliar, M., *Physiological Control of Blood Pumps Using Intrinsic Pump Parameters: A Computer Simulation Study.* Artificial Organs, 2006. **30**(4): p. 301-307.
16. Endo, G., Araki, K., Oshikawa, M., et al., *Control Strategy for Biventricular Assistance with Mixed-Flow Pumps.* Artificial Organs, 2000. **24**(8): p. 594-599.
17. Nose, Y. and Furukawa, K., *Current status of the Gyro centrifugal blood pump - Development of the permanently implantable centrifugal blood pump as a*

biventricular assist device (NEDO Project). Artificial Organs, 2004. **28**(10): p. 953-958.
18. Yi, W. *Physiological control of a rotary left ventricular assist device*. in *26th Chinese Control Conference*. 2007. Zhangjiajie, Hunan, China.
19. Gaddum, N., Timms, D. and Pearcy, M., *A Passively Controlled Bi Ventricular Support Device.* Artificial Organs, 2010. **34**(6): p. 473 - 480.
20. Fukamachi, K., Horvath, D.J., Massiello, A.L., et al., *An innovative, sensorless, pulsatile, continuous-flow total artificial heart: Device design and initial in vitro study.* J Heart Lung Transplant, 2010. **29**: p. 13-20.
21. Stevens, M.C., Wilson, S., Bradley, A., Fraser, J. and Timms, D., *Physiological control of dual rotary pumps as a biventricular assist device using a master/slave approach.* Artif Organs, 2014. **38**(9): p. 766-74.
22. Gregory, S.D., Pearcy, M. and Timms, D., *Passive control of a biventricular assist device with compliant inflow cannulae.* Artificial Organs, 2012. **36**(8): p. 683-90.
23. Gregory, S.D., Schummy, E., Pearcy, M., et al., *A compliant, banded outflow cannula for decreased after-load sensitivity of rotary right ventricular assist devices.* Artificial Organs, 2014.
24. Gregory, S.D., Timms, D., Gaddum, N.R., McDonald, C., Pearcy, M.J. and Fraser, J.F., *In-Vitro Evaluation of a Compliant Inflow Cannula Reservoir to Reduce Suck-Down Events with Extracorporeal, Rotary VAD Support.* Artificial Organs, 2011. **35**(8): p. 765-772.
25. Pauls, J.P., Stevens, M., Schummy, E., et al., *In-vitro evaluation of active and passive physiological control systems for biventricular mechanical circulatory support.* Annals of Biomedical Engineering, 2015. DOI: 10.1007/s10439-015-1425-1
26. Timms, D., Gregory, S., Greatrex, N., Pearcy, M.J., Fraser, J.F. and Steinseifer, U., *A compact mock circulation loop for the in vitro testing of cardiovascular devices.* Artificial Organs, 2011. **35**(4): p. 384-91.
27. McClean, D., Aragon, J., Jamali, A., et al., *Noninvasive calibration of cardiac pressure transducers in patients with heart failure: an aid to implantable hemodynamic monitoring and therapeutic guidance.* J Card Fail, 2006. **12**(7): p. 568-76.
28. Epstein, S.E., Beiser, G.D., Stampfer, M., Robinson, B.F. and Braunwald, E., *Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease.* Circulation, 1967. **35**(6): p. 1049-62.
29. Ambardekar, A.V., Lowes, B., Cleveland, J.C. and Brieke, A., *Overdrive pacing suppresses ectopy and minimizes left ventricular assist device suction events.* Circ Heart Fail, 2009. **2**: p. 516-517.
30. Felix, S.E.A., Martina, J.R., Kirkels, J.H., et al., *Continuous-flow left ventricular assist device support in patients with advanced heart failure: points of interest for the daily management.* European Journal of Heart Failure, 2012.
31. Guazzi, M. and Borlaug, B.A., *Pulmonary hypertension due to left heart disease.* Circulation, 2012. **126**: p. 975-990.
32. Fritz, B., Cysyk, J., Newswanger, R., Weiss, W. and Rosenberg, G., *Development of an inlet pressure sensor for control in a left ventricular assist device.* ASAIO Journal, 2010. **56**: p. 180-185.
33. Slaughter, M.S., Pagani, F.D., Rogers, J.G., et al., *Clinical management of continuous-flow left ventricular assist devices in advanced heart failure.* J Heart Lung Transplant, 2010. **29**: p. S1-S39.

34. Myers, T.J., Bolmers, M., Gregoric, I.D., Kar, B. and Frazier, O.H., *Assessment of arterial blood pressure during support with an axial flow left ventricular assist device.* J Heart Lung Transplant, 2009. **28**(5): p. 423-7.
35. Lampert, B.C., Eckert, C., Weaver, S., et al., *Blood pressure control in continuous flow left ventricular assist devices: efficacy and impact on adverse events.* Ann Thorac Surg, 2014. **97**(1): p. 139-46.
36. Fraser, K.H., Zhang, T., M.E., T., Griffith, B.P. and Wu, Z.J., *Computational fluid dynamics analysis of thrombosis potential in left ventricular assist device drainage cannulae.* ASAIO Journal, 2010. **56**(3): p. 157-63.
37. Hochareon, P., Manning, K.B., Fontaine, A.A., Tarbell, J.M. and Deutsch, S., *Correlation of in vivo clot deposition with the flow characteristics in the 50 cc penn state artificial heart: a preliminary study.* ASAIO Journal, 2004. **50**(6): p. 537-42.