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Haemodynamic Modeling of the Cardiovascular System Using Mock Circulation Loops to Test Cardiovascular Devices

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Abstract—**Comprehensive testing and evaluation of cardiovascular device function and performance is required prior to clinical implementation. Initial proof of concept investigations are conducted within in-vitro mock circulation loops, before proof of principle is demonstrated via *in-vivo* animal testing. To facilitate the rapid transition of cardiovascular devices through this development period, a testing apparatus was developed that closely models the natural human cardiovascular system haemodynamics. This mock circulation system accurately replicates cardiac function, coupled to systemic and pulmonary circulations. The physiological response produced by a number of clinical cardiovascular conditions can be actively controlled by variable parameters such as vascular resistance, arterial/venous compliance, ventricle contractility, heart rate, and heart /vascular volumes, while anatomical variations such as valve regurgitation and septal defects can be included. Auto-regulation of these parameters was attempted to reproduce the Frank-Starling mechanism, baroreceptor reflex, skeletal muscle pump, and postural changes. Steady state validation of loop performance was achieved by replicating the progression of a patient's clinical haemodynamics from heart failure, through VAD support, to heart transplantation. The system has been used to evaluate pulsatile and non-pulsatile ventricular assist devices, counter pulsation devices, non-invasive cardiac output monitors and cardiovascular stents. The interaction of these devices with the cardiovascular system was also investigated with regards to physiological control strategies and cannula placement. The system is a valuable tool for the accelerated progression of cardiovascular device development.**

I. Introduction

Cardiovascular disease (CVD) is prevalent worldwide, with the incidence predicted to increase as the population ages. In the USA alone, 36.9% of people currently suffer from some form of CVD, a percentage that is expected to rise to 40.5% by 2030 [1]. Treatment strategies for this population involve medical therapy, donor heart transplantation, or cardiovascular device intervention. Given the limited donor organ rates, interventional devices such as stents, prosthetic valves, and mechanical circulatory support devices are being developed to provide an alternative therapy for patients who no longer respond to medical therapy. In fact, it has been shown that the application of cardiovascular device therapy, in this case mechanical blood pumps, can reduce the mortality rates seen in patients treated with optimal medical therapy [2]. Furthermore, the development of diagnostic devices that assess patient haemodynamics, such as cardiac output monitors, will promote the identification of CVD and assist in selecting the most appropriate treatment strategy.

Cardiovascular devices progress through a lengthy development path from conception to clinical implementation, including stringent testing phases. Specifically, these tests involve *in-vitro* proof of concept, *in-vivo* proof of principle, and clinical validation. The *in-vitro* phase is an extremely important step, as it provides a chance to evaluate the device's performance and predict its ability to achieve its intended function on the bench top. Considerable time and expense can be saved prior to in-vivo testing, as the operation of the device can be refined in this environment.

In-vitro testing is conducted in a mock circulation loop (MCL), which is a mechanical representation of the human cardiovascular system. This environment allows for the predictable and repeatable setting of cardiovascular circulation parameters to evaluate the intended performance of the cardiovascular device. MCLs range from simple pulse duplicating circuits that include a means of creating an artificial heartbeat suitable for testing the durability of prosthetic valves [3], to more complex cardiovascular systems that are used to evaluate the haemodynamic performance of mechanical circulatory support devices [4].

However, these MCLs are typically designed for testing a single device, and do not combine many circulatory features. They also often lack the auto-regulatory feedback mechanisms of the natural cardiovascular system, such as the Frank-Starling mechanism, baroreceptor reflex and shifts to volume due to skeletal muscle pump and postural changes.

To address these short comings and limitations, a comprehensive MCL was developed to include most features of the cardiovascular system in combination with emerging auto-regulatory feedback responses. With slight modifications to the system for each application, cardiovascular devices such as abdominal aortic aneurism stents, extra-aortic counter-pulsation devices, and volume displacement / rotary ventricular assist devices (VAD) were evaluated. The interaction of these devices with the cardiovascular system was then investigated, both with respect to their operational control and site of connection.

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II. METHODS

A. Mock Circulation Loop Description

Accurate mechanical representation of the cardiovascular system and control of its parameters is required for the successful development of a MCL. To assist in the development and ensure improved haemodynamic results, a mathematical simulation was used to determine the physical properties of the system such as pipe dimensions and input pressures [5]. In both simulation and bench top MCL; cardiac chambers were connected to systemic and pulmonary circuits for representation of the complete cardiovascular system. A schematic of the MCL is shown in Figure 1, whilst a full description of the MCL is provided by Timms *et al* [6].

1) Heart: Left and right atrial and ventricular chambers were included and separated by mechanical swing check valves. These valve sections could be removed so that prosthetic valves such as trileaflet polyurethane or single/bi-leaflet mechanical valves could be inserted. The chambers were vertical tubes; however a transparent silicone mold of a cardiomyopathic heart could also be adapted for use in flow visualization studies [7, 8]. Real-time ventricular volumes and pressures were recorded throughout the cardiac cycle, which enabled the stroke volume, ejection fraction and pressure volume loops to be recorded. Septal and valve defects were incorporated with the use of strategically placed solenoid valves. Left and right coronary circulations were also included. Left and right ventricle and atrial function were independently controlled using 3/2 solenoid valves (VT325-035DLS, SMC Pneumatics, Brisbane, AUS). Crucial passive ventricular filling during diastole was achieved, while a finely controlled injection of compressed air via an electro pneumatic regulator (ITV2030-012BS5, SMC Pneumatics, Brisbane, AUS) represented systole. Real-time variations in contractility, systolic time and heart rate were possible; key features essential for the real-time reproduction of the Frank-Starling effect.

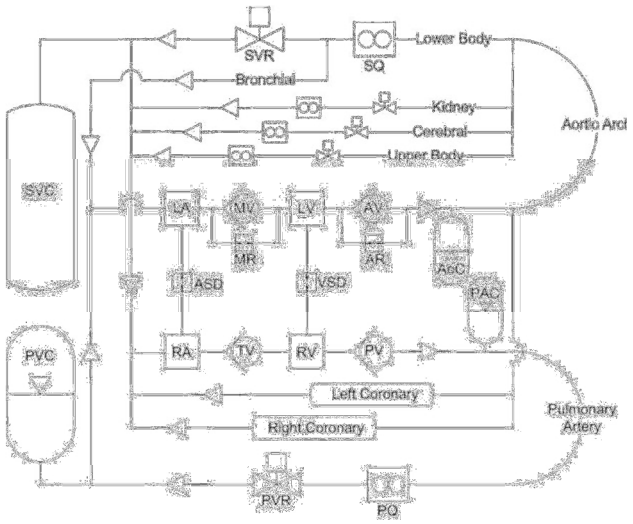

Fig. 1. Schematic of the mock circulation loop. LA = left atrium, MV = mitral valve, LV = left ventricle, AV = aortic valve, AoC = aortic compliance chamber, SQ = systemic flow meter, SVR = systemic vascular resistance valve, SVC = systemic venous compliance chamber, RA = right atrium, TV = tricuspid 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, ASD = atrial septal defect, VSD = ventricular septal defect, MR = mitral valve regurgitation, AR = aortic valve regurgitation.

2) Vasculature: Systemic and pulmonary vasculatures were represented by a five element Windkessel model, consisting of characteristic and peripheral resistance, arterial and venous compliance, and an inertial component. The systemic circulation was divided into four parallel loops, each with their own controllable level of resistance, which represented regional cerebral, kidney, upper and lower body flow. Bronchial circulation was also included.

Vascular resistance variability was obtained by the use of proportional control valves (EPV-375B, HASS Manufacturing, NY, U.S.A.). Variable aortic and pulmonary arterial and venous compliance was achieved using a series of selectable Windkessel chambers. The 6L systemic venous compliance chamber, partially filled with fluid, was attached to a regulated compressed air supply which alters internal pressure, effectively redistributing MCL fluid volume.

3) Control and Data Acquisition: Systemic and pulmonary pressures were recorded at multiple locations throughout the system using silicone based transducers (PX181B-015C5V, Omega Engineering, Connecticut, USA), while flow rates were detected using magnetic flow meters (IFC010, KROHNE, Sweden). Ventricular volumes were obtained using values taken from a magnetostrictive level sensors (IK1A, GEFRAN, Italy) multiplied by the chamber cross sectional area. Vascular resistance, arterial compliance, ventricle contractility, heart rate, systolic time, and control of the septal defects and valve regurgitation were all actively controlled via a digital signal processor and computer interface (DS1103, dSPACE Inc, Novi, MI, USA).

B. MCL Validation and Auto regulation

1) Validation: Variable healthy and pathological conditions including rest, exercise and left heart failure (LHF) were reproduced in the system. Steady state validation was achieved by recreating the haemodynamic values retrospectively obtained from the charts of a left heart failure patient throughout their course of treatment; from heart failure, to VAD support, to heart transplantation.

2) Auto regulation: A Frank-Starling mechanism, which alters ventricular contractility in response to end diastolic volume (EDV), was implemented in both ventricular chambers. A description of this controller and results are provided by Gregory *et al.* [9]. The emergence of a baroreceptor reflex, by the inclusion of a simple feedback PI controller which observed aortic pressure and caused valve position variations and thus systemic vascular resistance, maintained a set-point mean arterial pressure (MAP), however corresponding heart rate changes were not included. The performance of these emerging auto-regulatory responses were evaluated by replicating postural changes and changes to aortic pressure analogous to the Valsalva maneuver [10]. The transition from lying to standing was replicated by adjusting the level of compressed air pressure applied to the systemic venous chamber. This alteration effectively caused a redistribution of fluid throughout the

circuit, and thus momentary changes in right atrial venous return. Transitions in aortic pressure observed during the four phases of the Valsalva maneuver were effectively reproduced by firstly simulating intrathoracic compression of the thoracic aorta and pulmonary artery/vena cava by using the SVR and PVR valves to create an in-series resistance increase (phase I). This effectively restricted venous return to the heart (phase II), which activated the Frank-Starling effect and baroreceptor reflex. Thoracic compression was then released (phase III) by reversing the disturbance on SVR and PVR, which leads to an influx of venous return (phase IV) and secondary stimulation of auto-regulatory mechanisms [11].

C. Cardiovascular Device Testing

1) Devices: The performance and function of numerous clinical or emerging cardiovascular devices were previously evaluated using the mock circulation loop. VADs such as the Abiomed BVS5000 and AB5000, Thoratec PVAD, Ventracor VentrAssist, BiVACOR BV Assist/Replace, Sunshine Heart C-Pulse, and Medtronic BP-80 were connected, via atrial or ventricular inflow cannulation, to determine their influence on haemodynamic restoration. Preliminary investigations into the ability of the USCOM non-invasive cardiac output monitor to predict aortic flow were also undertaken.

2) Investigations: The design of the MCL enabled specific investigations into cardiovascular system / device interaction. In addition to the influence of inflow chamber selection on potential unloading of the heart with a view to myocardial recovery, cannula location within these chambers was also investigated to determine the optimal placement to improve ventricular chamber washout to reduce thrombus formation. Physiological control strategies to promote unloading, reduce the incidence of ventricular suction, and enhance VAD preload sensitivity to alter cardiac output to meet demand, were also successfully investigated in the MCL.

III. Results and Discussion

A. MCL Validation against Patient Data

Arterial pressure and flow rates of a patient progressing through therapy, replicated on the MCL, are described in Fig 2. Representative healthy conditions of 100 mmHg (MAP) and 5.5 l/min (mean systemic flow rate) were created, before a level of heart failure was induced by altering cardiac contractility and vascular resistance to reduce pressure and flow to 55 mmHg and 2.2 l/min respectively. VAD support using a Thoratec PVAD restored haemodynamics to 85 mmHg at 4.8 l/min. The values two days post-transplant of 60 mmHg at 4 l/min are representative of the administration of inodilators to reduce afterload in the attempt to offload the new heart. Following this period, post-transplant results of 100 mmHg at 5.4 l/min were created, which describes the ability of the donor heart to restore the patient to initial healthy conditions.

B. Auto-regulatory Performance

Haemodynamic values recorded in the MCL whilst replicating both Valsalva and a lie/stand/sit maneuver with and without the baroreceptor controller are described in Table I. These results demonstrate that the baroreceptor controller

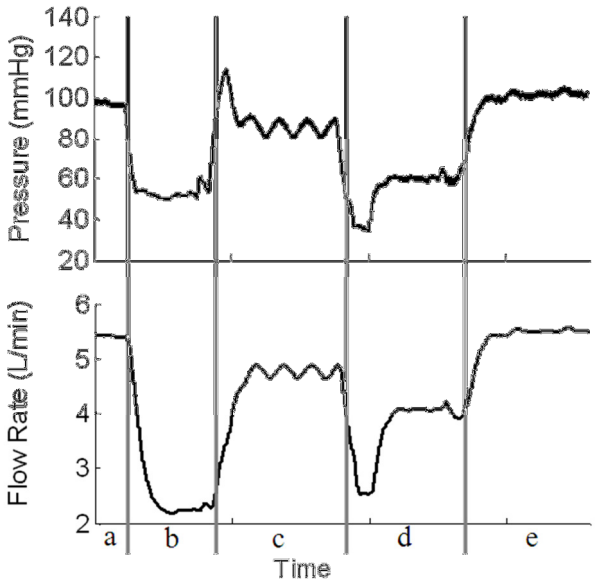

Fig. 2. Replication of patient haemodynamics (mean aortic pressure and systemic flow rate) throughout the progression of heart failure treatment. a) Normal LV function, b) heart failure, c) VAD support, d) two days post heart transplant, e) thirty days post heart transplant.

was effective at maintaining a set mean aortic pressure when faced with shifts in fluid volume or disturbances to SVR/PVR, by altering both systemic vascular resistance and cardiac contractility (the latter via the Frank-Starling controller).

Haemodynamic traces of the analogous Valsalva maneuver with auto-regulation are shown in Fig 3. The duration of the test was 60 seconds. Initial baroreceptor controller gains were tuned by trial and error to Kp= 0.01 V/mmHg and Ki = 0.001 V/(mmHg.s) to achieve a desired response, however this response has yet to be matched to clinical data. Meanwhile, the influence of heart rate and venous tone were not incorporated in the baroreceptor simulation at this stage, thus limiting its accuracy.

MAP trends were similar to those observed in human patients undergoing a Valsalva maneuver. The initial spike in MAP to 115 mmHg, due to the compression of the aorta during Phase I, is consistent with a rise in thoracic pressure when blocked forced expiration is initiated. A subsequent drop in MAP during Phase II to 82 mmHg was observed,

TABLE I
COMPARISON OF THE HEMODYNAMICS PRODUCED IN RESPONSE TO A VALSALVA MANEUVER AND POSTURAL CHANGES WITH AND WITHOUT THE BARORECEPTOR CONTROLLER

Valsalva								
	Baroreceptor On				Baroreceptor Off			
Phase	I	II	III	IV	I	II	III	IV
MAP(mmHg)	115	100	83	102	104	38	33	93
MPAP(mmHg)	16	37	37	14	15	44	45	16
MSQ(l/min)	4	1.7	2.4	4.5	4.4	2.2	2.1	4.7
Lie / Sit / Stand								
	Baroreceptor On			Baroreceptor Off				
	Lie	Stand	Sit	Lie	Stand	Sit		
MAP(mmHg)	100	96	102	100	59	79		
MPAP(mmHg)	16	8	11	16	9	12		
MSQ(l/min)	5.0	3.0	4.0	5.0	3.8	4.4		

MAP = mean aortic pressure, MPAP = mean pulmonary artery pressure, MSQ = mean systemic flow rate.

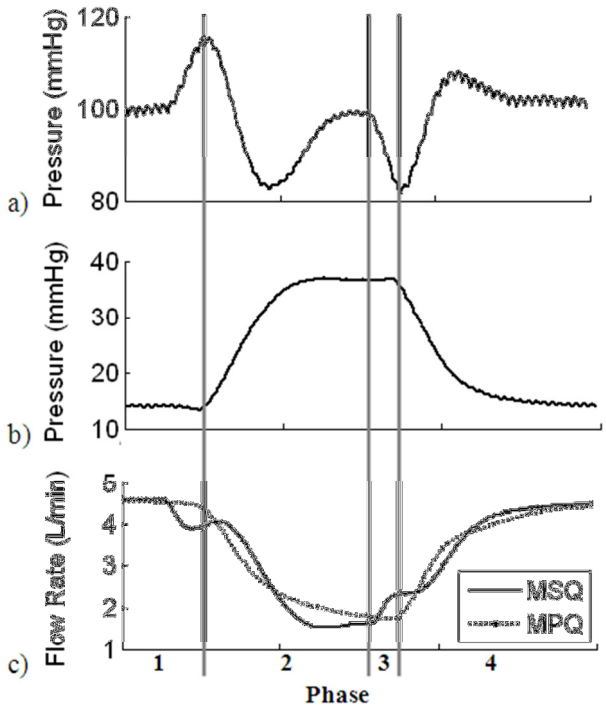

Fig. 3. A sixty second transition through the four phases of the analogous Valsalva maneuver recorded on the MCL. (a) Aortic pressure trace, (b) pulmonary artery pressure, (c) mean systemic (MSQ) and pulmonary (MPQ) flow rate.

representing a manifestation of the Frank-Starling response to a reduction in venous return due to the concomitant compression of pulmonary vessels. The influence of the baroreceptor controller can then be observed as MAP is returned to 98 mmHg. The release of vessel compression reversed the process, whereby an initial drop in MAP was seen, before an increase in contractility occurred when venous return increased, causing MAP to overshoot the set MAP of 100 mmHg. The slower acting baroreceptor controller then acted to reduce MAP back to the target value of 100 mmHg.

During this maneuver, relative systemic and pulmonary flow rates were found to change by up to 0.5 l/min, as fluid was redistributed throughout the body. This suggests that the control of cardiac output may be beneficial when supporting the circulation with mechanical pumps during these maneuvers.

C. Cardiovascular Device Testing

The haemodynamic performance of numerous cardiovascular devices has been tested within the MCL. As an example, Figure 4 describes the pressure and flow rate traces of the BiVACOR BV Assist device, having restored haemodynamics from a simulated biventricular heart failure condition.

IV. Conclusion

A MCL with emerging auto-regulatory features was developed, and provides a suitable testing platform to evaluate the performance of cardiovascular devices during the crucial proof of concept phase of development. Numerous clinical and emerging cardiovascular devices have been

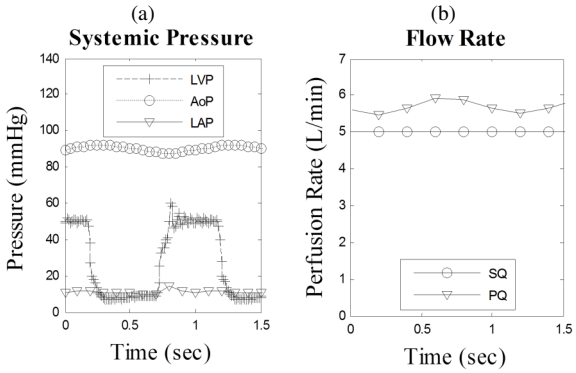

Fig. 4. Systemic pressure (a), and flow rates (b) for a condition of BiHF with BiVACOR® BV Assist support in the MCL. LAP – left atrial pressure, LVP – left ventricle pressure, AoP – aortic pressure.

evaluated with the MCL, both in regards to their functional performance and their interaction with the cardiovascular system. Continued improvement of this test facility and clinical validation of auto-regulatory features will improve the quality of results obtained *in-vitro*, thus saving considerable time and cost associated with *in-vivo* testing.

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