

Replication of the Frank-Starling Response in a Mock Circulation Loop

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Abstract—Mock circulation loops (MCLs) are used to evaluate cardiovascular devices prior to in-vivo trials; however they lack the vital autoregulatory responses that occur in humans. This study aimed to develop and implement a left and right ventricular Frank-Starling response in a MCL. A proportional controller based on ventricular end diastolic volume was used to control the driving pressure of the MCL's pneumatically operated ventricles. Ventricular pressure-volume loops and end systolic pressure-volume relationships were produced for a variety of healthy and pathological conditions and compared with human data to validate the simulated Frank-Starling response. The non-linear Frank-Starling response produced in this study successfully altered left and right ventricular contractility with changing preload and was validated with previously reported data. This improvement to an already detailed MCL has resulted in a test rig capable of further refining cardiovascular devices and reducing the number of in-vivo trials.

I. INTRODUCTION

MOCK circulation loops (MCLs) are mechanical representations of the heart and circulatory system and are essential for in-vitro evaluation of cardiovascular devices prior to in-vivo trials [1]. These test rigs range from basic designs consisting of a preload chamber and resistance valve [2] to complex arrangements including multiple compliance chambers, variable resistance and functioning ventricles [3, 4]. MCLs are usually designed specifically for evaluation of one cardiovascular device, such as a ventricular assist device (VAD) or heart valve [5, 6]. However, some systems have been developed with improved functionality and can be used to evaluate a wide range of devices [7, 8].

Rosenberg et al. [7] reported on the development of the Pennsylvania State University MCL which included both systemic and pulmonary circulations, arterial and venous compliance chambers, variable vascular resistance, and functioning ventricles. The MCL incorporates accurate representations of inertial, resistive and elastic properties of the heart and circulatory system under a range of simulated

conditions. However like many MCLs, an active ventricular Frank-Starling response (also referred to as Starling response) does not exist. The Starling response is a native autoregulatory mechanism that results in an increased ejection volume with increasing ventricular filling by increasing the force of ventricular contraction. Therefore, evaluation of cardiovascular devices is limited in MCLs without a Starling response as ventricular pressures, and hence cardiac output, incorrectly remain constant for changing ventricular volume.

Previous attempts to implement a Starling response in a MCL have been made. Baloa et al. [9] implemented an elastance based control scheme which calculated the desired ventricular pressure based on instantaneous ventricular volume with a bellows pump ventricle. A separate control loop was then required to regulate the ventricular pressure based on the output of the elastance control loop. While demonstrating changing ventricular pressure with changed ventricular volume, the end systolic pressure volume relationship (ESPVR), usually non-linear in humans [10], was linear. Meanwhile, no right ventricular Starling response was simulated. Loh et al. [11] developed, in simulation, a MCL Starling response based on the work completed by Baloa et al., but with the addition of right atrial compliance and pressure dependent flow. Again, this simulation included no right ventricular Starling response, and only a limited range of preload was evaluated.

A Starling response was implemented in a systemic only MCL with pneumatically operated ventricles by Pantalos et al. [12]. Little detail of the Starling implementation was given, however results were shown for varying Starling sensitivity. For all degrees of Starling sensitivity, the ESPVR appeared as though it would cross the x-axis at negative ventricular volumes. The x-intercept should occur at positive ventricular volumes as ventricular contraction will cease while a small residual volume remains [13]. A positive x-intercept was obtained by Ferrari et al. [14], who incorporated both left and right ventricular Starling responses in a MCL. This system controlled ventricular pressure based on ventricular volume with piston-cylinder type ventricles. While variable Starling response sensitivity was demonstrated with varying preload and afterload, the ESPVR was linear rather than concave towards the volume axis.

The aim of this study was to develop and implement a variable non-linear biventricular Starling response in a MCL with pneumatically operated ventricles. This system can then be employed to evaluate cardiovascular devices more accurately under a wide range of pathological conditions.

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II. METHODS

A. Mock Circulation Loop

A detailed MCL, based on a five element Windkessel model and consisting of systemic and pulmonary circulations, was used for Starling response simulation [1]. Ventricular and atrial systole were controlled through a series of regulators (ITV2030-012BS5, IR3000-04, AR40-04H-1 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 percentage (Figure 1). Ventricular pressure waveforms were smoothed by adjusting the electropneumatic regulator current supply at a frequency of 20Hz with a look-up table. Mechanical check valves were used to simulate the mitral, aortic, tricuspid and pulmonary valves to ensure unidirectional flow throughout the circuit. Windkessel chambers were employed to simulate lumped systemic and pulmonary arterial and venous compliance. Proportional control valves (EPV-375B, HASS Manufacturing, NY, U.S.A.) allowed easy manipulation of systemic and pulmonary vascular resistance for efficient transition between healthy and pathologic conditions. Cardiovascular device evaluation was incorporated through various access points throughout the circuit.

B. Starling Response Control

A Starling response was simulated in the MCL's pneumatic left and right ventricles through a proportional controller based on the real-time measurement of ventricular end diastolic volume (EDV). A schematic of the controller is shown in Figure 2. A natural logarithmic function of EDV was used to scale the electrical current signal sent to the regulators. The natural logarithmic function was interpolated from the ESPVR described by Guyton (2005) [15]. The sensitivity of the MCL's Starling response (and hence level of native ventricular function) was controlled by passing the output of the logarithmic function through a gain block. The gain block was used to proportionally scale the output of the ventricular pressure shaping lookup table, resulting in a time varying electropneumatic regulator current signal that was dependent on preload. To ensure suitably low systolic pressures at low ventricular volumes, an offset constant was added to the EDV. The value of offset varied with heart function and was chosen manually.

C. Starling Response Validation

MCL parameters were manipulated to simulate a healthy, resting condition without a Starling response. The Starling response was then initiated and the sensitivity gain and EDV offset were manually adjusted through trial and error to produce an appropriate degree of contractility with a set ventricular preload. The shape of the ESPVR was then evaluated by decreasing MCL volume until ventricular volumes approached zero. A valve attached to the systemic venous chamber (SVC) was then partially opened to slowly redistribute fluid throughout the system to observe the response to increasing preload. MCL volume was then adjusted to achieve simultaneous left and right atrial

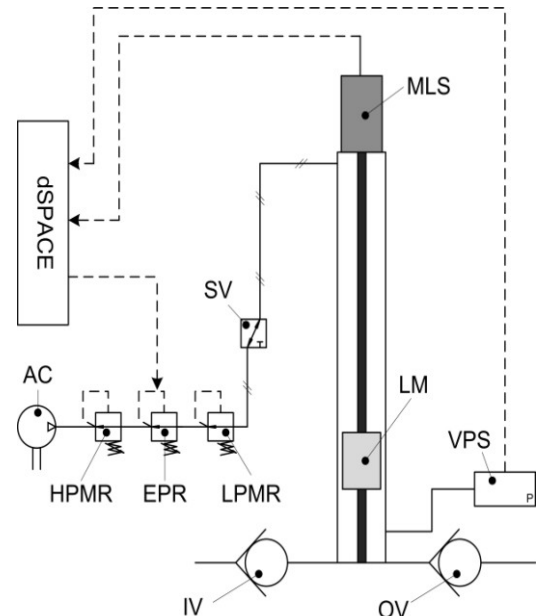


Fig. 1. Ventricle chamber schematic. AC = compressed air source, HPMR = high pressure manual regulator, EPR = electropneumatic regulator, LPMR = low pressure manual regulator, SV = solenoid valve, MLS = magnetostrictive level sensor, LM = level magnet, VPS = ventricular pressure sensor, IV = inflow valve, OV = outflow valve

pressures of 5, 10 and 15mmHg to observe the entire system response at various levels of preload. Both experiments were repeated for simulated conditions of mild and severe biventricular heart failure (BHF).

D. Data Acquisition

Haemodynamic parameters were captured at 100Hz using a dSPACE acquisition system (DS1103, dSPACE, MI, USA). Systemic and pulmonary flow rates were recorded using magnetic flow meters (IFC010, KROHNE, Sweden). Circulatory pressures were recorded using silicon-based transducers (PX181B-015C5V, Omega Engineering, Connecticut, USA). Ventricular volume was recorded using a magnetostrictive level sensor (IK1A, GEFTRAN, Italy) which, when combined with the left ventricular pressure trace, produced pressure-volume (PV) loops. Post processing of the PV loops enabled capture of left ventricular ejection fraction and stroke work.

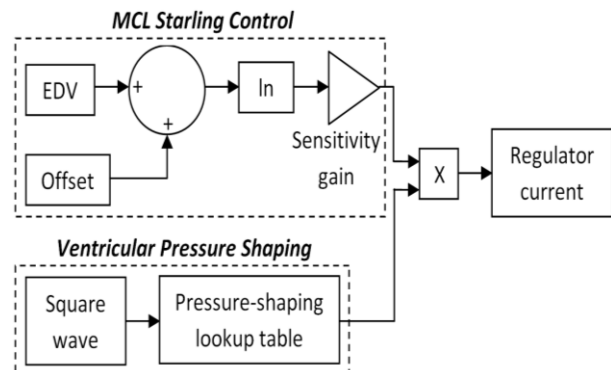


Fig. 2. Schematic of the MCL's Starling control and ventricular pressure shaping. EDV = end diastolic volume, ln = natural log function.

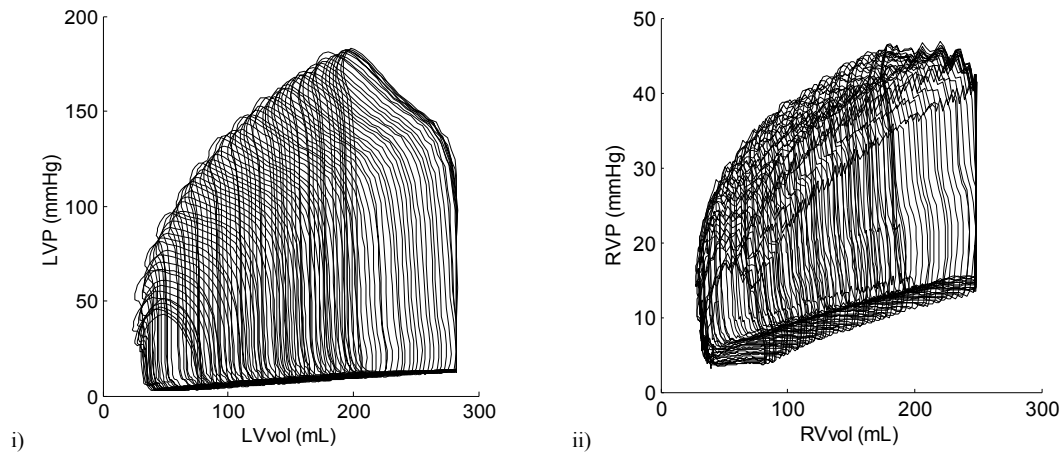


Fig. 3. Pressure-volume (PV) loops for i) left and ii) right ventricles in a healthy, resting simulation with gradually increasing preload. LVP = left ventricular pressure, LVvol = left ventricular volume, RVP = right ventricular pressure, RVvol = right ventricular volume.

III. RESULTS

PV loops for the left and right ventricles with varying preload were created to evaluate the MCL's simulated Starling response (Figure 3). As ventricular preload was increased, the end diastolic volume of each ventricle increased. This caused the MCL Starling control to increase the current supply to the electropneumatic regulators and hence increase the contractility of the ventricles. Figure 4 shows the left and right ventricular ESPVR for conditions of healthy, mild and severe heart failure. This result demonstrates the increased gradient of the ESPVR with increased heart function. At low volumes, the gradient of the ESPVR was 1.82, 1.18 and 0.38mmHg/mL for healthy, mild BHF and severe BHF respectively. The concave relation to the x-axis reduced these gradients to 0.43, 0.41 and 0.21mmHg/mL respectively for healthy, mild BHF and severe BHF. The right ventricular ESPVR gradient was also higher at low volumes, with values of 0.69, 0.23 and 0.1 for healthy, mild BHF and severe BHF respectively. For high volumes, the gradient for each condition had decreased to 0.1mmHg/mL.

The MCL's Starling response is further characterized in Table 1, which summarizes the resultant haemodynamics for three levels of preload in simulated conditions of healthy,

mild BHF and severe BHF. With an increase in left atrial pressure (LAP) from 5 to 15mmHg the systolic left ventricular pressure increased by 110mmHg in the healthy condition. This was reduced to 69mmHg in mild BHF, with severe BHF demonstrating a further reduction in ventricular contractility with only a 34mmHg difference with the same change in LAP. Mean systemic flow rate followed similar trends, with a 2.6L/min change in the healthy condition compared to only 1.0L/min in severe BHF with an LAP increase from 5 to 15mmHg. Although not as severe, similar trends were noted with the pulmonary haemodynamics. With a change in right atrial pressure from 5 to 15mmHg, the systolic right ventricular pressure increased 22mmHg in the healthy condition compared to only 13mmHg in the severe BHF case.

IV. DISCUSSION

Addition of an accurate Starling response in a MCL increases the system's ability to simulate the native heart's function and allows for more reliable evaluation and refinement of cardiovascular devices. Attempts to simulate a MCL Starling response have been made previously, however these systems generally only include the left heart and use linear ESPVRs which cross the x-axis at negative values [9, 11, 12, 14]. Although not shown at low volumes, the

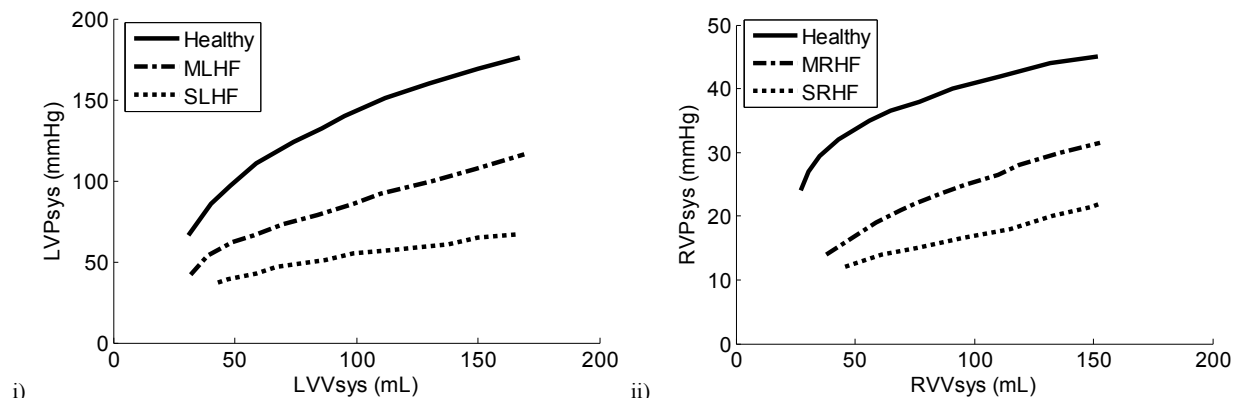


Fig. 4. End systolic pressure-volume relation (ESPVR) for conditions of healthy, mild heart failure and severe heart failure in the i) left and ii) right ventricles. MLHF = mild left heart failure, SLHF = severe left heart failure, MRHF = mild right heart failure, SRHF = severe right heart failure, LVPsys = systolic left ventricular pressure, LVVsys = end systolic left ventricular volume, RVPsys = systolic right ventricular pressure, RVVsys = end systolic right ventricular volume.

TABLE I

HAEMODYNAMICS FOR SIMULTANEOUS ADJUSTMENT OF LEFT AND RIGHT VENTRICULAR PRELOAD IN HEALTHY, MILD BIVENTRICULAR HEART FAILURE AND SEVERE BIVENTRICULAR HEART FAILURE

Condition	LAP (mmHg)	LVPsys (mmHg)	MAP (mmHg)	MSQ (L/min)	RAP (mmHg)	RVPsys (mmHg)	MPAP (mmHg)	MPQ (L/min)
Healthy	5	73	52	3.4	5	21	9.3	3.4
	10	141	110	5.2	10	33	20	5.2
	15	183	146	6.0	15	43	28	6.0
Mild BHF	5	59	39	2.8	5	19	8	2.8
	10	102	78	4.1	10	27	15	4.1
	15	128	99	4.7	15	34	20	4.7
Severe BHF	5	48	29	2.3	5	15	5	2.3
	10	68	48	3	10	23	10	3
	15	82	60	3.3	15	28	14	3.3

LAP = left atrial pressure, LVPsys = systolic left ventricular pressure, MAP = mean aortic pressure, MSQ = mean systemic flow rate, RAP = right atrial pressure, RVPsys = systolic right ventricular pressure, MPAP = mean pulmonary arterial pressure, MPQ = mean pulmonary flow rate.

ESPVRs generated in our study appear to cross the x-axis at positive values for all conditions in both the left and right ventricles. While often linear in smaller animals, the ESPVR is usually concave to the x-axis in humans [10]. The Starling response in our study achieved the concave shape through multiplication of EDV with a natural log function.

The ESPVR gradient matched closely with previously reported data for the left ventricle in healthy (0.6-2.22mmHg/mL) and heart failure conditions (0.28mmHg/mL) [9, 12, 14]. Brown et al. [16] reported values for a healthy human right ventricular ESPVR gradient vary between 0.32 and 1.23mmHg/mL at low right ventricular volumes, which also fits with our results. However, no data for the right ventricular ESPVR gradient at high volumes could be found. The ability to easily vary the Starling sensitivity in our controller enables simulation of almost any Starling response and is only limited by the minimum output capacity of the electropneumatic regulators. However, it should be noted that our controller only altered the Starling sensitivity and not the preload sensitivity of the ventricles, which would also include changes in heart rate.

The addition of a Starling response in the right ventricle for a pneumatically operated ventricle has not been reported previously. Throughout the validation process, the importance of a right ventricular Starling response was obvious, as it was this response which ultimately determined left ventricular preload. This demonstrates a noticeable limitation of systemic only Starling responsive MCLs, as they lack independent ventricular preload variability. Meanwhile, our study would also benefit from the addition of a controllable and non-linear end diastolic pressure volume relationship (EDPVR), which varies in humans and influences the filling capacity of the ventricles [10].

V. CONCLUSION

MCLs are a valuable tool for evaluation of cardiovascular devices, however, current MCLs lack accurate autoregulatory responses observed in-vivo. Implementation of the Starling response was achieved in a MCL with a proportional controller which adjusted pneumatic ventricular driving pressure based on ventricular end diastolic volume. The Starling response was implemented in both ventricles and successfully demonstrated increased ventricular contractility with increased preload. ESPVR curves were generated and validated against previously reported human

data to ensure the system response was a suitable human model under various healthy and pathological conditions. This improvement to a MCL will enable more accurate evaluation and further improvement of cardiovascular devices to treat end stage heart failure patients.

REFERENCES

- [1] Timms, D., et al., *A compact mock circulation loop for the in vitro testing of cardiovascular devices*. Artificial Organs, 2010. **IN PRESS**.
- [2] Ohashi, Y., A. Andrade, and Y. Nose, *Hemolysis in an electromechanical driven pulsatile total artificial heart*. Artificial organs, 2003. **27**(12): p. 1089-1093.
- [3] Liu, Y., et al., *Design and initial testing of a mock human circulatory loop for left ventricular assist device performance testing*. Artificial organs, 2005. **29**(4): p. 341-345.
- [4] Litwak, K., et al., *Ascending aorta outflow graft location and pulsatile ventricular assist provide optimal hemodynamic support in an adult mock circulation*. Artificial organs, 2005. **29**(8): p. 629-635.
- [5] Rose, M., T. Mackay, and D. Wheatley, *Evaluation of four blood pump geometries: fluorescent particle flow visualisation technique*. Medical Engineering & Physics, 2000. **22**: p. 201-214.
- [6] Castellini, P., M. Pinotti, and L. Scalise, *Particle image velocimetry for flow analysis in longitudinal planes across a mechanical artificial heart valve*. Artificial organs, 2004. **28**(5): p. 507-513.
- [7] Rosenberg, G., et al., *Design and evaluation of the Pennsylvania State University Mock Circulatory System*. ASAIO, 1981. **4**(April/June): p. 41-49.
- [8] Schima, H., et al., *A modular mock circulation for hydromechanical studies on valves, stenoses, vascular grafts and cardiac assist devices*. The International Journal of Artificial Organs, 1992. **15**(7): p. 417-421.
- [9] Baloa, L., J. Boston, and J. Antaki, *Elastance-based control of a mock circulatory system*. Annals of Biomedical Engineering, 2001. **29**: p. 244-251.
- [10] Burkhoff, D., I. Mirsky, and H. Suga, *Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers*. Am J Physiol Heart Circ Physiol, 2005. **289**: p. H501-H512.
- [11] Loh, M. and Y. Yu, *Feedback control design for an elastance-based mock circulatory system*. American Control Conference, 2004. Proceedings of the 2004, 2004. **2**: p. 1639-1644.
- [12] Pantalos, G., et al., *Characterization of an adult mock circulation for testing cardiac support devices*. ASAIO, 2004. **50**(1): p. 37-46.
- [13] Sagawa, K., *The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use*. Circulation, 1981. **63**: p. 1223-1227.
- [14] Ferrari, G., et al., *A computer controlled mock circulatory system for mono- and biventricular assist device testing*. The International Journal of Artificial Organs, 1998. **21**(1): p. 26-36.
- [15] Guyton, A.C., *Textbook of Medical Physiology*. 11 ed. 2005: W.B. Saunders Company.
- [16] Brown, K.A. and R.V. Ditchey, *Human right ventricular end-systolic pressure-volume relation defined by maximal elastance*. Circulation, 1988. **78**: p. 81-91.