7-2011

RPM and flow modulation for a continuous flow left ventricular assist device to increase vascular pulsatility : a computer simulation, mock circulation, and in-vivo animal study.

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RPM AND FLOW MODULATION FOR A CONTINUOUS FLOW LEFT
VENTRICULAR ASSIST DEVICE TO INCREASE VASCULAR
PULSATILITY:
A COMPUTER SIMULATION, MOCK CIRCULATION, AND IN-VIVO
ANIMAL STUDY

By

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University of Louisville, 2010

A Thesis
Submitted to the Faculty of the
Speed School of Engineering of the University of Louisville
as Partial Fulfillment of the Requirements
For the Professional Degree of

MASTER OF ENGINEERING

Department of Bioengineering
University of Louisville
Louisville, Kentucky

July 21, 2011

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ii

DEDICATION

This thesis is dedicated to my parents,

Mr. Michael F. Ising

and

Mrs. Debbie S. Ising.

ACKNOWLEDGMENTS

ABSTRACT

Purpose: Continuous flow (CF) left ventricular assist devices (LVAD) support diminishes vascular pressure pulsatility. Despite its recent clinical success and reliability, CF LVAD support has been associated with adverse events including gastrointestinal bleeding, aortic valve insufficiency, and hemorrhagic strokes. To overcome these limitations, we have developed flow/RPM modulation algorithms to provide vascular pulsatility using a CF LVAD.

Methods: The effects of timing and synchronizing the CF LVAD flow/RPM modulation to the native ventricle, modulation amplitude, and modulation widths were studied on the native ventricle and vasculature using computer simulation, mock loop, and animal model studies. A total of over 100 combinations of flow modulation algorithms to modulate CF LVAD flow/RPM were tested for partial and full LVAD support modes.

Results: Modulation of CF LVAD flow/RPM resulted in an increased arterial pressure pulsatility of up to 50 mmHg during asynchronous modulation and 20 mmHg during synchronous modulation. Synchronous CF LVAD RPM modulation allowed for a range of reduced left ventricular external work (LVEW) as compared to un-modulated CF LVAD support conditions. Full support co-

pulsation (high RPM during systole, low RPM during diastole) created greater pulse pressures as compared to counter pulsation (high RPM during diastole, low RPM during systole). However, all full support modulation timings yielded higher pulse pressure than normal full support CF LVAD flow at low ventricular contractilities. Importantly, reduction in LVEW and increase in pulsatility may be adjusted to user-defined values while maintaining the same average CF LVAD flow rate.

Conclusions: These LVAD flow/RPM modulations may reduce the incidence of adverse events associated with the CF LVAD therapy by increasing vascular pulsatility and reducing vascular impedance. Further, these methods of CF LVAD flow/RPM modulation may enable tailored unloading of the native ventricle to provide rest and rehabilitation (maximal unloading to rest followed by gradual reloading to wean), which may promote sustainable myocardial recovery.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES
(CONTINUED)

LIST OF FIGURES
(CONTINUED)

CHAPTER 1 - BACKGROUND

Epidemiology

Approximately 80 million Americans suffer from cardiovascular disease, which has become the leading cause of death among both men and women in the United States. Cardiovascular disease accounts for over 550,000 deaths per year and led to a projected $450 billion in healthcare costs in 2009. Of these 80 million, six million will develop chronic heart failure (**Figure 1**) [1]. Furthermore, one-year mortality rates for New York Heart Failure Association Class IV patients exceed 60%.
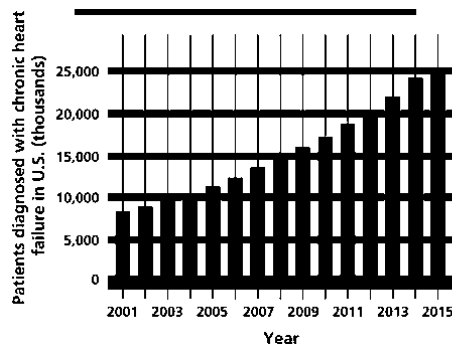
Figure 1: Chronic heart failure rates in the United States continue to increase, and are extrapolated to reach over 25 million Americans in 2015[1].

Pathology

In congestive heart failure (CHF), the heart is unable to deliver the necessary rate of sufficient blood, oxygen, and metabolites for the metabolic demands of organs and tissues. CHF can occur both acutely and chronically depending on the etiology of the disease. A patient can develop CHF abruptly in cases such as sudden onset of fluid overload, valvular dysfunction or a severe myocardial infarction. Chronically, heart failure can result due to persistent elevated work requirements of the heart which may be secondary to valve disease, hypertension, or ischemia among others. Further, reduced contractility can occur due to weakening of the cardiomyocytes or stiffening of the myocardium during CHF [2].

Physiology

During progression of CHF, mechanisms assist the heart and body to adapt to meet metabolic needs. Myocardial contraction increases as diastolic volume increases via increase in myosin-actin interaction, as described by the Frank-Starling Mechanism. Ventricular remodeling occurs as an adaptation in early

stages of heart failure in efforts to maintain necessary cardiac output. However, this can create an additive effect that eventually results in worsening heart failure. Additionally, the autonomic nervous system can release norepinephrine to increase the frequency of heart contractions. Similarly, the renin-angiotensin-aldosterone pathway along with release of natriuretic peptide results in changes in filling volumes and pressures. Early symptoms of left-sided failure are often associated with pulmonary congestion and edema. Activation of the renin-angiotensin-aldosterone system, caused by inadequate kidney perfusion, can lead to an increase in pulmonary vessel pressure and subsequent onset of hypoxia[3]. Furthermore, diminished arterial pressure pulsatility has been shown to increase vascular impedance and reduce arterial relaxation [4, 5].

Treatments

The gold-standard treatment for these patients, cardiac transplantation, has a 50% 10-year survival rate. While transplantation significantly improves the patient's quality of life[6], patients are required to take immunosuppressant medications, weakening their immune system. The frequency of available donor hearts limits the number of transplanted patients with less than 4,000 cardiac transplant surgeries are performed in the U.S. annually. Furthermore, over the

past five years there has been no significant increase in transplant rates, which suggests this therapy is not a practical long-term solution for the majority of CHF patients (**Figure 2**). Thus, these untransplanted patients are viable candidates for alternative therapy[7].
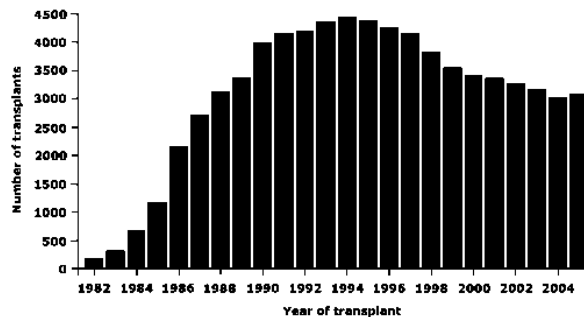
Figure 2: The number of heart transplant per year has not increased, and in recent history has actually been decreasing in frequency [7].

Alternatives to cardiac transplantation include medicinal therapies, techniques, and devices, which slow the deterioration of heart function and improve patients' functional status. Rest and relaxation of the cardiac muscle has long been the underlying theme of heart failure treatment. Originally, patients were sequestered to bed rest and limited mobility. Thus, while waiting for transplant or other therapy, the sick patients had a much-reduced quality of life from a combination of their disease and their treatment, including being bed-ridden and a forced reduction in their daily activities. Currently, medicinal therapies seek to reduce the afterload and disrupt the β-adrenergic receptor blockade. Medicinal therapies include the

4

administration of diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta-blockers, and others[8]. Yet, perhaps the most rapidly growing therapy in cardiovascular disease is mechanical circulatory support.

Development of mechanical circulatory support

In 1964, The National Heart Institute established the Artificial Heart Program. The following year, the National Institute of Health requested $40 million for the upstart of the program. Dr. Denton Cooley implanted the first American artificial heart in 1969 as a bridge to transplant. The device supported the patient for 64 hours till a heart could be found, however the patient survived little more than 30 hours post-transplant. Later that year, an NHI sponsored group on Cardiac Replacement concluded that left ventricular assist devices (LVAD) would be a promising area of research due to the current engineering short comings in developing a completely artificial heart (i.e. TETS system, biocompatibility issues, durability)[9].

In the three decades following the suggestion to explore the development of LVAD, solutions were found to a number of underlying issues that plagued the

original artificial heart programs. Specifically, engineers had sufficiently answered the issues of material biocompatibility and the life threatening driveline infections to make LVAD a legitimate therapy for end-stage heart failure patients. The use of textured titanium surface, titanium alloys, polymers and other biocompatible materials allowed for chronic device implantation without the risk of a clinically significant reaction[10]. Further, experience with cannula designs and drivelines resulted in improvements of the percutaneous lines that exit the body and resulted in reducing the infection risk[11].

The majority of devices developed during these three decades were categorized by their pulsatile flow that mimicked the native heart. The devices used membranes that were actuated, using a fill and eject cycle, similar to the native ventricle. The first generation of implantable pulsatile flow LVADs (Thoratec IVAD and HeartMate XVE, Worldheart Novacor) weighed up to 1kg and took up to one half liter (volume) of space inside the implanted patient abdominal cavity. The size restriction excluded smaller males, and most females as candidates for therapy [12]. These pulsatile flow mechanical circulatory support devices were effective in providing long-term (> 6 months) support.

However, the durability of the pulsatile pumps was sub-optimal (~18 months). The pulsatile device has a predictably high incidence of mechanical failure in the

second year of support, with the most common failing mechanism being inflow valve insufficiency [13]. The challenge of mechanical circulatory assist device durability was addressed with the introduction of smaller, compact design, second-generation blood pumps. Rotary pumps, which produce continuous, non-pulsatile flow, have reduced the number of moving parts to a single impeller/ rotor. The reduction in moving parts has resulted in clinical experience demonstrating improved durability and lower power consumption [14].

Left ventricular assist device (LVAD) implantation has increased in popularity as a therapeutic measure for bridging to transplantation in patients with end-stage heart failure, and is gaining wider clinical acceptance as destination therapy in patients ineligible for transplantation [14-16]. Further, there is hope that these devices can be operated in such a way as to promote myocardial recovery. During support they have been shown to be capable of partially reversing many of the genetic, functional, and morphological hallmarks of the failing heart[17-23], in addition to allowing device removal without transplantation in a small fraction of patients[24, 25]. Recent evidence indicates that while there are differences in the magnitude of unloading between pulsatile flow (PF) and continuous flow (CF) pumps, both are capable of achieving normalization of some cellular damage markers[26], and continuous flow pumps appear to be just as effective if not better than pulsatile flow pumps in bridging patients to transplantation[27].

Furthermore, support in patients who do not meet transplant criteria, destination therapy, has shown longer survival in continuous flow as compared to pulsatile flow devices[14]. Given the apparent similarity in the survival benefit offered to heart failure patients by these devices, CF LVAD has gained greater acceptance as they have fewer moving parts, higher mechanical reliability[28], and are considerably smaller, minimizing thrombogenic surface area and enabling implantation in smaller adults as compare to their pulsatile counterparts.

Amidst the growing popularity of CF LVAD, however, there remain unanswered questions regarding the long-term physiological effects of CF LVAD support. CF LVAD significantly diminish vascular pressure pulsatility compared to PF LVAD and anecdotal reports have indicated the development adverse events including gastrointestinal bleeding, hemorrhagic strokes, increased vascular impedance, and progression of aortic valve insufficiency in HF patients chronically supported by CF LVAD [4, 29-31]. PF LVAD phasically unload the native ventricle, creating variable loading of the native myocardium while maintaining end-organ perfusion, which may affect weaning and promotion of myocardial recovery [32]. CF LVAD continuously unload the native ventricle providing consistent ventricular loading. However, this makes it difficult to modulate the myocardial load without altering the LVAD flow and subsequently affecting the end-organ perfusion.

Gradual reloading of the heart while maintaining end-organ perfusion could be achieved by modulation of blood pump motor speeds/flow. Modulation of blood pump motor speeds/flow has been suggested as a potential mechanism to artificially increase vascular pulsatility in both ventricular assist devices [33-39] and total artificial hearts[40-43]. Flow modulation of ventricular assist devices is affected by the timing of flow modulation to the native myocardial contraction. Early LVAD modulation strategies focused on asynchronous modulation of LVAD flow, as it was simpler to implement [33, 38]. Cox et al., Letsou et al., and Shi et al. simulated sinusoidal synchronous LVAD flow modulation but did not vary the timing of LVAD flow modulation [35, 36, 39]. Vandenberghe et al. varied the timing of synchronous support but did not vary the LVAD flow modulation amplitude or pulse width. Further, Vandenberghe et al. derived model parameters from sheep which is different from human values [34] . The effects of synchronizing and timing of the modulation of LVAD motor speeds/flow to the native myocardium, modulation amplitude, and modulation width have only recently been reported as a byproduct of this thesis work [44].

In this study, the effects of timing and synchronizing the LVAD motor speed and flow modulation, modulation amplitude, and modulation widths on the native ventricle and vasculature are investigated. Experiments were performed using a computer simulation model, a mock circulation model, and acute animal studies.

CHAPTER 2 – COMPUTER SIMULATION

Introduction

Computer simulation is an important step in the design process for LVAD control strategies and has been repeatedly shown valuable in the literature. Testing in computer simulation is a financially efficient and time saving way to test multiple iterations of various control designs. Several strategies of LVAD control have been studied using computer simulation models including suction detection[45-47], estimation and control of aortic pressure[48], exercise responsive control[49], and preload dependent pump flow[50]. We hypothesized that modulation of LVAD flow will increase arterial pressure pulsatility and alter left ventricular pressures, volumes, and workloads. Further, the effect on the native ventricle will be dependent on timing, amplitude, and pulse width of the LVAD flow modulation. The objective of this computer simulation study was to investigate the effects of timing and synchronizing LVAD flow modulation on the native ventricle and vasculature with varying modulation amplitudes and widths.

Cardiovascular System Simulation

A previously reported computer simulation model of the human cardiovascular system was modified to simulate heart failure using Matlab (Mathworks, MA). This computer simulation model was validated and has been used in previous studies to develop and test physiologic control strategies for mechanical circulatory support devices [4, 51-53]. A more detailed description of the simulation model is provided by Giridharan et. al[53].

Briefly, the computer model subdivides the human circulatory system into an arbitrary number of lumped parameter blocks, each characterized by its own resistance, compliance, pressure, and volume of blood. Two idealized elements, resistance and storage, were used to characterize each block. The storage element provides zero resistance to flow, whereas the resistive element has zero volume. The model has 13 elements: four valves and nine blocks, including left and right ventricles, pulmonary and systemic circulations, vena cava, aorta, and coronary circulation (**Figure 3**). Ventricles were characterized by a time varying

compliance. The remaining blocks were characterized by passive elements. The coronary block consisted of time varying resistive and compliance elements.
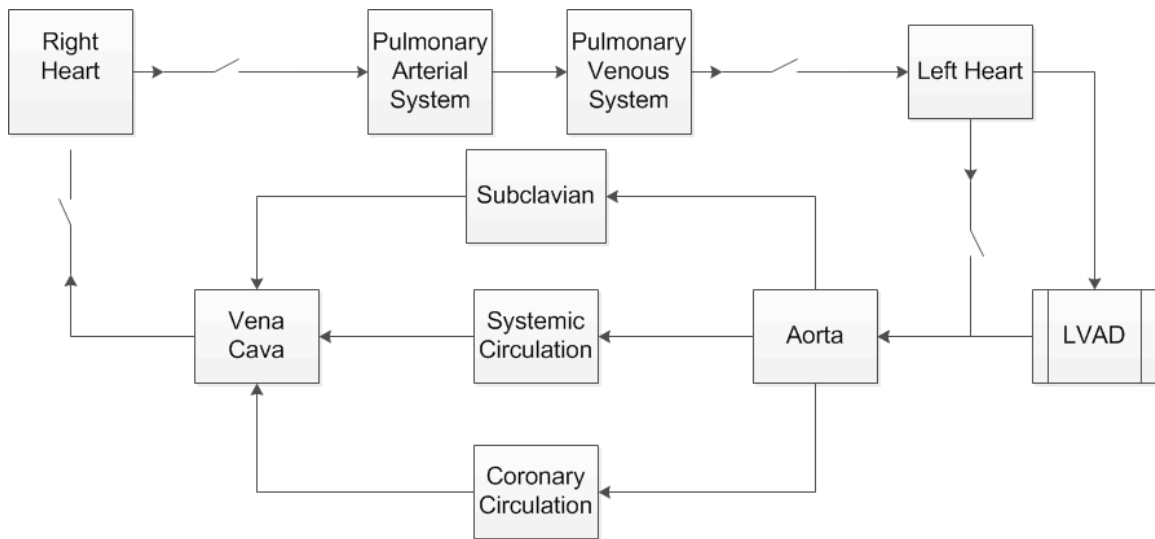
Figure 3: Schematic of the lumped parameter human circulatory system model.

LVAD Model

A model of a CF LVAD was integrated into previously published computer simulation model. Simulations were conducted to predict acute hemodynamic responses including coronary flows, ventricular pressure-volume loops, left ventricular external work, arterial pressures, and vascular pulsatility parameters (mean arterial pressure (MAP), energy equivalent pressure (EEP), surplus hemodynamic energy (SHE)) for partial (mean LVAD flow = 2.5 ± 0.1 L/min) and full LVAD support (mean LVAD flow = 5.0 ± 0.1 L/min) modes.

The LVAD flow modulation waveforms were constructed using a piecewise-defined function with no LVAD retrograde flows. CF LVAD retrograde flows increase vascular pulsatility, but was not considered as they can increase hemolysis and lead to higher myocardial loads and ventricular wall stresses. The piecewise-defined function was divided into pulse and nadir phases (**Figure 4a**). The pulse width was defined as the portion of the LVAD flow waveform where the instantaneous flow equaled or exceeded the mean flow. The nadir phase was defined as the portion of the LVAD flow waveform where the instantaneous flow was less than or equaled the mean flow. Unification of the pulse and nadir phases created one complete LVAD flow waveform. Pulse widths from 20%-80% were simulated for each level of synchronous LVAD flow modulation. Pulse widths of 40%, 50% and 60% were created with the same flow modulation amplitudes and mean flows (**Figure 4b**). The pulse width conditions of 20%, 30%, 70%, and 80% required varying flow modulation amplitudes but maintained same average flow rates. Both asynchronous LVAD flow modulation (20 beats/min, 40 beats/min, 60 beats/min) and synchronous LVAD flow modulation (80 beats/min) were tested.
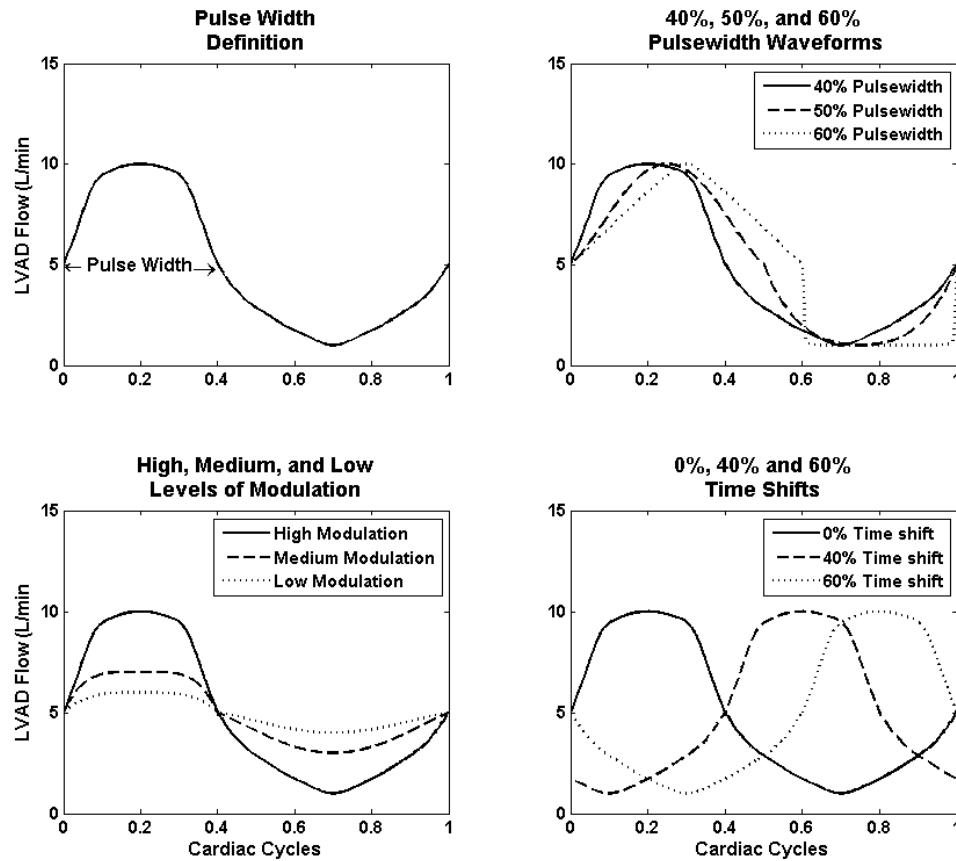
Figure 4: (a) LVAD flow waveform with a 40% pulse width. **(b)** LVAD flow waveforms with 40%, 50%, and 60% pulse width. **(c)** LVAD flow waveforms with high, medium, and low flow modulation. **(d)** A 40% pulse width LVAD flow waveform with a 40% and 60% time shift.

Different levels of LVAD flow modulation amplitudes were simulated for partial and full LVAD support testing. Partial support LVAD flow modulations were tested at low pulsatility, medium pulsatility, and high pulsatility. The amplitudes of partial support LVAD flow modulations were 1 L/min, 2 L/min, and 4 L/min for low,

medium, and high pulsatility modes, respectively. The amplitudes of full support LVAD flow modulations were 1 L/min, 4.5 L/min, and 9 L/min for low, medium, and high pulsatility modes, respectively (**Figure 4c**). The effects of timing the synchronous LVAD flow modulation to the native myocardial contraction were tested by varying the time shift, which represents the timing of the LVAD flow modulation in relation to the cardiac cycle (**Figure 4d**). Specifically, LVAD flow modulation was initiated at 0% (co-pulsation mode - both native ventricular contraction and LVAD flow modulation are in unison), 20%, 40% (counter pulsation mode-LVAD flow modulation initiated during native ventricular diastole), 60%, and 80% of the native cardiac cycle, A total over 150 combinations of varying pulse widths, beat frequencies, time shifts, and amplitudes of CF LVAD flow were simulated.

All simulations were initiated with limit cycle (steady state) values of a failing heart. At time t=0, the simulated device was turned on with a flow modulation. The model circulatory system reached a limit cycle within 300 cardiac cycles. The simulation was continued to 500 cardiac cycles. The mean values of pressures, flows, and volumes were reported only for the last 50 beats. The computer model was assumed to have no process noise and the deviation in steady-state value

was less than 1mmHg for pressures, 0.05L/min for flow rates, and 2mL for ventricular volumes.

Results

Effect of level of support

Increasing levels of CF LVAD support, irrespective of CF LVAD flow modulation, reduced LVEW, pulse pressures, MAP and SHE and augmented diastolic coronary flow and myocardial supply demand ratio (CoF/LVEW), from baseline heart failure values (no LVAD support) (**Tables 1-3**). CF LVAD flow modulation increased the range of LVEW, pulse pressures, coronary flows, MAP, SHE and myocardial supply demand ratios achievable with the same mean CF LVAD flow rates, **Table 2**.

	Pulse Pressure (mmHg)	Mean LVAD Flow (L/min)	LVEW (mmHg*mL)	dCoF (mL/min)	CoF/ LVEW $(mmHg*mL*10^{-2})^{-1}$
Failure	35	0	2854	59	2
Partial Support	15	2.5 ± 0.1	1792	64	3
Full Support	1	5.0 ± 0.1	411	80	14

Table 1: Pulse pressure, left ventricular external work (LVEW), diastolic coronary flow (dCoF), and myocardial supply demand ratio (CoF/LVEW) obtained during baseline heart failure and with partial and full CF LVAD support without any CF LVAD flow modulation.

	Parameter	Pulse Pressure (mmHg)	LVEW (mmHg*mL)	dCoF (mL/min)	CoF/ LVEW $(mmHg*mL*10^{-2})^{-1}$
Synchronous	Full Support	1 - 21	76 - 830	73 - 85	7 - 75
Synchronous	Partial Support	14 - 21	1417 - 2220	61 - 68	2 - 3
Asynchronous	Full Support	2 - 52	317 - 500	77 - 82	11 - 18
Asynchronous	Partial Support	18 - 26	1562 - 1873	63 - 66	2 - 3

Table 2: Range of pulse pressures, left ventricular external work (LVEW), diastolic coronary flow (dCoF), and myocardial supply demand ratio (CoF/LVEW) obtained by modulating the CF LVAD flow. These results demonstrate that modulation and timing of CF LVAD flow resulted in a range of LVEW and CoF without altering the mean LVAD flow, which may enable LVAD weaning protocols and myocardial recovery strategies without altering mean LVAD flow

Effect of flow modulation amplitude:

Greater LVAD flow modulation amplitudes increased arterial pressure pulsatility and Surplus Hemodynamic Energy (SHE). Synchronous full support LVAD with the high flow modulation of 9 L/min (max/min = 10/1 L/min) produced arterial pulse pressures up to 19 mmHg while low flow modulation produced an arterial pulse pressure of 1.3 mmHg. For asynchronous full support, a maximum arterial pulse pressure of 52 mmHg was obtained with an LVAD flow modulation of 9L/min (max/min = 10/1 L/min) at 20 bpm. Both are significantly greater than pulse pressure of 0.7 mmHg when providing full support with CF LVAD with no flow modulation.

Increasing LVAD flow modulation augmented the range of LVEW, diastolic CoF, and the myocardial supply and demand ratio achievable for both full and partial support (**Figure 5**). At full LVAD support test condition, LVEW range increased from 294 – 485 mmHg*mL at low LVAD flow modulation test conditions to 76 – 830 mmHg*mL at high LVAD flow modulation test conditions. During full LVAD support, the range of diastolic CoF and myocardial supply and demand ratio increased from 77 - 81 mL/min and 12 - 17 $(mmHg*mL*10^{-2})^{-1}$ at low LVAD flow modulation test conditions to 73 - 85 mL/min and 7 - 75 $(mmHg*mL*10^{-2})^{-1}$ at high LVAD flow modulation test conditions. During full LVAD support, different levels

of flow modulation resulted in a MAP range of 95 - 98 mmHg, EEP range of 96 -

106 mmHg, and SHE range of 697 – 10863 ergs/cm^3.
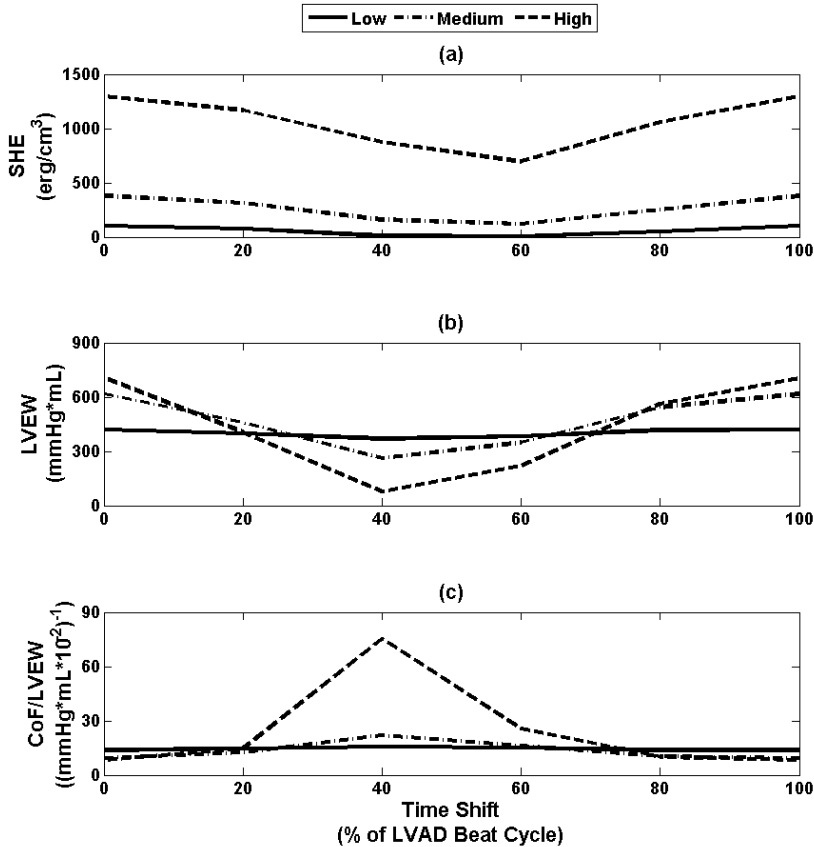
Figure 5: The effect of amplitude modulation and timing on (a)Surplus hemodynamic energy (SHE), (b) left ventricular external work (LVEW) and (c) myocardial supply and demand ratio (CoF/LVEW. Effects of timing are amplified with increased modulation amplitude. Effects are shown for a synchronous 60 percent pulse width at low (1L/min), medium (4.5 L/min), and high (9 L/min) LVAD flow amplitude modulations. These results indicate that higher amplitude modulation leads to higher SHE, and a larger variation in LVEW and myocardial supply demand ratio (CoF/LVEW) based on LVAD flow modulation timing.

During partial LVAD support, LVEW range increased from 1675 - 1888 mmHg*mL at low LVAD flow modulation test conditions to 1417 - 2220 mmHg*mL at high LVAD flow modulation test conditions. The range of diastolic CoF and myocardial supply and demand ratio increased from 63 - 65 mL/min and 2.5 - 2.8 $(mmHg*mL*10^{-2})^{-1}$ at low LVAD flow modulation test conditions to 61 - 68 mL/min and 2.1 - 3.4 $(mmHg*mL*10^{-2})^{-1}$ at high LVAD flow modulation test conditions. During partial LVAD support conditions, different levels of flow modulation resulted in MAP, EEP, and SHE ranges from 78 - 81 mmHg, 80 - 82 mmHg, and 333 - 2144, respectively.

Effect of Timing:

Timing during synchronous LVAD modulation affected LVEW, diastolic CoF, and CoF/LVEW significantly (**Figures 5,6,7**). Asynchronous LVAD modulation timing had negligible effect on any measured parameter, when averaged over several cardiac cycles (**Figure 5**). During synchronous full LVAD support with high pulsatile waveforms, the maximum achievable LVEW, occurred at time shift of 0% and ranged from 407 – 662 mmHg*mL. Minimum achievable LVEW occurred at time shifts of 40% to 60%, ranged from 76-149 mmHg*mL. Maximum diastolic CoF (up to 85 mL/min) occurred when the apex of the LVAD flow modulation waveform occurred during native ventricular diastole (counter pulsation).

Minimum diastolic CoF occurred when the apex of the LVAD flow modulation waveform coincided with native ventricular systole (co-pulsation). A change in time shift from 0% to 40% corresponded with a change in CoF/LVEW ranges of 7 - 8 $(mmHg*mL*10^{-2})^{-1}$ to 26 - 75 $(mmHg*mL*10^{-2})^{-1}$ at full LVAD support.
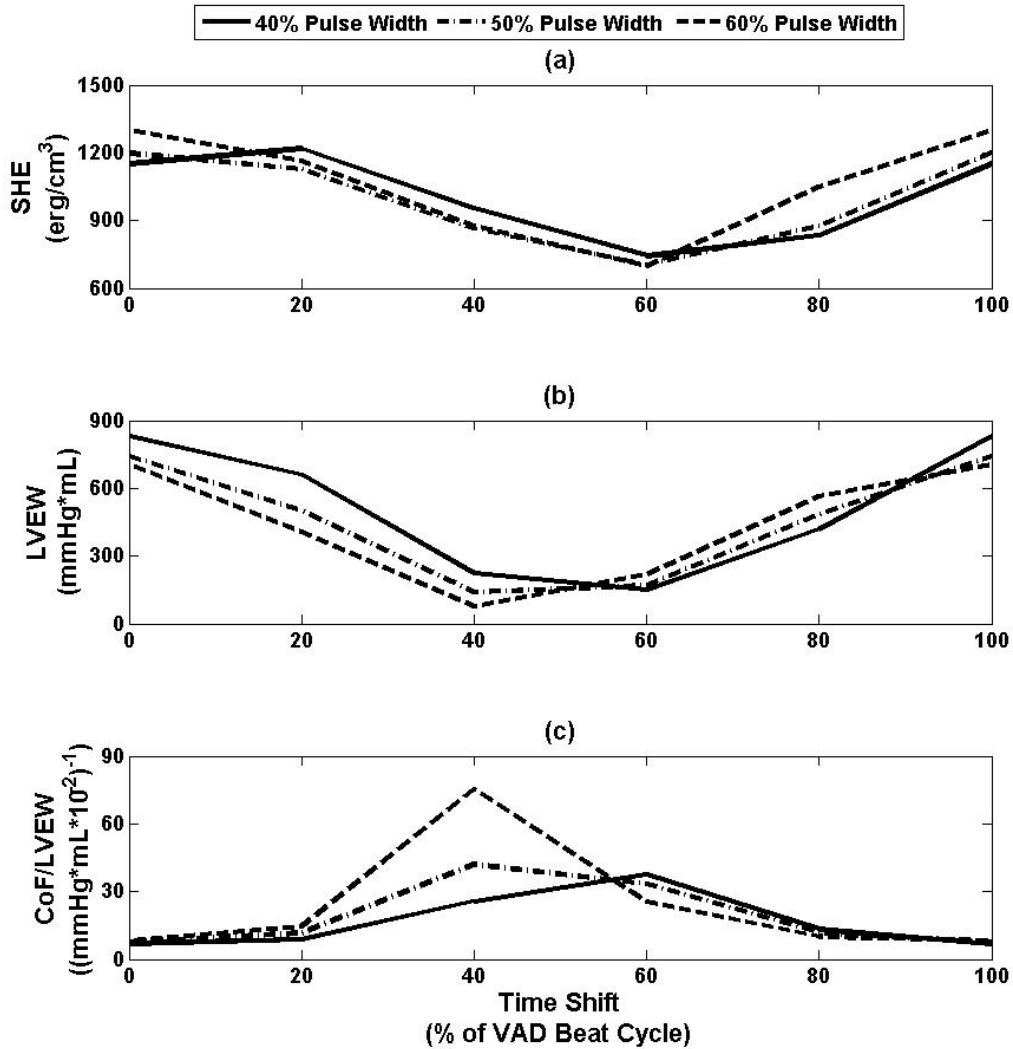
Figure 6: The effects of pulse width and timing on (a) Surplus hemodynamic energy (SHE), (b) left ventricular external work (LVEW) and (c) myocardial supply and demand ratio (CoF/LVEW). Counterpulsation (60% pulse width and 40% time shift) produced minimum LVEW and maximum CoF/LVEW. Effects are shown for synchronous high (9 L/min) LVAD flow amplitude modulations at each pulse width (40%, 50%, 60%). These results indicate that 60% pulse width in co-pulsation mode (0 time shift) produces the highest pulsatility (SHE) while counter pulsation mode (40 time shift) produces the highest myocardial supply demand ratio (CoF/LVEW).
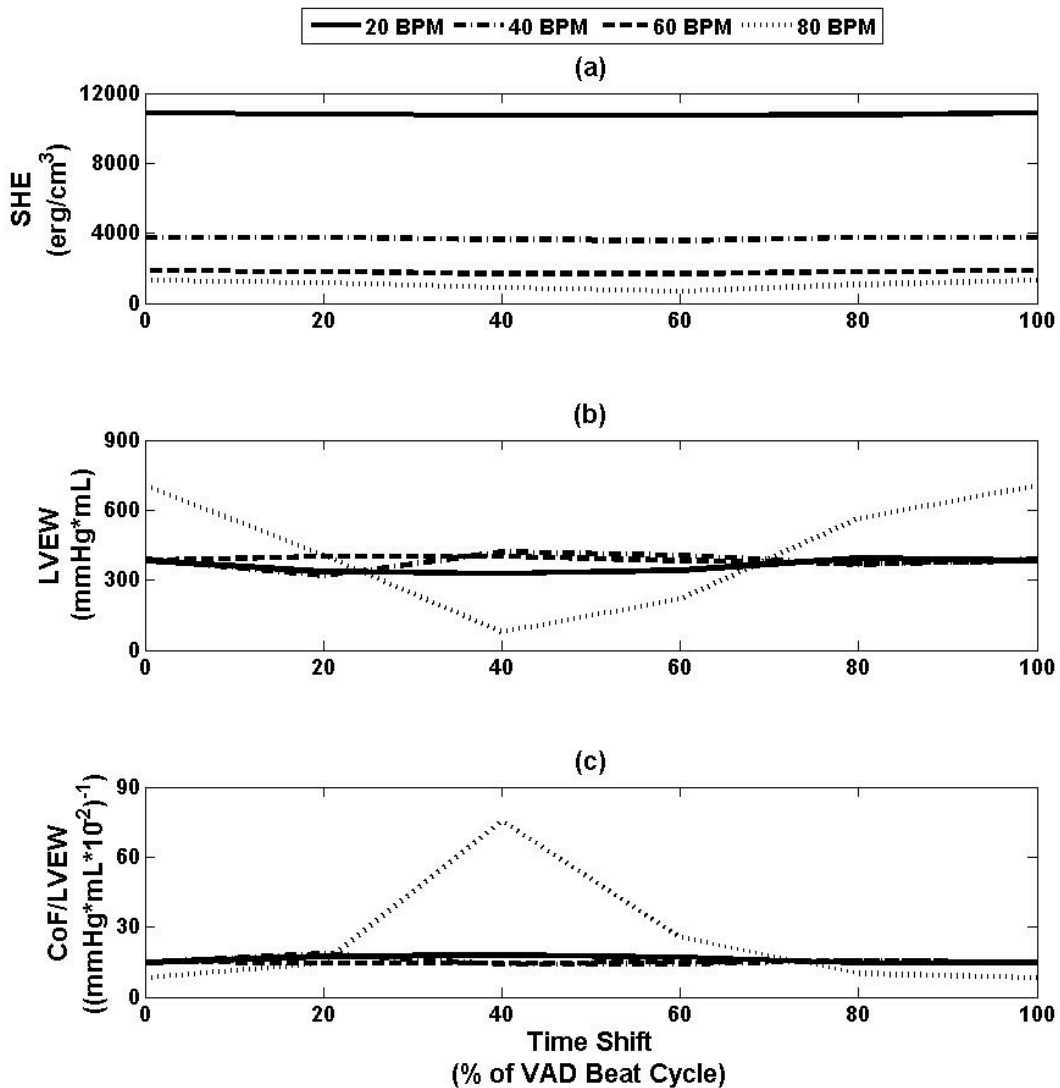
Figure 7: The effects of LVAD flow modulation rate and timing on (a) Surplus hemodynamic energy (SHE), (b) left ventricular external work (LVEW) and (c) myocardial supply and demand ratio (CoF/LVEW). Slower LVAD flow modulations produced higher SHE. Timing showed little effect on SHE, LVEW, and CoF/LVEW for asynchronous LVAD flow modulation (20 BPM. 40 BPM. 60 BPM) as opposed to the effects seen on synchronous LVAD flow modulation (80 BPM).

The effects of timing the LVAD flow modulation during partial support test conditions were similar to full support test conditions. During partial LVAD support, maximum LVEW ranged from 2057 - 2220 mmHg*mL at 0% time shift. Minimum LVEW (1417 – 1510 mmHg*mL) were obtained during time shifts of 40-60%. Maximum diastolic CoF (67 - 68 mL/min) occurred when the maximum LVAD flow was during ventricular diastole, while minimum diastolic CoF (61-– 62 mL/min) occurred when maximum LVAD flow was during ventricular systole. CoF/LVEW ranged from 2.1 - 2.3 $(mmHg*mL*10^{-2})^{-1}$ at 0% time shifts to 3.2 - 3.4 $(mmHg*mL*10^{-2})^{-1}$ at 40% time shifts.

Effect of pulse width

Changing the CF LVAD flow modulation pulse width without altering pulse amplitude affected LVEW, diastolic CoF, and CoF/LVEW (**Figure 6**). However, the changes are not as pronounced as the effects of timing.

At full LVAD support test condition with synchronous modulation, the ranges of LVEW were 149 - 830, 139 - 739, and 76 - 706 mmHg*mL for pulse widths of 40%, 50%, and 60%. Diastolic CoF changed from 73 - 83, 76 - 84, 75 - 85 mL/min at 40%, 50%, and 60% pulse widths. CoF/LVEW at 40%, 50%, and 60% pulse widths corresponded with ranges of 7 - 38, 8 - 42, and 8 - 75

(mmHg*mL*10^{-2})$^{-1}$. Pulse widths of 20%, 30%, 70%, and 80% required alteration of the CF LVAD flow modulation amplitude to maintain the average flow rates. Thus, the effect of timing could not be independently discerned from the effect of altered CF LVAD flow modulation amplitude for these pulse widths. During asynchronous modulation at full LVAD support, the ranges of LVEW were 351 - 500, 355 - 459, and 317 - 420 mmHg*mL for pulse widths of 40%, 50%, and 60%. Pressure-volume loops are shown in **Figure 8**.
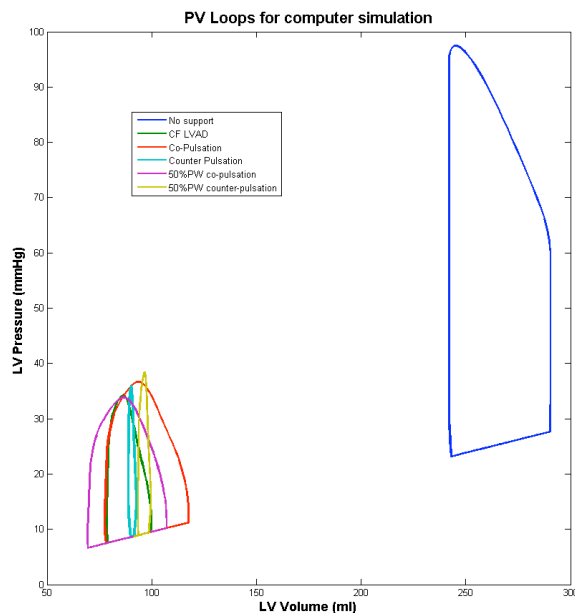
Figure 8: Pressure volume loops for no LVAD support, CF LVAD support, pure co-pulsation LVAP flow modulation (0% time shift, 40% pulse width), pure counter pulsation LVAD flow modulation (40% time shift, 60% pulse width, LVAD flow modulation with a 50% pulse width starting at systole (50%PW co-pulsation), and LVAD flow modulation with a 50% pulse with starting at diastole (50%PW counter-pulsation). Ventricular volumes were reduced to normal range during LVAD support irrespective of support condition.

Diastolic CoF changed from 77 - 80, 78 - 81, and 78 - 82 at 40%, 50%, and 60% pulse widths. CoF/LVEW at 40%, 50%, and 60% pulse widths corresponded to ranges of 11 - 16, 13-- 16, and 14 - 18 $(mmHg*mL*10^{-2})^{-1}$.

During partial LVAD support with synchronous LVAD flow modulation, LVEW ranged from 1493 - 2045, 1491- 2117, **1**458- 2034, and 1555 - 1944 mmHg*mL at 20%, 40%, 60%, and 80% pulse widths respectively. The same pulse widths corresponded with diastolic CoF ranges of 62 - 67, 62 - 67, 62 - 68, and 63 - 66 mL/min, respectively. At 20%, 40%, 60%, and 80% pulse widths, the range of myocardial supply and demand ratios varied from 2.3 - 3.2, 2.2 - 3.2, 2.3 - 3.3, and 2.4 - 3.0 $(mmHg*mL*10^{-2})^{-1}$.

Asynchronous modulation at partial LVAD support produced LVEW ranges of 1562 - 1873, 1641 - 1856, and 1637 - 1770 mmHg*mL at pulse widths of 40%, 50%, and 60%. Diastolic CoF was 63 - 66 mL/min for all pulse widths. The same pulse widths corresponded to CoF/LVEW ranges of 2.5 - 3.0, 2.5 - 2.8, and 2.6 - 2.9 $(mmHg*mL*10^{-2})^{-1}$. CF LVAD flow modulation pulse width does not considerably alter pulse pressure, MAP, EEP, and SHE.

Synchronous vs. Asynchronous Modulation

During asynchronous LVAD flow modulation, LVEW, diastolic CoF, LVV and CoF/LVEW varied between cardiac cycles in one LVAD flow modulation waveform period (**Figures 9,10,11**) while consistent ranges obtained during synchronous LVAD support and continuous flow LVAD support. Decreasing the rate of asynchronous full support LVAD flow modulation increased the achievable arterial pressure pulsatility, EEP, and SHE. A maximum arterial pulse pressure of 59 mmHg was achieved at a slow LVAD flow modulation rate of 20 bpm (**Figure 9**). This is significantly greater than synchronous full support CF LVAD with high flow modulation (19 mmHg at a modulation frequency of 80 bpm). However, synchronous full and partial support LVAD flow modulations allowed for a larger range of average LVEW, diastolic CoF, and myocardial supply and demand ratio ranges compared to asynchronous full and partial support LVAD flow (**Tables 2,3**).
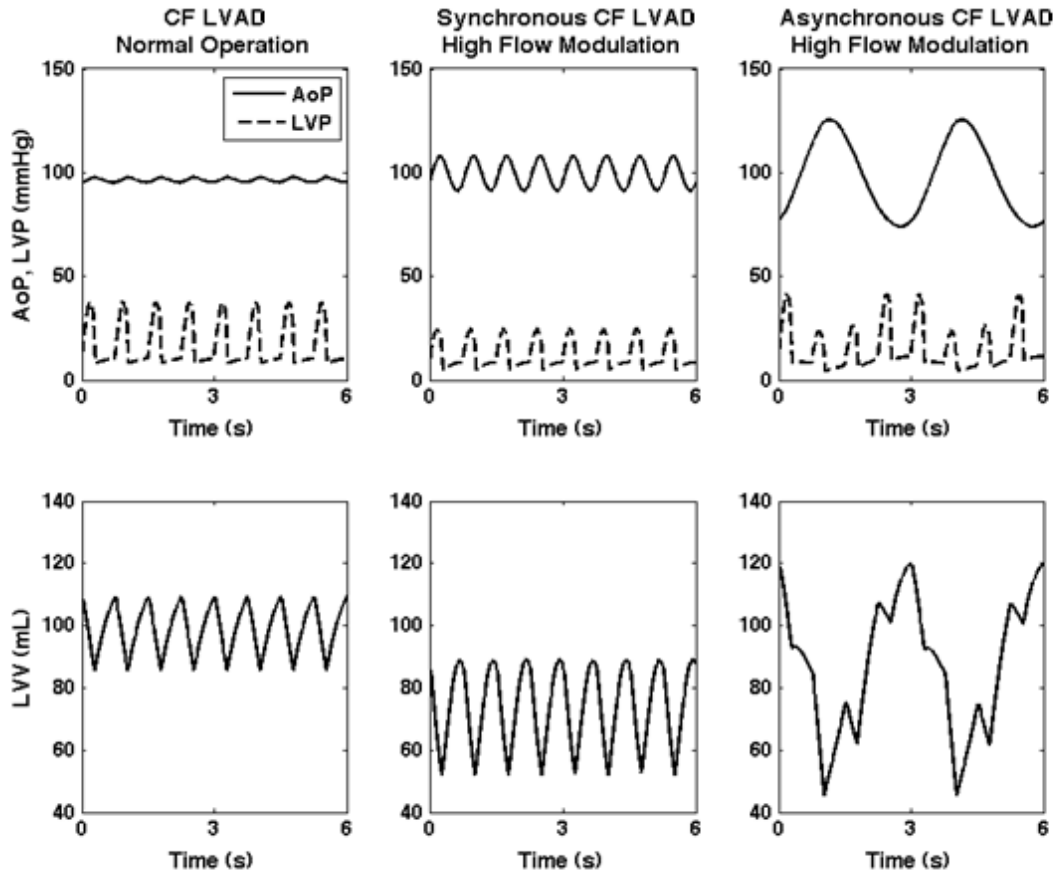
Figure 9: AoP, LVP, LVV for Normal CF LVAD, Synchronous CF LVAD with high flow modulation, and asynchronous CF LVAD with high flow modulation. Synchronous CF LVAD modulation increases AoP Pulsatility while maintaining consistent ranges of LVP and LVV. Asynchronous CF LVAD modulation at 20 BPM increases pulse pressure over synchronous modulation while creating varying LVP and LVV.
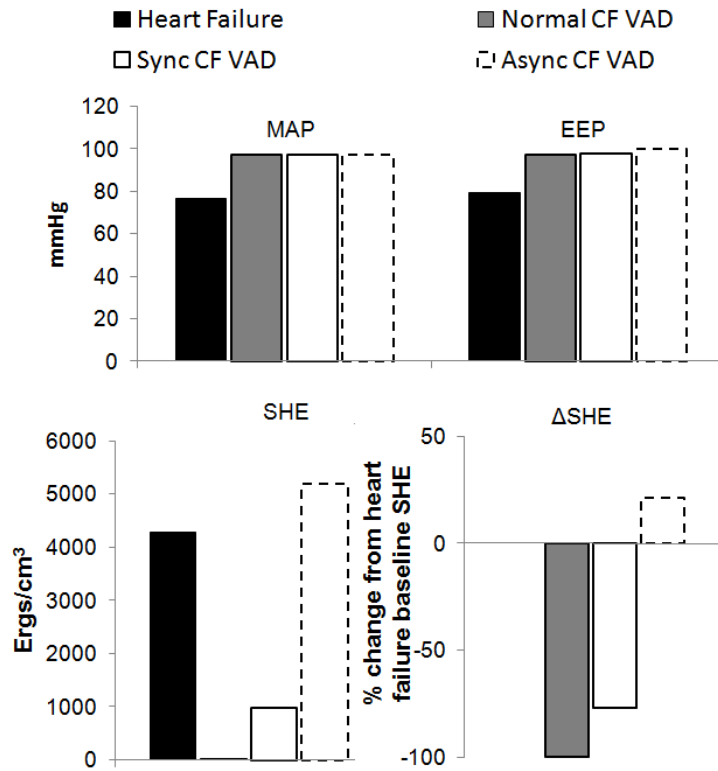
Figure 10: Values of MAP, EEP and SHE for Asynchronous, Synchronous, Normal (no CF LVAD flow modulation), and no CF LVAD support. These results demonstrate that CF LVAD flow modulation does not affect the mean arterial pressure. However, asynchronous CF LVAD flow modulation significantly increased SHE.
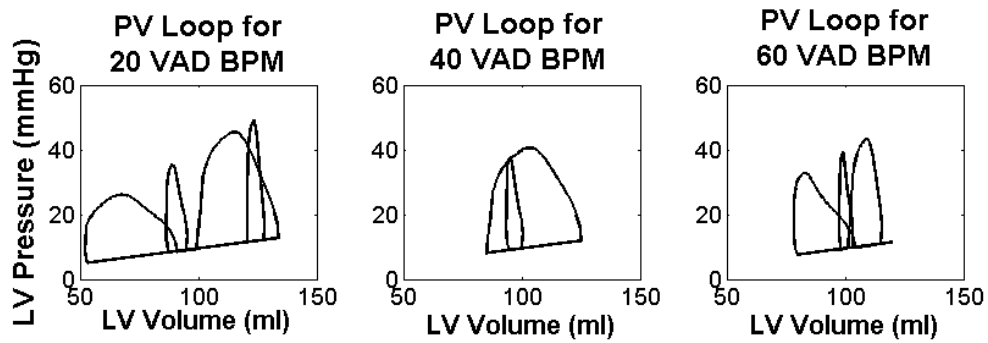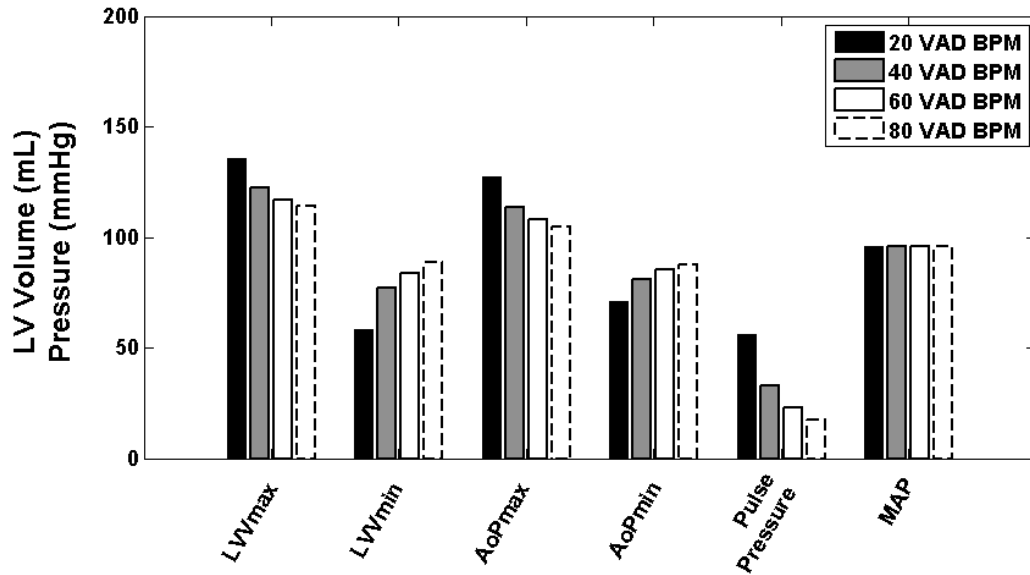
Figure 11: Maximum and minimum values of left ventricular volume (LVV) and aortic pressure (AoP), pulse pressure, mean arterial pressure (MAP), and ventricular pressure-volume loops showing the varying ventricular pressures and volumes for different modulation rates of CF LVAD. Specifically, higher left ventricular volume variability occurs at lower CF LVAD flow modulation rates.

30

	CF LVAD bpm	MAP (mmHg)	EEP (mmHg)	SHE (erg/cm^3)
Full Support	20 bpm	95.9 - 98.1	103.6 - 106.1	9,976 - 10,863
	40 bpm	95.9 - 98.0	98.5 - 100.8	3,325 - 3,752
	60 bpm	96.0 - 97.9	97.2 - 99.3	1,567 -1,850
	80 bpm	95.6 - 98.0	96.3 - 98.9	697 - 1,301
Partial Support	20 bpm	79.9 - 80.2	81.3 - 81.6	1,583 - 2.058
	40 bpm	79.6 - 80.4	80.5 - 82.0	1,097 - 2,144
	60 bpm	79.9 - 80.2	80.8 - 81	1,047 - 1,399
	80 bpm	78.6 - 81.3	80.0 - 82.1	333 - 1,899

Table 3: Range of values of mean arterial pressure (MAP), energy equivalent pressure (EEP), and surplus hemodynamic energy (SHE) obtained with high modulated CF LVAD flow during full and partial support at 20, 40, 60, and 80 (synchronous modulation) bpm.

Discussion

The results of this computer simulation study establish that arterial pulsatility and ventricular work can be affected significantly by modulating CF LVAD flow. Arterial and ventricular hemodynamic waveforms were altered by varying the timing, amplitude, and width of the CF LVAD flow modulation pulse for the same average CF LVAD flow rates. Importantly, a range of LVEW and CoF values can

be obtained for the same mean CF LVAD flow rate by altering the CF LVAD flow modulation. Currently, to increase LVEW to wean the patient from the device or to promote myocardial recovery, the CF LVAD flow rate is lowered, which may affect end-organ perfusion. Modulation and timing of CF LVAD flow resulted in a range of LVEW and CoF without altering the mean LVAD flow. Thus, modulation of CF LVAD flow may be beneficial in developing control strategies for CF LVAD to obtain a desired myocardial oxygen supply and work level, particularly towards optimizing the myocardial recovery process and developing weaning protocols for patients who are likely to experience myocardial recovery without changing the average CF LVAD flow and affecting end organ perfusion.

Diminished pressure pulsatility due to CF LVAD support has been reported to diminish aortic wall thickness, and volume ratio of smooth muscle cells [4, 54]. Further, anecdotal reports have indicated the frequent development of adverse events including gastrointestinal bleeding, hemorrhagic strokes, increased vascular impedance and progression of aortic valve insufficiency in HF patients chronically supported by CF LVAD[4, 29-31]. The increase in vascular pulsatility due to CF LVAD flow modulation may prevent or help reduce the severity of these adverse events associated with diminished pulsatility.

Maximum LVEW occurred at 0% time shift (co-pulsation mode) while minimum LVEW occurred at 40% time shift (counter-pulsation mode). Counterpulsation mode produced higher myocardial supply demand ratio (CoF/LVEW) but reduced vascular pulsatility compared to the co-pulsation mode. However, vascular pulsatility with counter pulsation mode was still higher than what was observed with no CF LVAD flow modulation. Altering the timing affected the SHE and EEP values but the highest values of SHE were obtained during asynchronous support with the LVAD modulating at 20 bpm (**Figure 7, Table 3**). During synchronous LVAD flow modulation, co-pulsation mode (0% time shift) resulted in higher SHE values compared to the counter pulsation mode (40% time shift). These results suggest that some optimization may be needed to tailor the CF LVAD flow modulation strategies to individual patients. During asynchronous LVAD flow modulation at low frequencies and high flow modulations, maximum pressure pulsatility was achieved. However, High LVAD flow over the period of several cardiac cycles creates favorable conditions for suction events. Algorithms to detect and prevent suction have been developed are currently used in LVADs[55, 56].

A normal human heart produces a peak flow rate of 30-35 L/min and minimum flow of ~0 L/min, resulting in an aortic pressure pulsatility of approximately 40 mmHg. A failing heart produces a peak flow rate of 20-25 L/min, but still results in

an aortic pressure pulsatility of 30-35 mmHg due to higher vascular impedance [4]. We limited the peak flow rate of the simulated CF LVAD flow waveform to 10 L/min to keep within the performance limitations of current LVADs. The minimum flow rate was limited to 1 L/min to prevent retrograde flow. These limitations in simulated peak and minimum CF LVAD flows limited the maximum achievable arterial pressure pulse with synchronous CF LVAD support to 19 mmHg. The achievable arterial pressure pulse can be significantly increased by allowing higher values of peak CF LVAD flow rates with improvement in LVAD technology. While retrograde flows also increase aortic pressure pulsatility, it should be avoided as it may increase device related hemolysis, LV volumes and LV wall stresses[57].

Limitations

There are several limitations associated with the computer simulation model. The performance of the computer simulation during failing heart test condition is representative of clinical observations from a purely hemodynamic viewpoint. Clearly, a computer simulation is not intended to replace the importance and significance of *in vivo* models and is incapable of replicating all expected clinical responses, but it does provide a valuable initial step. For instance, the simulation cannot mimic neurohumoral responses, tissue remodeling, activation of

regulatory proteins, or changes in genetic phenotype, but it can demonstrate feasibility of concepts. However, these limitations have been addressed in the *in-vivo* animal model studies detailed in chapter 4. Computer models rely upon many assumptions that may have a dramatic influence upon the interpretation of results. For example, the computer model for this study assumes ideal valves that open and close instantaneously, Newtonian blood, a constant diastolic ventricular compliance, does not account for inertial or gravitational effects, and the effects of wave reflection. The effect of LVAD flow modulation in mock circulation and animal experiments, presented in chapters 3 and 4, overcome some of these limitations. Importantly, blood behaves as a Newtonian fluid at higher velocities in large vessels and the LVAD. The computer simulation does enable prediction of hemodynamic and ventricular pressure-volume responses. The effect of CF LVAD flow modulation can also be quantified in *in-vitro* mock circulation systems and *in-vivo* animal models. However, these models have several significant limitations not present in the computer simulation that may affect the accurate quantification of aortic pulse pressure and LVEW. Specifically, mock circulation models usually lump total systemic compliance which is significantly lower than aortic compliance[58]. The lower value of lumped systemic compliance would artificially augment pressure pulsatility, which may lead to reports of up to 61 mmHg of pressure pulsatility with less than 5 L/min of flow pulsatility [24]. Similarly, animal models have significantly different aortic and

arterial compliance values than humans [59]. These altered compliance values would lead to an inaccurate estimation of aortic pressure pulsatility, **Figures 9, 20, and 27**. Further, *in-vitro* mock circulation systems typically underestimate the reduction in left ventricular peak pressures due to pneumatic/hydraulic drivers, which may lead to inaccurate estimation of LVEW. Despite its limitations, a computer simulation model with a simulated aorta may be the simplest method to adequately quantify the effects of CF LVAD flow modulation. Modulation of CF LVAD rpm/flow would increase power consumption and bearing wear which may be minimized in next generation magnetically suspended CF LVAD. To ensure that the strategies presented in this manuscript are pump independent, we use flow modulation instead of rpm/power modulation. Pump inertia, friction, and loading profiles will vary from pump to pump and affect the relationship between rpm/power modulation and flow modulation. The rpm/power modulation needed to achieve the flow modulation will be different for each device in mock circulation and animal studies only being representative of the specific pumps used in each study. The values of SHE, EEP, pressures, flows, and work are representative and clinically relevant values obtained from literature but may vary due to intra-patient variability. Despite these limitations, it is hoped that the computer simulation findings enable the further development and testing of new control strategies, devices, and experimental protocols that can be translated to an *in*

vivo model to validate clinical viability of techniques that promote for myocardial recovery.

CHAPTER 3 – MOCK CIRCULATION

Introduction

While they cannot replace in-vivo animal testing and clinical trials, in-vitro mock

loop testing is an important step in the design process. In-vitro mock loops are

used for experimental protocol development, device performance testing,

feedback control algorithm design, as well as training of clinical staff. The in-vitro

test system has the ability to mimic the Frank-Starling response and produces

physiologic characteristic hemodynamic measurements and pressure volume-

relationships. The in-vitro mock loop used in this testing has been verified and

well published with multiple devices having been evaluated using it [58, 60-63].

Cases found to yield the most promising results (i.e. co-pulsation and counter-

pulsation) were further tested using this experimental setup. We hypothesized

that modulation of LVAD RPM will increase arterial pressure pulsatility and

enable alteration of left ventricular pressures, volumes, and workloads. Further,

we hypothesized that the magnitude of these effects on the native ventricle will

be dependent on LVAD modulation timing. The objective of this mock circulation study was to investigate the effects of LVAD RPM modulation on the ventricle and vasculature with varying modulation amplitudes, widths, and frequencies and compare the results to computer simulation.

Methods and Materials

Mock Circulatory Loop

The mock circulation system used in this experiment consisted of a silicone left ventricle, aorta, arterial resistance and compliance, venous reservoir and atrial compliance (**Figure 12**). Ventricular pressure, heart rate, loop volume, resistances, and compliances were adjusted to reproduce hemodynamic pressure and flow waveforms of the physiology of an adult human in heart failure based on clinical findings. Aortic (proximal and distal) and LVAD flows were measured using Transonic Flow Probes (Transonic Systems, Ithica, NY). Aortic (proximal and distal), and atrial pressures were measured using single tipped Millar pressure catheters and left ventricle pressure and volume were measured using Millar a pressure-volume conductance catheter (Millar Instruments, TX). Ventricle systolic and diastolic time periods and pressure, vacuum, and motor percentages were controlled by the pneumatic ventricle driver (LB Engineering,

Germany). A HeartWare (Miami Lakes, FL) HVAD was used as the LVAD in this study. The centrifugal pump has been implanted regularly in Europe, is currently awaiting FDA approval for bridge to transplantation, and is undergoing clinical trials for destination therapy in the US [64, 65].
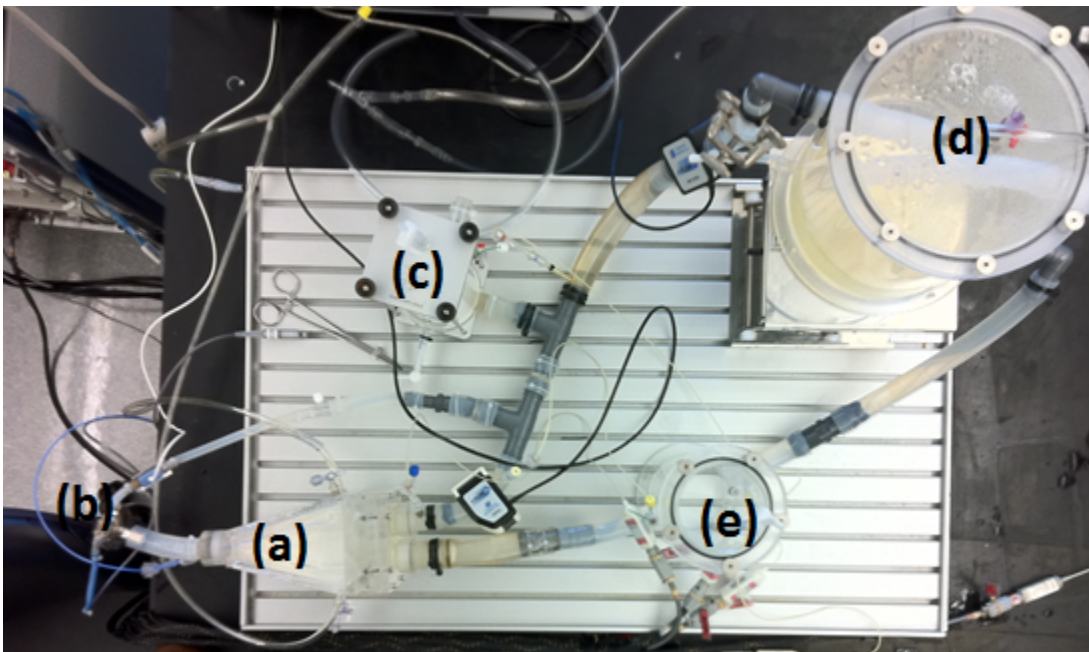
Figure 12: Mock Circulation loop with (a) left ventricle, (b) HeartWare LVAD, (c) arterial compliance, (d) venous reservoir, and (e) atrial compliance.

LVAD Controller

The LVAD controller was programmed by engineers at HeartWare under the direction of the investigators to enable LVAD pump speed modulation (**Figure**

13). In the mock circulation studies, the controller modulated the LVAD speed up and down by the same given RPM step around a user defined base speed. The HVAD has pump has operational speed limits of 1800 – 4000 RPM. Delta T was defined as the period of time the pump was in high or low RPM (pulse and nadir rpm). The pump would be in the high RPM for Delta T and the low RPM for Delta T resulting in one modulation period being twice the value of Delta T. For example, if a Delta T of 0.4 sec was chosen at a 2900±1100 RPM (mean RPM±modulation amplitude) modulation, the pump would operate at 4000 RPM for 0.4 seconds followed by 1800 RPM for 0.4 seconds and then repeat the cycle. The complete modulation cycle would take 0.8 seconds.
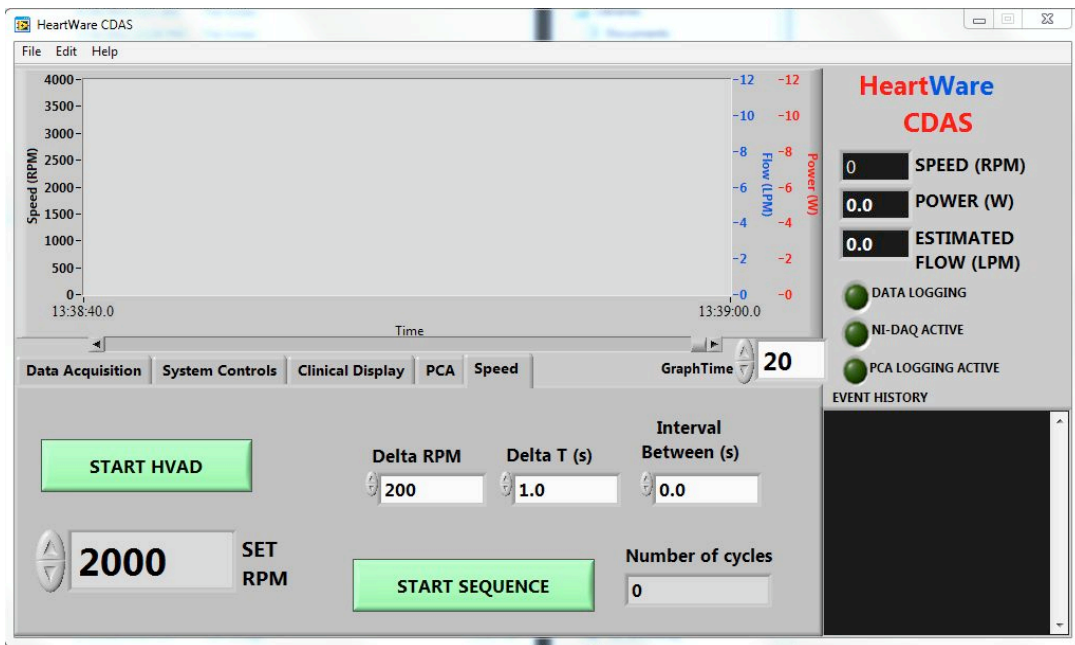
Figure 13: Screenshot of LVAD controller

Experimental Protocol

Three ventricle contractilities (high, medium, and low) were used in this study. High contractility produced baseline heart failure pressures in the mock loop with no LVAD. High, medium, and low contractility resulted in peak ventricle pressures of 142 mmHg, 104 mmHg, and 80 mmHg. The mock circulation cannot automatically reduce the contractility based on myocardial load. Thus, different ventricular contractilities were simulated to match a range of ventricular contractilities that is observed during unloading/ of the native ventricle using VAD/LVAD support. The cardiac cycle produced by the driver was 0.795 sec (75.5 BPM), while the LVAD operated at .800 seconds.

Base speeds for this study were chosen at 2900 and 3200 RPM. A base speed of 2900 allowed for maximum RPM modulation (2900±1100 RPM) (base RPM ± modulation RPM) and steps of 2900±800 RPM, 2900±500 RPM, and 2900±300 RPM. 3200 RPM completely unloaded the ventricle and was chosen as a full support baseline with no modulation. Modulations were done around a 3200 RPM base speed at 3200±800 RPM, 3200±500 RPM, and 3200±300 RPM. In this experiment, periods of 0.4, 0.5, 0.8, and 1.6 were chosen resulting in cycle

periods of 0.8 seconds, 1.0 seconds, 1.6 seconds, and 3.2 seconds. For synchronous modulation, the LVAD RPM modulation period was set at 0.4 seconds. The 0.005 second offset between LVAD cycle period (0.8 seconds) and cardiac cycle (0.795 seconds) allowed for the LVAD to pass from co-pulsation to counter pulsation LVAD RPM modulation. The small 5 ms difference between the native ventricle and the pump produced a slightly asynchronous support that would capture the effect of timing of the LVAD to the native ventricle in a 200 second data set. At each of the three contractilities, the LVAD was modulated at the described RPM levels at each of the modulation periods. Additionally data sets were recorded for the LVAD running in CF fashion at each contractility in 100 RPM steps (i.e. 2000 RPM, 2100 RPM, 2200 RPM, etc.

Data Analysis

Data was analyzed using Matlab (MathWorks, Natick, MA) and Hemodynamic Evaluation and Assessment Research Tool (HEART) program [66]. Pressure, flow, and volume waveforms were used to calculate the following hemodynamic parameters: cardiac output; aortic systolic, diastolic, and mean pressures; left ventricular systolic, end diastolic, and peak pressures; left ventricular external work; and aortic and LVAD flows. For synchronous LVAD RPM modulation and

no LVAD RPM modulation, all hemodynamic parameters were calculated on a beat-to-beat basis. Three beats were averaged for calculating co-pulsation and counter pulsation hemodynamics; the beat found to be in pure co-pulsation or counter pulsation and the previous and following beats. When evaluating synchronous modulation, the hemodynamic values obtained for the modulation beats were compared to those when operating the LVAD in a CF fashion at flow within 10% of mean LVAD flow. Asynchronous modulation cases were evaluated over the full LVAD modulation cycle (i.e. multiple beats) and reported values are the average of 200 seconds of RPM modulation. Pressure-volume loops were constructed by plotting ventricular pressure against ventricular volume, where each loop represents one complete cardiac cycle (one beat). Characterizing hemodynamic parameters and pressure-volume loops were calculated for all experimental conditions.

Results

Effects of Contractility

Increased contractility led to greater flow through aortic valve during CF LVAD support. **Table 4** shows flow through the aortic valve proximal to the LVAD

outflow graft, modulation of LVAD flow rates due to ventricle contraction, and LVAD speed necessary to achieve mean LVAD flows of 3.0±0.2L/min, 4.0±0.2L/min, and 5.0±0.2L/min at high, medium, and low ventricle contractilities. Decreasing ventricle contractility resulted in lower LVAD speed necessary for equivalent LVAD flow. Additionally, increased ventricle contractility resulted in a higher change in LVAD flow. At LVAD flow rates of 3.0±0.2L/min, 4.0±0.2L/min, and 5.0±0.2L/min, the change in LVAD flow was 2.6L/min, 2.5L/min, and 2.3L/min for low contractility, 3.6L/min, 3.4L/min, and 3.2L/min for medium contractility, and 5.4L/min, 4.8L/min, and 4.4L/min for high contractility. Further, lower ventricle contractility resulted in reduced flow through the aortic valve. At an LVAD flow rate of 3.0±0.2L/min, flow through the aortic valve diminished from 1.7L/min at high contractility to 0.8L/min at medium contractility and 0.4L/min at low contractility.

VADF (L/min)	Contractility								
	High			Medium			Low		
	AoFroot	max/min VADF	RPM	AoFroot	max/min VADF	RPM	AoFroot	max/min VADF	RPM
3.0±0.2	1.7	5.9/0.5	2800	0.8	4.9/1.3	2400	0.4	4.3/1.7	2200
4.0±0.2	1.0	6.5/1.7	3100	0.2	5.9/2.5	3000	0.0	5.3/2.8	2900
5.0±0.2	0.2	7.3/2.9	3500	0.0	6.6/3.4	3400	0.0	6.1/3.8	3500

Table 4: Flow through the aortic valve proximal to the LVAD outflow graft (AoFroot), maximum and minimum LVAD flow rates (max/min VADF), and LVAD speed (RPM) necessary to achieve LVAD flows (VADF) of 3.0±0.2L/min, 4.0±0.2L/min, and 5.0±0.2L/min at high, medium, and low ventricle contractilities. The LVAD was operating in a CF fashion and the variation in flow shown in max/min VADF is due to contraction and relaxation of the ventricle.

During synchronous co-pulsation LVAD RPM modulation, increased ventricular contractility increased maximum and minimum LVAD flows (**Table 5**). Change in LVAD flow increased from 9L/min at low contractility to 9.7L/min and 11.1L/min at medium and high ventricular contractilities, respectively. In co-pulsation LVAD RPM modulation, mean LVAD flow increased as ventricle contractility decreased for maximum LVAD speed modulation (2900±1100 RPM). Differing from co-pulsation LVAD RPM modulation, in counter pulsation mode, LVAD flow did not vary greatly between high, medium, and low contractilities with flow rates of 4.1L/min, 4.3L/min, and 4.1 L/min, respectively. Similarly to continuous flow, decreased contractility resulted in a reduction in flow through the aortic valve for

both co-pulsation and counter pulsation LVAD RPM modulation. During co-pulsation LVAD RPM modulation flow through the aortic valve was 1.5L/min, 0.3L/min and 0.0L/min and during counter pulsation LVAD RPM modulation flow through the aortic valve was 1Lmin, 0.1L/min, and 0.0L/min for high, medium, and low ventricle contractility, respectively. Low ventricular contractility best mimics the effects of LVAD unloading the native ventricle and is used in the remaining of the results section, unless otherwise noted.

Synchronous LVAD Modulation	Contractility								
	High			Medium			Low		
	AoFroot (L/min)	VADF (L/min)	max/min VADF	AoFroot (L/min)	VADF (L/min)	max/min VADF	AoFroot (L/min)	VADF (L/min)	max/min VADF
Co-pulsation	1.5	2.9	8.5/-2.6	0.3	3.5	8.4/-1.3	0.0	3.6	8.2/-0.8
Counterpulsation	1	4.1	5.4/2.5	0.1	4.3	6.0/2.9	0	4.1	6.4/1.9

Table 5: Flow through the aortic valve proximal to the LVAD outflow graft (AoFroot), mean LVAD flow (VADF), and maximum and minimum LVAD flow rates (max/min VADF) at high, medium, and low ventricle contractilities for co-pulsation and counter pulsation LVAD flow modulation.

Synchronous vs. Asynchronous Modulation

During asynchronous LVAD RPM modulation, LVEW, LVV, and mean LVAD flow varied between cardiac cycles occurring during one LVAD RPM modulation cycle

as compared to consistent ranges obtained during synchronous LVAD support and continuous flow LVAD support. Decreasing the rate of asynchronous full support LVAD RPM modulation increased the achievable arterial pressure pulsatility, EEP, and SHE (**Table 6**).

	Modulation Period		MAP (mmHg)	EEP (mmHg)	SHE (erg/cm³)
3200 ±800 RPM	1.6 sec		92.9 - 95.6	95.2 - 97.7	2666 - 3604
	0.8 sec		89.4 - 95.0	90.5 - 95.6	792 - 1692
	0.5 sec		88.3 - 98.8	88.7 - 98.9	223 - 959
	0.4 sec		89.0 - 97.6	89.3 - 99.8	49 - 398
2900 ±1100 RPM	1.6 sec		83.3 - 85.3	87.3 - 89.4	5037 - 6100
	0.8 sec		79.0 - 83.8	80.8 - 85.1	1500 - 2760
	0.5 sec		74.8 - 86.8	75.5 - 87.2	400 - 1752
	0.4 sec		75.9 - 89.2	76.4 - 89.3	105 - 617

Table 6: Range of values of mean arterial pressure (MAP), energy equivalent pressure (EEP), and surplus hemodynamic energy (SHE) obtained with maximum modulated CF LVAD RPM around base RPMs of 2900RPM and 3200RPM modulation periods of at 1.6 sec, 0.8 sec, 0.5 sec, and 0.4 sec (synchronous modulation).

A maximum arterial pulse pressure of 65 mmHg was achieved at a slow LVAD RPM modulation rate of with a 1.6 second modulation period (3.2 second cycle period) of 2900±1100RPM. This is considerably greater than synchronous co-pulsation CF LVAD with a period of 0.4 seconds (20 mmHg at a modulation) and

synchronous counter pulsation CF LVAD (11 mmHg) with a similar RPM modulation.

Effects of Timing

Co-pulsation and counter pulsation modulation of LVAD RPM (2900±1100RPM) both increased pulse pressure 210% and 98%, respectively, as compared to normal CF LVAD operation with similar mean LVAD flow. However, counter pulsation yielded more than a 50% smaller percent increase from normal CF LVAD operation in aortic pressure pulsatility as compared to the greater percent increase produced by co-pulsation (**Figure 14**).
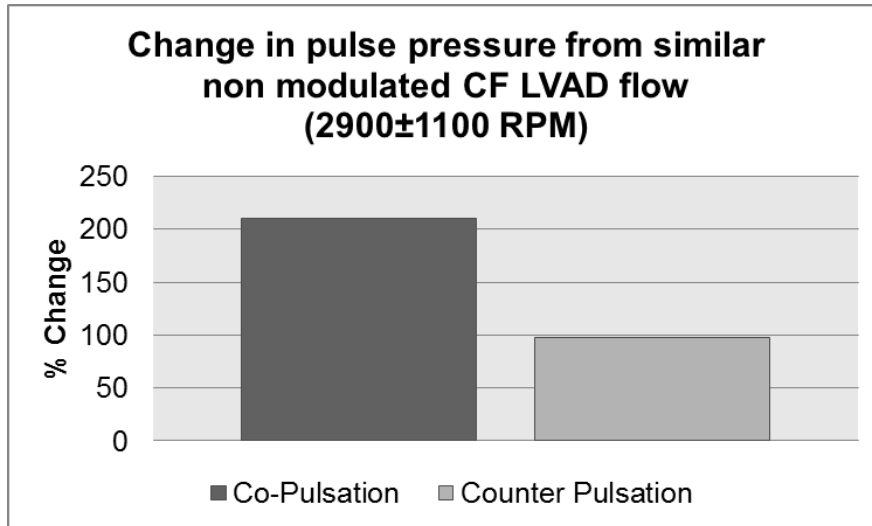
Figure 14: Percent change in pulse pressure during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow (mean RPM ± modulation RPM).

As compared to co-pulsation, counter pulsation LVAD RPM modulation resulted in higher mean LVAD flow (3.6L/min vs. 4.1L/min) and MAP (76 mmHg vs. 89 mmHg) at LVAD RPM modulation of 2900±1100 RPM (**Figure 15**). Co-pulsation (2900±1100 RPM) increased stroke volume 12% as compared to CF LVAD at similar flow. Alternatively, counter pulsation (2900±1100 RPM) reduced stroke volume 20% as compared to CF LVAD at similar flow (**Figure 16**). **Figure 12** shows pressure volume loops for co-pulsation and counter pulsation at 2900±1100 RPM and the corresponding pressure volume loops for CF LVAD with similar mean LVAD flow, 2700 RPM and 3000 RPM, respectively. Both co-pulsation and counter pulsation of LVAD RPM at 2900±1100 RPM decreased LVEW nearly 20% from similar mean CF LVAD flow (**Figure 17**).
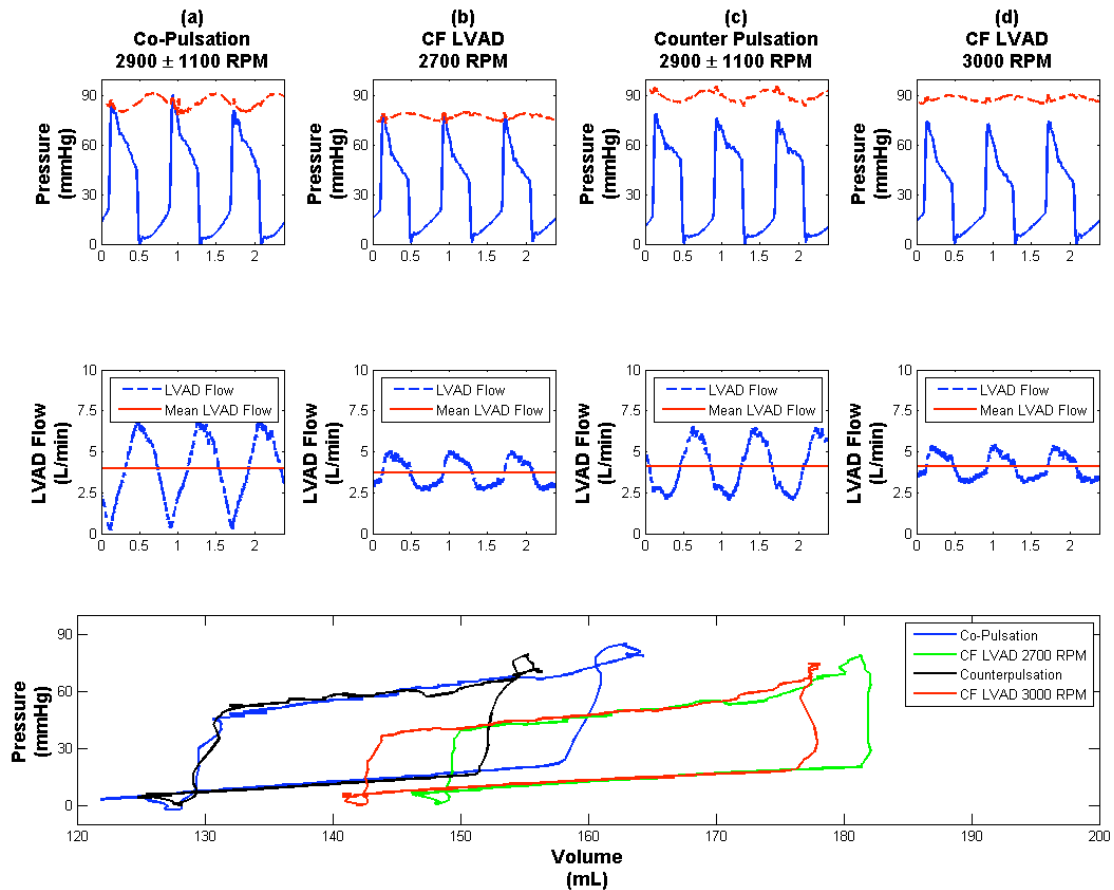
Figure 15: Aortic pressure, left ventricular pressure, LVAD flow, mean LVAD flow and pressure volume loops for (a) co-pulsation LVAD modulation at 2900±1100 RPM, (b) CF LVAD at 2700 RPM, (c) counter pulsation LVAD RPM modulation at 2900±1100 RPM, and (d) CF LVAD at 3000 RPM. Co-pulsation at 2900±1100 RPM and CF LVAD at 2700 RPM had similar mean LVAD flows. Further, counter pulsation at 2900±1100 RPM and CF LVAD at 3000 RPM had similar mean LVAD flows.

Figure 16: Percent change in stroke volume during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow (mean RPM ± modulation RPM).
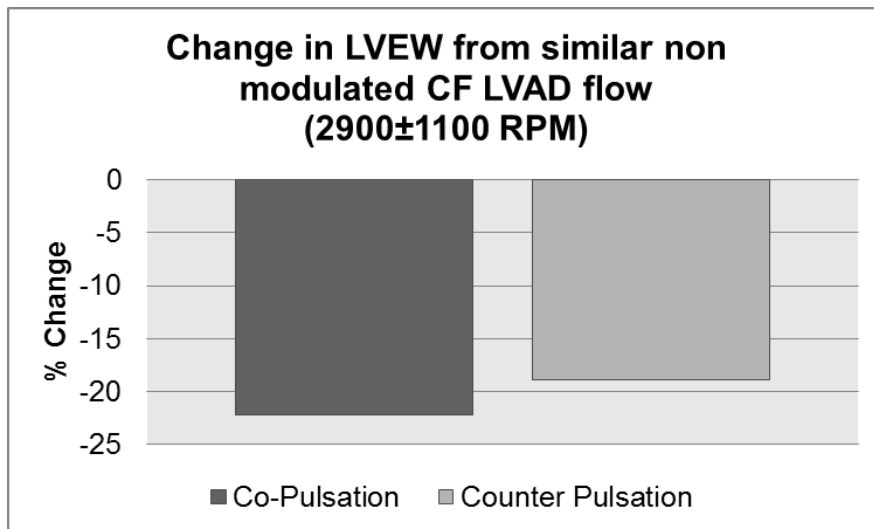
Figure 17: Percent change in LVEW during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow (mean RPM ± modulation RPM).

Effects of Modulation Amplitude

Decrease in RPM modulation amplitude does not considerably change mean VADF. However, during co-pulsation LVAD RPM modulation a decrease in modulation amplitude slightly increased mean LVAD flow. Mean LVAD flow increased from 3.64 L/min to 3.69 L/min, 3.76 L/min, and 3.82 L/min at RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM, respectively, during co-pulsation LVAD RPM modulation with a base of 2900 RPM. Alternatively, a decrease in LVAD RPM modulation slightly increased mean LVAD flow during counter pulsation LVAD RPM modulation. Changes in RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM with a base of 2900 RPM resulted in mean LVAD flows of 4.10 L/min, 4.08 L/min, 4.01 L/min, and 3.98 L/min, respectively, for counter pulsation LVAD RPM modulation (**Figure 18**).
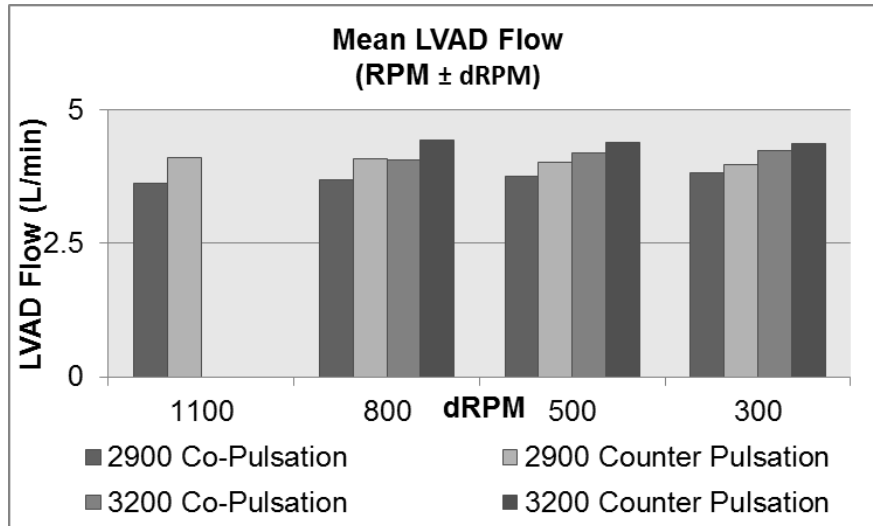
Figure 18: Mean LVAD flow for co-pulsation and counter pulsation LVAD RPM modulation for base RPMs of 2900 RPM and 3000 RPM and for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.

Decrease in RPM modulation amplitude resulted in diminished pulse pressures. All co-pulsation LVAD RPM modulations resulted in an increase of pulse pressure as compared to CF LVAD with a similar mean LVAD flow. Similarly, counter pulsation LVAD RPM modulation resulted in increased pulse pressures of 98%, 42%, and 36% for LVAD RPM modulations of 2900±1100 RPM, 2900±800 RPM, and 3200±800 RPM. However, counter pulsation LVAD RPM modulations of 2900±500 RPM, 2900±300 RPM, 3200±500RPM, and 3200±300 RPM resulted in diminished pulse pressures from CF LVAD with a similar mean LVAD flow of -28%, -61%, -10%, and -56%, respectively (**Figure 19**). Slower LVAD RPM modulation resulted in increased pulse pressures (**Figure 20**). These

change in pulse pressure trends resulted in similar trends for SHE. All co-pulsations resulted in increased SHE from CF LVAD with a similar mean LVAD flow. Furthermore during counter pulsation LVAD RPM modulation, SHE decreased from CF LVAD with a similar mean LVAD flow of 92% and 92% at a base of 2900 RPM and 76% and 94% at a base of 3200 RPM, for RPM modulation amplitudes of 500 RPM and 300 RPM, respectively (**Figure 21**).
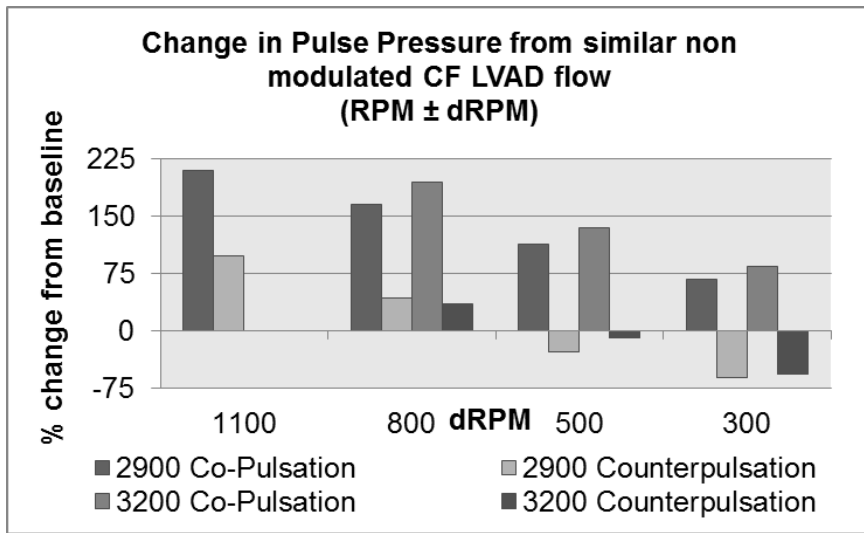
Figure 19: Percent change in pulse pressure during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow for base RPMs of 2900 and 3200 for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.
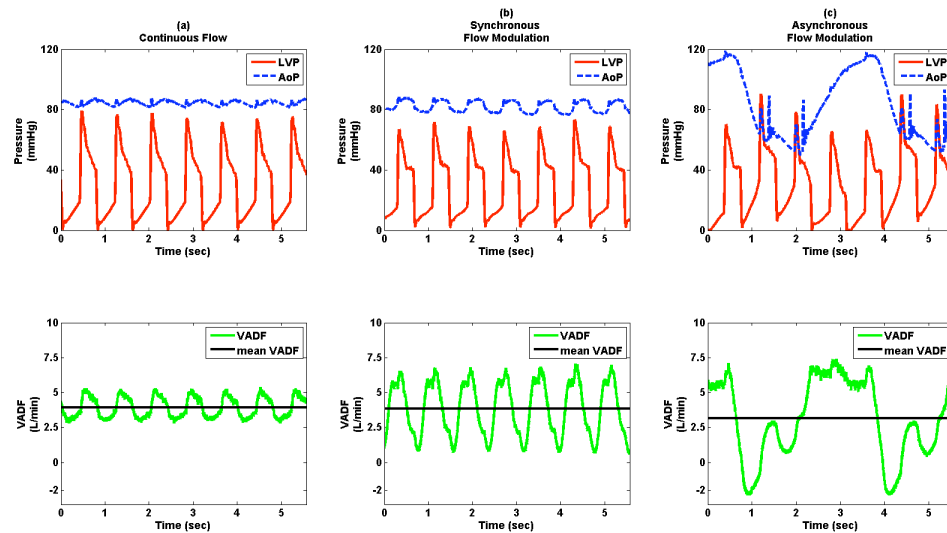
Figure 20: Aortic pressure (AoP), left ventricular pressure (LVP), and LVAD flow (VADF) for (a) Normal CF LVAD, (b) Synchronous CF LVAD (2900±1100RPM) (mean RPM ± modulation RPM), and (c) asynchronous CF LVAD (2900±1100RPM). Synchronous CF LVAD modulation increases AoP Pulsatility while maintaining consistent ranges of left ventricular pressure and volumes. Slow asynchronous CF LVAD modulation at 19 BPM increases pulse pressure over synchronous modulation while creating varying left ventricular pressure volumes.
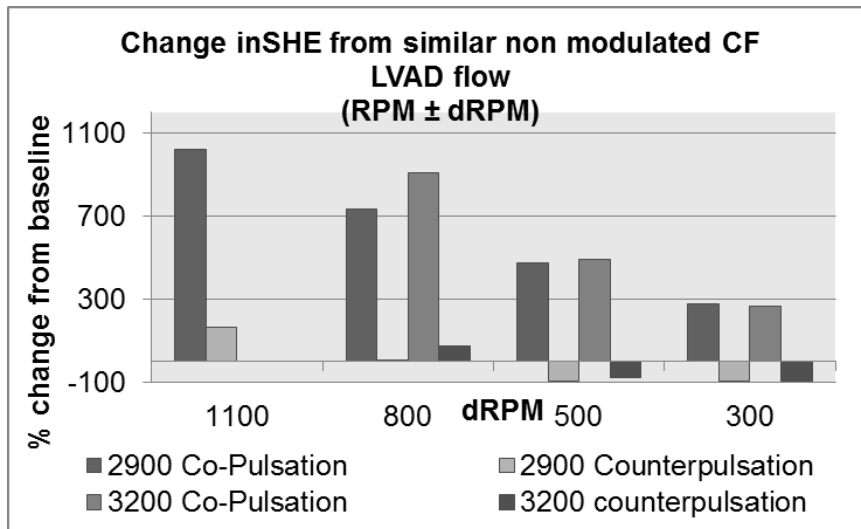
Figure 21: Percent change in SHE during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow for base RPMs of 2900 and 3200 for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.

During co-pulsation LVAD RPM modulation, change in LVAD flow was diminished as RPM modulation amplitude was decreased from 1100 RPM to 800 RPM, 500 RPM, and 300 RPM. Specifically, for a base of 2900 RPM, change in LVAD flow decreased from 9.0 L/min at 1100 RPM to 7.2 L/min, 5.2 L/min and 4.1 L/min at 800 RPM, 500 RPM, and 300 RPM, respectively. Similarly for base RPM of 3200, change in LVAD flow decreased from 7.1 L/min at 800 RPM modulations to 5.3 L/min at 500 RPM modulations and 4.1 L/min at 300 RPM modulations (**Figure 21**). These corresponded to changes in LVAD flow from CF

LVAD with a similar mean LVAD flow of 242% (±1100 RPM), 176% (±800 RPM), 112% (±500 RPM), and 60%(±300 RPM) at base RPM of 2900 and 201%(±800 RPM), 122%(±500 RPM), and 72%(±300 RPM) at base RPM of 3200 (**Figure 22**).

During counter pulsation LVAD RPM modulation, change in LVAD flow was diminished as RPM modulation amplitude was decreased from 1100 RPM to 800 RPM, 500 RPM, and 300 RPM. Specifically, for a base of 2900 RPM, change in LVAD flow decreased from 4.5 L/min (91%) at 1100 RPM to 3.0 L/min (29%), 1.6 L/min (-36%) and 1.1 L/min (-56%) at 800 RPM, 500 RPM, and 300 RPM, respectively. Similarly for base RPM of 3200, change in LVAD flow decreased from 3.3 L/min (42%) at 800 RPM modulations to 2.0 L/min (-14%) at 500 RPM modulations and 1.2 L/min (-49%) at 300 RPM modulations where the percent change from CF LVAD with a similar mean LVAD flow is in parentheses (**Figures 22 and 23**).
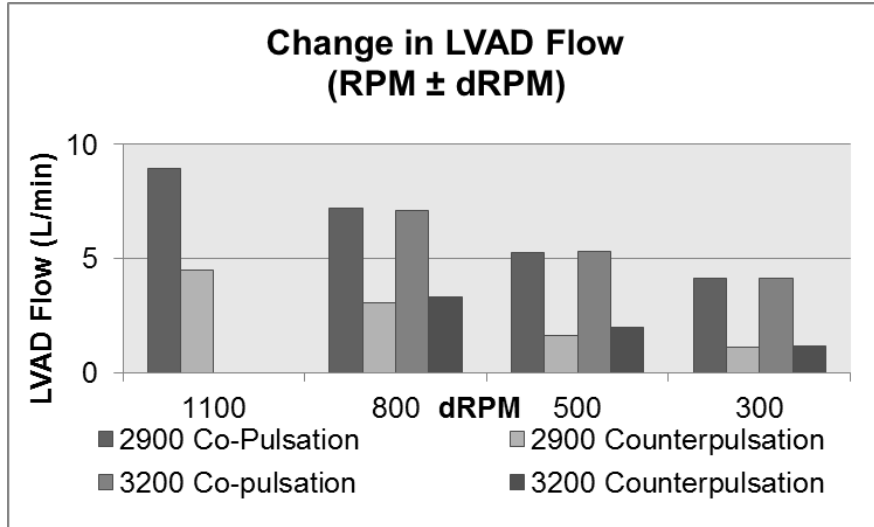
Figure 22: Change in LVAD flow for co-pulsation and counter pulsation LVAD RPM modulation for base RPMs of 2900 RPM and 3000 RPM and for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.
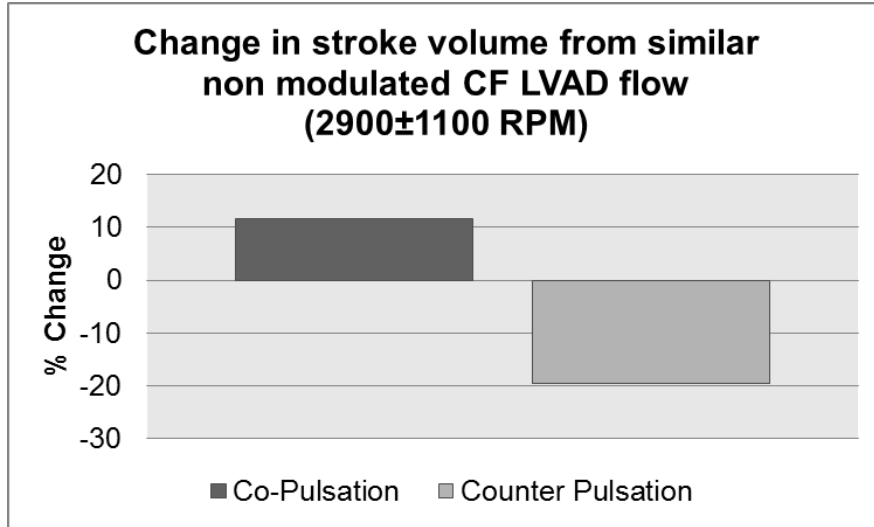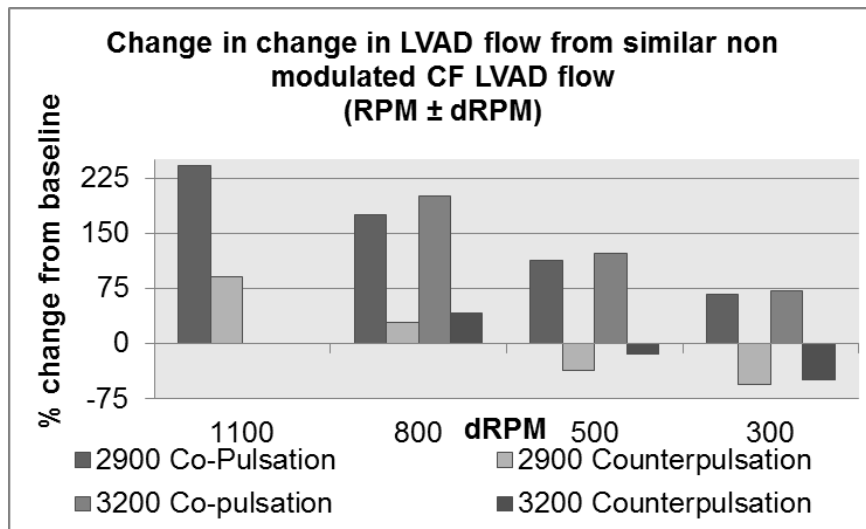

Figure 23: Percent change in change in LVAD flow during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow for base RPMs of 2900 and 3200 for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.

The decrease in LVAD RPM amplitude modulation of 2900±1100 RPM, 800 RPM, and 500 RPM and 3200±800 RPM, 500 RPM, and 300 RPM during co-pulsation LVAD RPM modulation resulted in attenuation of change in stroke volume from CF LVAD of similar mean flow. Specifically, change in stroke volumes of 12%, 11%, and 6% and 6%, 10%, and 8% resulted from co-pulsation LVAD RPM modulations of 2900±1100 RPM, 800 RPM, and 500 RPM and 3200±800 RPM, 500 RPM, and 300 RPM. Counter pulsation LVAD RPM modulation resulted in change in stroke volumes of -20%, -18%, and -16% and   -14%, -11%, and -7% for the previously describe cases. Co-pulsation and counter pulsation LVAD RPM modulation of 2900±300 RPM resulted in increases of 36% and 35% respectively (**Figure 24**).
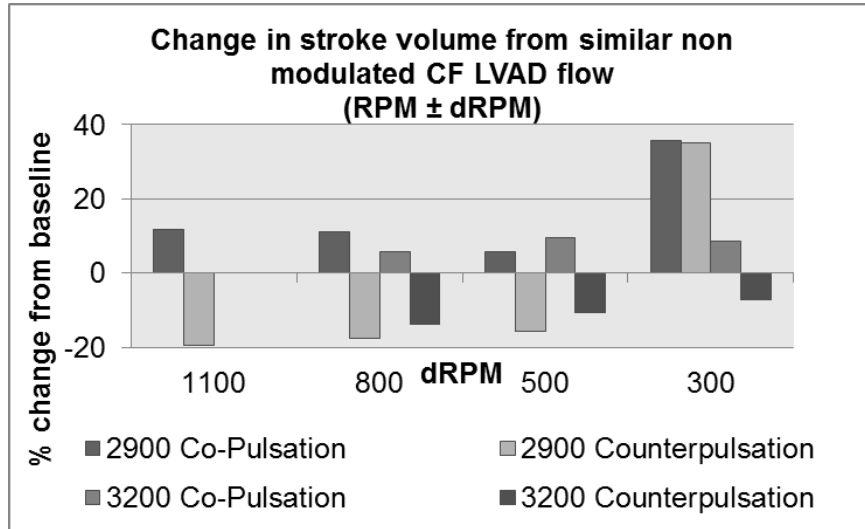
Figure 24: Percent change in stroke volume during co-pulsation and counter pulsation LVAD RPM modulation from CF LVAD of similar mean flow for base RPMs of 2900 and 3200 for RPM modulation amplitudes of 1100 RPM, 800 RPM, 500 RPM, and 300 RPM.

Discussion

The results of this study validate the conclusion that established arterial pulsatility and ventricular work can be affected significantly by modulating CF LVAD flow from previous work [44]. Arterial and ventricular hemodynamic waveforms were altered by varying the timing and amplitude of the CF LVAD RPM modulation and compared to non-modulation CF LVAD flow with similar mean flows.

Diminished arterial pulse pressure has been suggested in a mechanism that results in increased bleeding events, acquired von Willebrande syndrome, and other adverse events prevalent in the clinical use of CF LVAD [67, 68]. Reduced pressure pulsatility that occurs during CF LVAD has been reported to diminish aortic wall thickness and volume ratio of smooth muscle cells [4, 54]. Additionally, anecdotal reports have indicated the frequent development of adverse events including gastrointestinal bleeding, hemorrhagic strokes, increased vascular impedance and progression of aortic valve insufficiency in HF patients chronically supported by CF LVAD [4, 29-31]. The increase in vascular pulsatility due to CF LVAD flow modulation may prevent or help reduce the severity of these adverse events associated with diminished pulsatility. Ando et al previously suggested that partial support co-pulsation LVAD RPM modulation can increase pulse pressure near levels of no support in healthy goats [69]. However, this was achieved with considerable retrograde flow through the device, which resulted in a 66% increase in end-diastolic LVP suggesting an increase in LVEW. Furthermore, at low RPM modulation amplitudes, counter pulsation LVAD RPM modulation would actually provide smaller pulse pressures than non-modulated CF LVAD flow. This further loss of pressure pulsatility may result in increased occurrence of adverse events.

Both co-pulsation and counter pulsation LVAD RPM modulation resulted in a decreased LVEW as compared to CF LVAD. Further, counter pulsation LVAD RPM modulation caused a greater decrease in stroke volume than the same co-pulsation LVAD RPM modulation and as a percent decrease from CF LVAD with similar mean LVAD flows. Alternately, counter pulsation LVAD RPM modulation reduced arterial pulse pressure as compared to co-pulsation LVAD RPM modulation. Counterpulsing by modulating LVAD RPM resulted in smaller variation in flow as the native ventricular contraction caused a high flow during systole while high LVAD RPM increased flow during diastole, leading to a smaller variation in flow during the cardiac cycle compared to copulsation mode. However, the arterial pulse pressure with counter pulsation LVAD RPM modulation at high RPM modulation amplitudes (1100 RPM, 800 RPM) was still higher than observed with no LVAD RPM modulation. Altering the timing of synchronous LVAD RPM modulation from counter pulsation to co-pulsation mode resulted in increased pulse pressure, EEP, and SHE. However, asynchronous modulation produced the highest ranges of MAP, EEP, and SHE, as predicted by the computer simulation results. Asynchronous LVAD RPM modulation resulted in beat-to-beat variances in pressures and volumes of the native ventricle. These variations in beat-to-beat pressures and volumes may be counterproductive for reversal of heart failure and ultimate recovery of the patient for device explantation [32].

It should be noted that retrograde flows also increase aortic pressure pulsatility, it should be avoided as it may increase device related hemolysis, LV volumes and LV wall stresses [57, 69]. Retrograde flow was present in this study during asynchronous LVAD modulation with high RPM modulation of 1100 RPM. This resulted in prolonged periods of the LVAD operating at its baseline of 1800 RPM. Additionally, this occurred during co-pulsation LVAD RPM modulation at 2900±1100 RPM.

A normal human heart produces a peak flow rate of 30-35 L/min and minimum flow of ~0 L/min, resulting in an aortic pressure pulsatility of approximately 40 mmHg. A failing heart produces a peak flow rate of 20-25 L/min, but still results in an aortic pressure pulsatility of 30-35 mmHg due to higher vascular impedance [4]. Current LVAD technology is limited in the maximum achievable flows. In this study, peak LVAD flows of 8.5 L/min occurred during co-pulsation LVAD RPM modulation at 2900±1100 RPM and asynchronous LVAD RPM at 3200±800RPM with a period of 1.6 seconds. The current LVAD technology limitations restrict the maximum achievable pressure pulse, ventricular unloading, and modulation amplitude. With technological improvements, higher flows and RPM modulation amplitudes may allow for increased pulse pressure, reduced LVEW, and prevention of retrograde flow through the LVAD at maximum RPM modulation.

Limitations

There are several limitations associated with the mock circulation model. For instance, the mock circulation cannot mimic neurohumoral responses, tissue remodeling, activation of regulatory proteins, or changes in genetic phenotype, but it can demonstrate feasibility of concepts and allow for design testing and improvements without the use of chronic living animal models, which allow for nuerohumoral responses, tissue remodeling, activation of regulatory proteins, and changes in genetic phenotype. Furthermore, mock circulation models use lump total systemic compliance which is significantly lower than aortic compliance[58]. The lower value of lumped systemic compliance would artificially augment pressure pulsatility, which may lead to reports of up to 61 mmHg of pressure pulsatility with less than 5 L/min of flow pulsatility [24]. In our study, we minimized this effect by having a large compliance element with low flow resistance near the aortic root. This enabled a close approximation of physiologic aortic compliance and approximately 20 mmHg pressure pulsatility with synchronous LVAD modulation amplitudes of ~9 L/min, as predicted by computer simulation results. Similarly, animal models have significantly different aortic and arterial compliance values than humans [59]. These altered compliance values would lead to an inaccurate estimation of aortic pressure pulsatility, **Figures 9, 20, and 27**. Further, in-vitro mock circulation systems typically underestimate the

reduction in left ventricular peak pressures due to pneumatic/hydraulic drivers, which may lead to inaccurate estimation of LVEW. In this study, three levels of ventricular contractility were used to mimic the reduced ventricular contractility. However, in this mock circulation study, fixed ventricular contractility may have resulted in higher calculated LVEW during counter pulsation LVAD RPM modulation which resulted in lower stroke volumes than co-pulsation LVAD RPM modulation but similar peak pressures.

The computer model assumed ideal valves that open and close instantaneously, Newtonian blood, a constant diastolic ventricular compliance, does not account for inertial or gravitational effects, and the effects of wave reflection. The mock circulation model overcame these limitations as it accounted for variable diastolic ventricular compliance, inertial and gravitational effects, and the effects of wave reflection. Further, the mock circulation model used mechanical valves which model realistic valve opening and closing times. However, mechanical valves resulted in ringing during valve closure, which was filtered out during analysis. The animal experiments had native valves with realistic opening and closing without any valve ringing. The mock circulation used a mixture of plasmalyte solution and water, which is also a Newtonian fluid. However, at these high velocities, blood acts as a Newtonian fluid. The ventricular contractility in the mock circulation model is not affected by the degree of ventricular unloading. We

tried to overcome this limitation by manually reducing the ventricular contractility. However, a more accurate ventricular volume dependent contractility was achieved in the computer simulation and animal experiments.

Modulation of CF LVAD RPM would increase power consumption and bearing wear which may be minimized in using the HeartWare HVAD, a magnetically suspended CF LVAD. This study only reports the results using the HeartWare centrifugal HVAD LVAD. Pump inertia, friction, and loading profiles will vary from pump to pump and affect the relationship between RPM modulation and flow modulation and the resulting power consumption. The rpm modulation needed to achieve specific levels of flow modulation will be different for each device which can be calculated from the pump models.

The mock circulation only represents systemic circulation as it was only intended to test a LVAD and not a right ventricular assist device or bi-ventricular assist device. To test flow modulation to these other devices, a pulmonary circulation must be added. The instrumentation used to record hemodynamics possesses inherent errors (pressure error = ±1mmHg, flow errors = ±0.5L/min) which the authors attempted to minimize by using GLP compliant test equipment and calibration techniques.

Comparison of Computer Simulation and Mock Circulation Results

Both computer simulation and mock circulation experiments showed similar results when comparing non-modulation, synchronous modulation, and asynchronous modulated LVAD flow/RPM (**Figures 9, 20**). However, Inconsistencies were present during comparisons of computer simulation [44] and mock circulation results. Specifically, in the computer simulation, co-pulsation of LVAD flow resulted in increased LVEW while mock circulation results showed a decrease in LVEW from CF baselines. Additionally, counter pulsation LVAD flow modulation produced increased pulse pressures in the computer simulation and decreased pulse pressures in the mock circulation as compared to non-modulated LVAD flow. It is important to note differences in the study design of the experiments and specifically the LVAD used in each, which may have resulted in the described inconsistencies. In the computer simulation the LVAD was modeled as a flow source in order to allow for back calculation for various pump specific RPM for individual LVAD to produce simulated flows. Pump inertia, friction, and loading profiles will vary from pump to pump and affect the relationship between rpm/power modulation and flow modulation. The computer simulation was designed to be applicable to any pump that could produce the constructed flow waveforms under the pressure conditions. However, this did not allow for simulation of the heart ejecting through the LVAD as

various pumps would have differing resistances that were not present in the flow source. Conversely, in the mock loop studies the ventricle ejected through the pump. This difference may have resulted in the computer simulation showing increase in LVEW during co-pulsation LVAD flow modulation and the mock loop study showing a decrease in LVEW during co-pulsation LVAD RPM modulation.

Counterpulsing by modulating LVAD RPM resulted in smaller variation in flow as the native ventricular contraction caused a high flow during systole while high LVAD RPM increased flow during diastole, leading to a smaller variation in flow during the cardiac cycle compared to copulsation mode. This, combined with ejection through the aortic valve due to higher mock ventricular contractility may have produced the diminished pulse pressure present during counter pulsation LVAD RPM/flow modulation in the mock circulation experiments as compared to the computer simulations. In the mock circulation study, the ventricle ejected volume while the LVAD was operating in a low speed resulting in a much higher minimum aortic pressure than seen in the computer simulation. Additionally, in-vitro mock circulation systems typically underestimate the reduction in left ventricular peak pressures due to pneumatic/hydraulic drivers, which may lead to inaccurate estimation of LVEW and in this instance resulted in lower calculated LVEW in the mock circulation loop as compared to the computer simulation.

The computer simulation maintained precise control over mean, peak, and minimum LVAD flows. Conversely, the HVAD used in the mock loop studies could only control RPM and not specific flows. In mock circulation studies, co-pulsation and counter pulsation LVAD RPM modulation resulted in differing mean LVAD flow rates. In this case the two modulation timings could not be directly compared as they were in the computer simulation and may have resulted in varying degrees of change from non-modulated LVAD flow/rpm baselines. Furthermore, the computer simulation allowed for multiple pulse widths which enabled pure co-pulsation and counter pulsation LVAD flow modulation. The HVAD controller could only produce a 50% pulse width due to programming limitations and thus was not in "pure" co-pulsation or counter pulsation. **Figure 8** shows in computer simulations that synchronization with a 50% pulse width would yield decreased LVEW as compared to 40% pulse width during co-pulsation and increased LVEW compared to 60% pulse width during counter pulsation. Additionally, since the HVAD controller could not be triggered off of an ECG or pressure waveform, the controller was phased in and out of co-pulsation and counter pulsation modes by offsetting the LVAD cycle time (0.8 seconds) and the beat time (0.795 seconds) by 0.005 seconds. Future iterations of the HVAD controller will include ECG triggering and pulse width features.

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CHAPTER 4 – Pilot *in-vivo* ANIMAL STUDY

<u>Introduction</u>

Computer simulation and mock circulatory model testing are important steps in the development of LVAD control strategies. However, they cannot replace *in-vivo* animal testing and clinical trials as they cannot mimic neurohumoral responses, tissue remodeling, activation of regulatory proteins, or changes in genetic phenotype. Animal model testing is an important step in proving device and control strategy safety for the ultimate advancement to clinical therapy. However, normal animal models do not adequately simulate a human in heart failure to allow for efficacy testing. Thus, we present preliminary findings of LVAD RPM modulation in an ischemic bovine heart failure model and normal calf. We hypothesize that modulation of LVAD RPM will increase arterial pressure pulsatility and alter left ventricular pressures, volumes, and workloads. Further, the effect on the ventricle will be dependent on timing. We hypothesized that modulation of LVAD RPM will increase arterial pressure pulsatility and enable alteration of left ventricular pressures, volumes, and workloads. Further, we hypothesized that the magnitude of these effects on the native ventricle will be dependent on LVAD modulation timing. The objective of this pilot animal study

was to investigate the effects of LVAD RPM modulation on the ventricle and vasculature with varying modulation amplitudes, widths, and frequencies and compare the results to computer simulation and mock circulation results.

Methods and Materials

Animals

Male, mixed-breed calves (n=2) were used in this study. Heart failure was induced in the two animals using micro-embolization techniques and implanted with HeartWare LVAD 60-days later for LVAD RPM modulation testing while under anesthesia. The HeartWare HVAD centrifugal LVAD was used in this study. All animals received humane care and were handled in accordance with National Institutes of Health and the University of Louisville animal care committee guidelines. All experimental procedures were approved by the University of Louisville Institutional Animal Care and Usage Committee.

LVAD Controller

The LVAD controller was programmed to modulate LVAD RPM by engineers at HeartWare under the direction of the investigators (**Figure 25**). For the *in-vivo*

animal studies, the controller modulated the LVAD speed up and down by user given RPM steps around a user defined base speed. The HeartWare HVAD has pump defined speed limits of 1800 – 4000 RPM. The controller allowed for modulation periods with a minimum of 0.20 seconds in 0.01 second increases. The pump would be in high RPM (base RPM plus high RPM modulation amplitude) for the high RPM period and the low RPM (base RPM minus low RPM modulation amplitude) for the low RPM period. For example, if a high RPM period of 0.35 sec was chosen with an 1100 RPM modulation amplitude, a low RPM period of 0.4 sec with an 800 RPM modulation amplitude, and a base RPM of 2900, the pump would operate at 2100 RPM for 0.4 seconds followed by 4000 RPM for 0.35 seconds and then repeat the cycle. The complete modulation cycle would take 0.75 seconds. The controller also allowed for ECG-triggered modulation. Once the ECG signal went above a user defined threshold, the LVAD would operate through the modulation cycle and then wait for the next instance where the ECG threshold was exceeded before operating through the modulation cycle again.
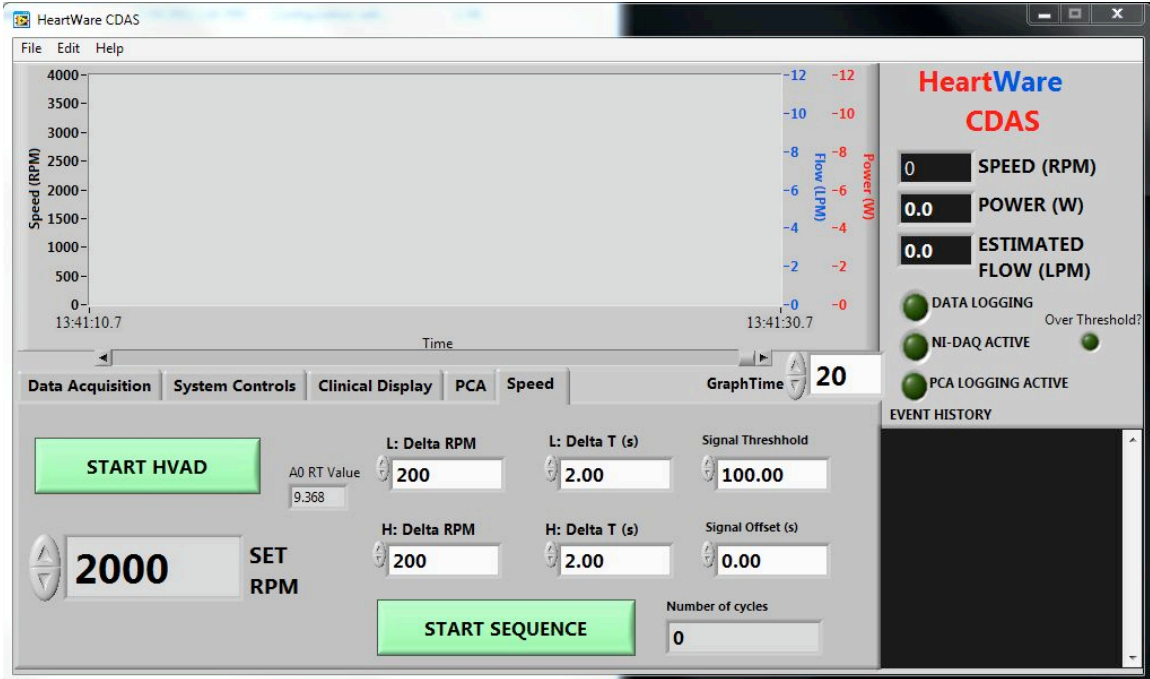
Figure 25: Screenshot of LVAD controller

Terminal Study

Sixty-days after micro-embolization (n=2) a terminal study was performed to measure the acute hemodynamic effects of LVAD RPM modulation. Anesthesia was induced and maintained in the proper fashion. The animal was placed on the operating table in right lateral recumbency. Fluid-filled arterial and venous catheters were placed in the left carotid artery and jugular vein for blood sampling. A left thoracotomy was performed. Ribs #4 and #5 were resected. The pericardium was opened and the LVAD implanted.

At the start of the LVAD RPM modulation experiment, a single-tip, high-fidelity micromanometer catheter (Millar Instruments, Houston,TX) was placed in the aorta and a dual pressure-volume conductance catheter (Millar Instruments, Houston, TX) was advanced from the left atrium across the mitral valve into the left ventricle for simultaneous measurement of aortic, left atrial, and left ventricular blood pressures. A transit-time ultrasonic flow probe (Transonics, Ithaca, NY) was placed around the pulmonary artery to measure cardiac output.

Data Reduction

All transducers were pre- and post-calibrated against known physical standards to ensure measurement accuracy. Calibration curves for the volume conductance catheter were constructed using static and dynamic tests pre- and post-experiment. Hemodynamic data were collected at 400Hz, signal conditioned, and A/D converted for digital analysis using our GLP compliant data acquisition system.

To determine the acute effects of LVAD RPM modulation, pressure and flow waveforms were used to derive heart rate, left ventricular end-diastolic pressure, left ventricular peak-systolic pressure, $\pm dP/dt$, mean aortic pressure, systolic aortic pressure, diastolic aortic pressure, aortic pulse pressure, HR x LVPpeak

systolic, a standard index of cardiac metabolic demand, pulmonary artery flow as an index of cardiac output, and CO normalized to animal weight. Hemodynamic indices were calculated on a beat-to-beat basis for each 30 second data set with the Hemodynamic Evaluation and Assessment Research Tool (HEART) program developed in Matlab (Version 6.5, MathWorks, Natick, MA). All analyzed beats in each data set (approximately 30 to 50beats/30 second data set) were averaged to obtain a single representative mean value for each calculated variable.

Preliminary Results

LVAD RPM modulation was tested in two animals. In one animal, no data sets of non-modulated flow were taken for comparison. In one animal non-modulated LVAD RPM (2900RPM) and counter pulsation LVAD RPM modulation were compared (2900±1100RPM) (mean RPM ± modulation RPM). Mean and diastolic coronary flows were increased 24% and 80%, respectively, during counter pulsation LVAD RPM modulation. However, systolic coronary flow was decreased by 30%. Aortic pulse pressure was increase from 2 mmHg at CF LVAD to 15 mmHg at counter pulsation LVAD RPM modulation. However, in these two cases, heart rate, mean LAVD flow, and cardiac output were 20% greater during LVAD RPM modulation than during non-modulated CF LVAD (**Table 7**). Additionally, ventricular volume was decreased during counter

pulsation LVAD RPM modulation as compared to non-modulated LVAD RPM (**Figure 26**). During asynchronous LVAD RPM modulation, pressures and volumes varied on a beat to beat basis and pulse pressure of up to 10 mmHg were achieved (**Figure 27**).

Condition	HR	SV	CO	VADF	LVPed	LVPpks	MAP	AoPpulse	CAFmean	CAFavgsys	CAFavdias
CF VAD 2900 RPM	70	66	4.6	4.4	8	34	44	2	163	143	163
Counter pulse 2900 + 1100	85	65	5.5	5.3	9	53	41	15	202	100	294
% change	20	-1	19	20	13	54	-6	793	24	-30	80

Table 7: Heart rate (HR), stroke volume (SV), cardiac output (CO), mean LVAD flow (VADF), left ventricular end diastolic pressure (LVPed), peak systolic left ventricular pressure (LVPpks), mean aortic pressure (MAP), aortic pulse pressure (AoPpulse), mean coronary flow (CAFmean), mean systolic coronary flow (CAFavsys), and mean diastolic coronary flow (CAFavdias) for CF LVAD and counter pulsation LVAD RPM modulation with same mean VADF.
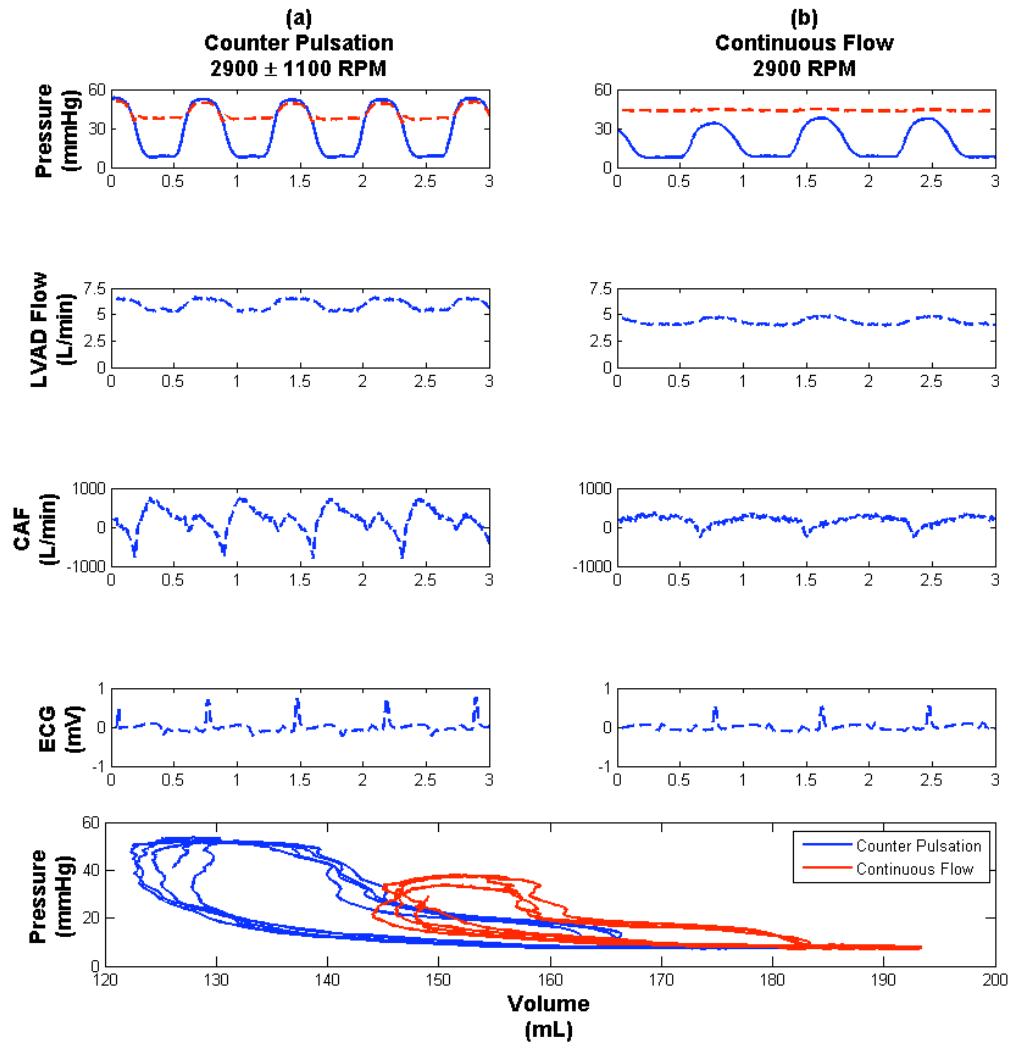
Figure 26: Aortic pressure, left ventricular pressure, LVAD flow, coronary artery flow (CAF), ECG, and pressure volume loops for counter pulsation LVAD RPM modulation (2900±1100RPM) (mean RPM ± modulation RPM) and non-modulated LVAD RPM (2900RPM).
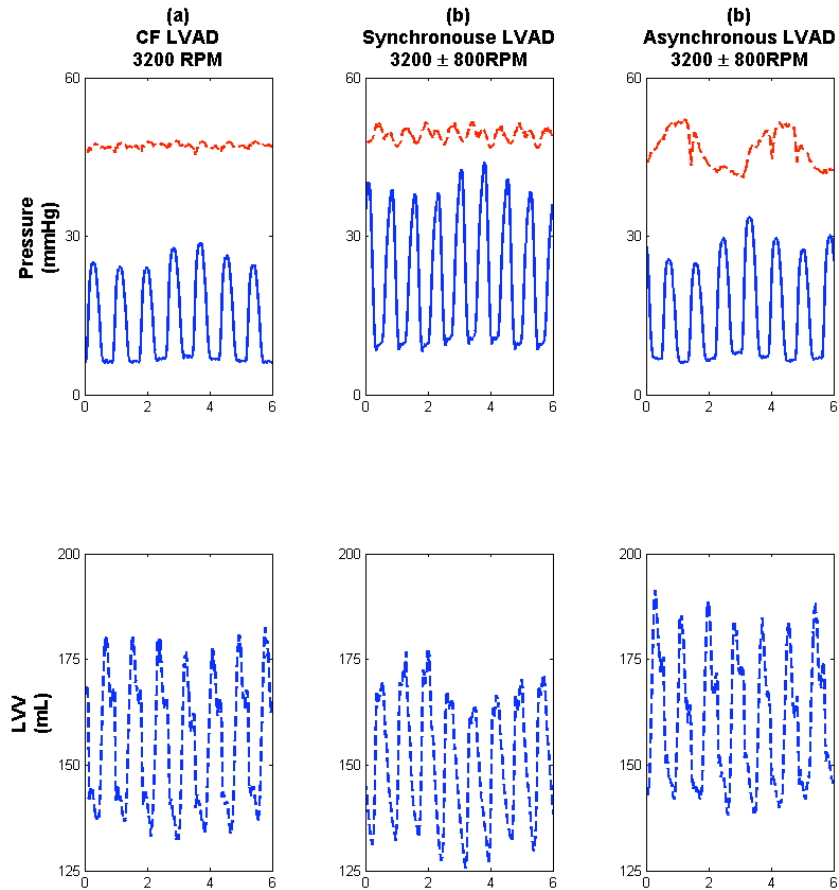
Figure 27: Aortic pressure, left ventricular pressure, left ventricular volume for Normal CF LVAD, Synchronous CF LVAD (3200±800RPM), and asynchronous CF LVAD (3200±800RPM) (mean RPM ± modulation RPM). Synchronous CF LVAD modulation increases AoP Pulsatility while maintaining consistent ranges of left ventricular pressure and volumes. Asynchronous CF LVAD modulation at 19 BPM increases pulse pressure over synchronous modulation while creating varying left ventricular pressure volumes.

Discussion

The pilot animal study produced similar results as the computer simulation and mock circulation studies in proving that LVAD RPM modulation can reduce left ventricular volumes and increase arterial pulse pressure. Additionally, animals studied showed increased pressure pulsatility with slow asynchronous LVAD RPM modulation.

Unfortunately, the hemodynamic state of the animal cannot be held constant through all measurement sets due to changes in medications, deterioration of the surgical preparation, loss of blood volume, and other factors. Further, full unloading was not always achieved with the calf model as the calf has a significantly higher cardiac output compared to humans. Thus, in **Figure 26** synchronous LVAD RPM modulation is only providing partial support, and thus results in a higher pulse pressure than non-modulated LVAD flow, which is fully unloading the ventricle. Additionally, **Figure 27** (a) CF LVAD 3200RPM and (c) Asynchronous LVAD 3200±800RPM are from a different animal than (b) Synchronous LVAD 3200±800RPM. These data sets were chosen as they were the only three cases of full support showing their respective LVAD RPM modulation. The initial pilot study is severely limited in its ability to show comparative results and draw definitive conclusions. However, we have shown

that preliminary findings in an *in-vivo* animal model produce similar results to those seen in computer simulations and mock circulation models.

Limitations

Animal models are not as stable of a testing platform as the computer simulation and mock circulation studies due to deterioration of the surgical preparation, effects of drugs, and variabilities in heart rates, ventricular contractilities and resistances due to physiologic and neurohormonal responses and other mechanisms. This results in increased variation between data sets and a diminished ability to directly compare data sets, which was minimized by collection of several intermediate baselines to facilitate comparisons. The acute animal model incorporates neurohumoral responses, and activation of regulatory proteins which are absent in the computer simulation and mock circulation studies. Animal models have significantly different aortic and arterial compliance values than humans [59]. Specifically, the calf model has a significantly higher compliance compared to humans. These altered compliance values would lead to a lower and inaccurate estimation of aortic pulse pressure due to LVAD modulation compared to computer simulation and mock circulation experiments, **Figures 9, 20, and 27**.

Modulation of CF LVAD RPM increased power consumption and potentially increases bearing wear which may be minimized in using the HeartWare HVAD, a magnetically suspended CF LVAD. This study only reports the results using the HeartWare centrifugal HVAD LVAD. Pump inertia, friction, and loading profiles will vary from pump to pump and affect the relationship between RPM modulation and flow modulation and the resulting power consumption. However the principles of RPM/flow modulation and increasing vasculature pulsatility is pump independent as evinced by the computer simulation study. The instrumentation used to record hemodynamics possesses inherent errors (pressure error = ±1mmHg, flow errors = ±0.5L/min) which the authors attempted to minimize by using GLP compliant test equipment and calibration techniques.

Conclusions

The results of this study establish that arterial pulsatility and ventricular work can be affected significantly by modulating CF LVAD flow. Arterial and ventricular hemodynamic waveforms were altered by varying the timing, amplitude, and width of the LVAD flow modulation pulse for the same average LVAD flow rates. Importantly, a range of LVEW and CoF values can be obtained for the same mean CF LVAD flow rate by altering the LVAD flow modulation without significantly affecting end-organ perfusion. Thus, these LVAD flow/RPM modulations may reduce the incidence of adverse events associated with the CF LVAD therapy by increasing vascular pulsatility and reducing vascular impedance. Further, these methods of LVAD flow/RPM modulation may enable tailored unloading of the native ventricle to provide rest and rehabilitation (maximal unloading to rest followed by gradual reloading to wean), which may promote sustainable myocardial recovery.

CHAPTER 5 - Works Cited

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60. Koenig, S.C., et al., *Hemodynamic and pressure-volume responses to continuous and pulsatile ventricular assist in an adult mock circulation.* ASAIO J, 2004. **50**(1): p. 15-24.

61. Giridharan, G.A., et al., *Physiologic control of rotary blood pumps: an in vitro study.* ASAIO J, 2004. **50**(5): p. 403-9.

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66. Koenig, S.C., et al., *Integrated data acquisition system for medical device testing and physiology research in compliance with good laboratory practices.* Biomedical Instrumentation & Technology, 2004. **38**(3): p. 229-240.

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69.   Ando, M., et al., *Electrocardiogram Synchronized Rotational Speed Change Mode in Rotary Pumps Could Improve Pulsatility.* Artificial Organs.

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Education

Future (*Fall 2011*)	University of Louisville School of Medicine Class of 2015
2010 – Present	University of Louisville JB Speed School of Engineering Master of Engineering Department: Bioengineering Concentration: Bioelectronics and Medical Devices
2005 – 2010	University of Louisville JB Speed School of Engineering Department: Bioengineering Bachelor of Science *With Honors*

Research Experience

August 2010 – Present	University Cardiothoracic Surgical Associates Mentors: Mark Slaughter, MD; Mike Sobieski, RN, CCP

- Research Associate for five ventricular assist device FDA trials (HeartWare HVAD (BTT & DT), Thoratec Heartmate II (BTT & DT), Worldheart Levacor)
- Research Associate for Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS)
- Research Associate for one stem cell and two mitral valve studies in conjunction with CTSN and NHLBI on an NIH funded grant.
- One of three team members contributing to the Society of Thoracic Surgeons National Database.

August 2008 – Present	Cardiovascular Innovation Institute Mentors: Mark Slaughter, MD; Steven Koenig, PhD; Guruprasad Giridharan, PhD

- Developed novel ventricular assist device control system (U.S. patent application 61/348,549, $100,000 proof of concept grant from the University of Louisville, support from HeartWare). Will be tested in both clinical approved and pre-clinical development stage device.
- Investigated short-term effects on cardiovascular circadian variation by continuous flow ventricular assist device. Data collection for long-term study is ongoing.

- Retrospectively investigated effects of obesity on ventricular assist device therapy.
- Performed under Good Laboratory Practice pre-clinical device testing in preparation for FDA IDE including assisting in review, analysis, and final report generation.
- Trained in instrumentation, data acquisition and analysis, and developing experimental protocols for acute and chronic device testing.
- Trained in in-silico computer modeling and in-vitro mock loop experimentation for prediction of hemodynamic effects of mechanical circulatory support devices.
- Trained in-vitro hemolysis testing for FDA IDE and 510K approvals.
- Trained in blood and tissue harvesting and histological and pathological assessment.
- Trained in blood coagulation experimental protocols including aggregometer and western blot tests.

January – August 2008   Microfluidics Lab
Mentor: Palaniappan Sethu, PhD

- Developed devices for single cell isolation using flow cytometry.
- Trained in cell culturing
- Trained in cell immunofluorescence

Peer Reviewed Publications

1. **Ising MS**, Warren SP, Slaughter MS, Koenig SC, Sobieski MA, Giridharan GA. Flow modulation algorithms for a continuous flow ventricular assist device to increase vascular pulsatility: A computer simulation study. *Journal of Cardiovascular Engineering and Technology*. 2011, p. 1 – 11.

2. Sobieski MA, Giridharan GA, **Ising MS**, Slaughter MS, and Koenig SC. Blood Trauma Test Methodology for Mechanical Circulatory Support Devices. *Biomedical Instrumentation and Technology*, *Accepted April 2011*

3. Slaughter MS, **Ising MS**, Tamez D, O'Driscoll G, Voskoboynikov N, Bartoli C, Koenig SC, and Giridharan GA. Increase in circadian variation after continuous flow ventricular-assist device implantation. *J Heart Lung Transplant*. 2010 Jun; 29(6):695-7. Epub 2010 Mar 5.

4. Coyle LA, **Ising MS**, Gallagher C, Bhat G, Kurien S, Sobieski MA, Slaughter MS. Destination Therapy: One-Year Outcomes in Patients with BMI Greater than 30. Artif Organs. 2010 Feb; 34(2):93-7. Epub 2009 Dec 7.

Abstracts in Peer Reviewed Conference Proceedings

1. **Ising MS**, Koenig SC, Sobieski MA, Slaughter MS, Giridharan GA. Flow Modulation Algorithms for Intra-Aortic Blood Pumps to Reduce Coronary Steal. To be presented at 2011 BMES Annual Meeting.

2. **MS Ising**, MD Rodefeld, SC Koenig, MA Sobieski, J Chen, SH Frankel, GA Giridharan. Computer simulation and mock circulation models of Fontan circulation for testing ventricular and cavopulmonary devices. Presented at the 57th Annual ASAIO Conference, Washington DC, 2011.

3. **Ising MS**, Slaughter MS, Birks E, Sobieski MA, Sherwood L, Hawes M, Stewart R, Bolt W, Koenig S. Pre-Clinical GLP Study of Impella 2.5 (Abiomed, Danvers, MA) for 5-Days Left Ventricular (LV) Support. Presented at the 57th Annual ASAIO Conference, Washington DC, 2011.

4. **Ising MS**, Warren SP, Slaughter MS, Koenig SC, Sobieski MA, Giridharan GA. Delivering Physiologic Pulse Pressures with Continuous Flow Ventricular Assist Devices. Presented at the 56th Annual ASAIO Conference, Baltimore, MD.

5. Sobieski MA, Giridharan GA, **Ising MS**, Slaughter MS, and Koenig SC. Methodology of hemolysis testing of mechanical circulatory support devices. Presented at the 56th ASAIO Conference, May 27-29, 2010, Baltimore, MD.

6. Slaughter MS, **Ising MS**, Tamez D, O'Driscoll G, Voskoboynikov N, Bartoli CR, Koenig SC, Giridharan GA. Reappearance of a normal circadian rhythm after ventricular assist device implantation. HFSA Conference, Boston, MA, 2009

7. Giridharan GA, **Ising MS**, Slaughter MS, Sobieski M, Koenig SC. Hemodynamic Responses to Pulsatile and Continuous Flow LVAD in an Ischemic Cardiac Dysfunction Calf. Presented at the 55th Annual ASAIO Conference, Dallas, TX, 2009.

Awards and Recognition

1. 2011 Outstanding Graduate Student Award - University
2. Herschede Engineering Award - International
3. American Society of Artificial Organs Young Innovator Fellowship - International
4. Alfred T. Chen Scholarship Award - University
5. Honorable Order of Kentucky Colonels
6. University of Louisville Honor Scholar
7. University of Louisville Honors Program
8. University of Louisville Honors Program International Travel Seminar
9. Sigma Chi Leadership Grant - International
10. University of Louisville Dean's List
11. Order of Omega Greek Honor Society
12. Tau Beta Pi Engineering Honor Society
13. Omicron Delta Kappa Leadership Honor Society
14. University of Louisville Trustees Academic Scholarship
15. Ambrake Scholarship - Local
16. Builder's Exchange Scholarship
17. University of Louisville Homecoming King Candidate
18. University of Louisville Mr. Cardinal Candidate

Extracurricular Activities

1. Sigma Chi Fraternity
   - Scholarship Chair, Social Chair, Assistant Pledge Educator, Greek Week Chair
   - Nominated for International Awards
        i. Order of the Scroll
        ii. Dr. George C. Ruhle Outstanding Scholar Award
2. Biomedical Engineering Society
   - President
3. UofL Dance Marathon
   - Executive Council
4. Student Government Productions
   - Executive Director
5. Soccer
   - Greater Louisville Soccer League Champions (2007, 2008, 2009)
   - Kentucky State Cup Runner-up (2006)
   - Six-time University Intramural Champion

Conferences Attended

1. American Society of Artificial Organs - 2009, 2010
2. Biomedical Engineering Society - 2009
3. Gordon Research Conference: Assisted Circulation - 2009
4. South Regional Orientation Workshop - 2007, 2008
5. American Medical Student Association Conference - 2007

Societies

1. Sigma Chi Fraternity
2. Order of Omega Greek Honor Society
3. Tau Beta Pi Engineering Honor Society
4. Omicron Delta Kappa Leadership Honor Society
5. Biomedical Engineering Society
6. American Society of Artificial Organs

Service to University

1. Student Orientation Staff
2. UofL Parking Appeals Committee - Student Representative
3. CAPS Mentor
4. Freshman Honors Guide
5. Prospective Student Shadow Host
6. UofL "First Look" - Student Representative
7. UofL Honors Accolade - Volunteer
8. Brown Fellows Interview - Student Representative
9. South Regional Orientation Workshop - Volunteer

Service to Community

1. UofL Dance Marathon
2. Wrap Up America
3. Big Brothers, Big Sisters
4. University Child Health Specialists Literacy Program
5. St. Joseph's Orphan's Picnic
6. Wrap Up Louisville
7. Best of Louisville Bash