DEVELOPMENT OF A MINIMALLY INVASIVE DEVICE BASED THERAPY INCORPORATING SIMULTANEOUS ADJUSTABLE PASSIVE SUPPORT AND SYNCHRONOUS ACTIVE ASSIST DESIGNED TO TREAT CONGESTIVE HEART FAILURE

A Dissertation

by

MICHAEL R. MORENO

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2009

Major Subject: Biomedical Engineering

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May 2009

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ABSTRACT

Development of a Minimally Invasive Device Based Therapy Incorporating Simultaneous Adjustable Passive Support and Synchronous Active Assist Designed to Treat Congestive Heart Failure. (May 2009)

Michael R. Moreno, M.S., M.S., B.S., Florida International University

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The technology described herein is a device based therapy targeting recovery of cardiac function in patients with congestive heart failure. This represents a shift in the present paradigm wherein available treatment options conservatively target inhibiting disease progression, e.g. non-adjustable cardiac support devices and/or alleviating symptoms, e.g. blood pumps for circulatory assist. Specifically, the innovation is a minimally invasive device incorporating adjustable passive cardiac support and synchronous active cardiac assist – device based technology designed to provide rehabilitative physical therapy for the heart muscle, mediating restorative remodeling processes to facilitate recovery of cardiac function. CHF affects more than 5.3 million people in the U.S. with 550,000 new cases diagnosed each year. For 300,000 Americans in end-stage failure, transplant is the preferred treatment; however, with less than 3,000 hearts available this treatment plan is epidemiologically trivial. The development of a therapeutic option targeting *recovery of cardiac function* would be a substantial advancement in the

treatment of heart failure, and consequently a great benefit to the healthcare economy, biomedical science, and society as whole.

Device performance was assessed in an acute implantation in an ovine model of acute heart failure (esmolol overdose). In the study it was confirmed that the device which was designed to be collapsible into a 1 ½" diameter deployment tube and could be deployed using minimally invasive procedures. In examining pressure-volume loops, it was confirmed that the passive component of the device enabled a leftward shift in the end-diastolic pressure-volume relationship; important as disease typically shifts this relationship to the right. Further, it was verified that the active component of the device was capable of restoring stroke work lost in the esmolol induced failure model. Finally, the device did not invert the curvature of the heart, did not interfere with normal cardiac function, and remained in place through an intrinsic pneumatic attachment and thus did not require tethering to the myocardium. The versatile combination of support and assist provide the cardiologist with powerful therapeutic options to treat a wide variety of patient specific anomalies – with the primary target, rehabilitation of the heart and recovery of cardiac function and performance.

DEDICATION

This work is dedicated to my two beautiful children - my son, Matthew, and my daughter, Erica. In them, their young spirits, and inquisitive minds, I find great inspiration. Though they are as yet too young to understand what I've been going through these past few years – I know one day they will. And I hope, when that day comes, they will also understand how much I love them and how much I appreciate their support and faith in me.

ACKNOWLEDGEMENTS

I simply cannot adequately express the gratitude that I feel for my graduate advisors Dr. John C. Criscione and Dr. James E. Moore Jr., without whom none of this would have been possible. Both men are brilliant in their own respect and have given much to the field of biomedical engineering. Dr. Criscione provided a magnificent opportunity for me to work under his guidance in the pursuit of my doctorate. He has been an invaluable source of wisdom and inspiration. I have the utmost respect for him as a man of great integrity and passion. Our philosophical discussions about life have been as important to my development as my training in mechanics. Consequently, he has become more than a mere academic advisor to me. For all he has given I am eternally grateful. Dr. Moore saw potential in a 'second career' undergraduate, and provided great opportunity for me to explore possibilities I didn't even know existed. He subsequently served as my masters' thesis advisor and continues to open doors for me, academically and professionally. The bulk of my present achievements have been accomplished working under his guidance. He remains a valuable source of counsel and a close personal friend. For all he has given, I am eternally grateful. I would also like to thank my committee members, Dr. Cote, Dr. Miller, and Dr. Hyman, for their guidance and support throughout the course of this research. Finally, I would like to thank my brother Tony for his financial and moral support throughout my long and winding academic career. I'm sure some may have questioned such a high risk investment, but for some reason he's always believed in me. And for that, I am again, eternally grateful.

NOMENCLATURE

ACE	Angiotensin-Converting Enzyme
ACSD	Adjustable Cardiac Support Device
AMI	Acute Myocardial nfarction
AoP	Aortic Pressure
BPM	Beats Per Minute
CABG	Coronary Artery Bypass Surgery
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
CRI	Constant Rate of Infusion
CSD	Cardiac Support Device
CVP	Central Venous Pressure
DCCD	Direct Cardiac Compression Devices
ECG	Electrocardiogram
ED	End-Diastolic
EDP	End-Diastolic Pressure
EDPVR	End-Diastolic Pressure Volume Relationship
EF	Ejection Fraction
EPC	Endothelial Progenitor Cells
ES	End-Systolic
FDA	Food and Drug Administration

HR	Heart Rate
IABP	Intra-Aortic Balloon Pump
IV	Intravenous
LV	Left Ventricle or Left Ventricular
LVAD	Left Ventricular Assist Device
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MPC	Mesenchymal Precursor Cells
MR	Mitral Regurgitation
NYHA	New York Heart Association
OPTN	Organ Procurement and Transplantation Network
PCCS	Postcardiotomy cardiogenic shock
Ped	End-Diastolic Pressure
Pes	End- Systolic Pressure
PGA	Polyglycolic Acid
PLA	Polylactic Acid
PMA	Pre-Market Approval
Pmax	Maximum pressure
Pmin	Minimum pressure
PV	Pressure-Volume
RV	Right Ventricle or Right Ventricular

SAVR	Surgical Anterior Ventricular Restoration
SV	Stroke volume
SW	Stroke work
TNF	Tissue Necrosis Factor
VAD	Ventricular Assist Device
Ved	End-Diastolic Volume
Ves	End-Systolic Volume
Vmax	Maximum volume
Vmin	Minimum volume
VSD	Ventricular Septal Defect

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1. INTRODUCTION: CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a major public health issue in the "developed world" and an emerging health problem in the "developing world". CHF affects more than 5.3 million people in the U.S., with 550,000 new cases diagnosed each year. The associated mortality rate is about 40% within 2 years of diagnosis; patients with the most advanced stages of disease have a one-year mortality rate that exceeds 50%. Treatment is expensive with costs that are escalating. Approximately 20% of hospitalizations are due to acute CHF, incurring a health-care system cost of $34.4 billion [1]. Total inpatient and outpatient medical costs have been estimated to be in excess of $50 billion per year [2].

1.1 Progression of Congestive Heart Failure

CHF has a complex etiology and is a progressive disorder thought to be initiated by some index cardiac event. Coronary artery disease precipitates approximately 70% of CHF cases. Acute myocardial infarction (AMI) due to obstruction of a coronary artery is a common initiating event that can ultimately lead to heart failure. The hemodynamic and symptomatic states of the patient worsen over time causing further damage despite the absence of additional clinically apparent adverse events [3].

This dissertation follows the style of *ASME Journal of Medical Devices.*

One of the major maladaptive changes after a major heart attack or cardiac event is an initial decline in pumping capacity of the heart. This leads to the activation of a variety of compensatory mechanisms, and subsequently, a phenomenon known as cardiac or left ventricular (LV) remodeling (i.e. a geometrical change in the architecture of the left ventricle) and aberrant cardiac motion. LV remodeling is a progressive phenomenon characterized globally by changes in LV chamber size and shape. There are also implications at the cellular level, i.e. ongoing loss of cardiomyocytes, myocyte hypertrophy and interstitial fibrosis [4, 5]. LV remodeling dramatically alters the mechanical environment, which in turn influences growth and remodeling processes. Thus, a positive feedback loop emerges leading to acute dysfunctional cardiac pumping, pathologic neurohormonal activation, and the inability of the remodeled LV to respond appropriately to compensatory mechanisms. Ultimately, this leads to a stage where the aggregate end-organ changes that occur within the cardiomyopathic ventricle progress to the point that no amount of neurohormonal stimulation can maintain cardiovascular homeostasis. At this point heart failure may progress independent of the neurohormonal status. Considering the strong role of LV remodeling in promoting a maladaptive cardiac geometry, preventing or reversing remodeling has emerged as an important target in the treatment of CHF [6].

1.2 Pathophysiology of Left Ventricular Remodeling in Heart Disease

As the disease progresses there is a change in the shape of the ventricle from a prolate ellipse to a more spherically shaped ventricle [7]. This transformation from elliptical to spherical shape and associated functional changes are directly related to future deterioration in LV performance and less favorable clinical outcomes in patients with heart failure [8-11]. Clinical data provides increasing evidence that LV remodeling can contribute to the progression of heart failure by virtue of the de novo mechanical and energetic burdens that are created by the physiologically unfavorable changes that occur in the remodeled ventricle [12]. As the load on the ventricle at end-diastole contributes importantly to the afterload that the ventricle faces at the onset of systole, any dilation of the LV will increase the work of the ventricle leading to increased oxygen utilization. Apart from the increase in LV end-diastolic volume, LV wall thinning also occurs. Thus increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional "afterload mismatch" that may further contribute to a decrease in forward cardiac output (CO), [13-16]. Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium with resultant worsening of LV function [17-19], as well as increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (e.g. TNF – tissue necrosis factor, interleukin-1).

Progressive LV dilation and subsequent remodeling is one of the mechanisms that lead to LV wall stress and myocardial stretch [20, 21]. Increased LV wall stress may lead to sustained expression of stretch-activated genes (angiotensin II, endothelin and tumor necrosis factor) [22-24] and/or stretch activation of hypertrophic signaling pathways as stretch triggers myocyte responses both by inducing the release of humoral factors that are important in the initiation and maintenance hypertrophy, as well as via the direct activation of the relevant signaling pathways [12, 25]. All these changes lead to desensitization of the cardiovascular system to normal homeostatic mechanisms.

LV dilation and increased LV sphericity are also sensitive indicators of poor long-term clinical outcome [9, 26]. For the sake of simplicity, cardiac wall stress can be related to the ratio of the product of pressure in the ventricles and ventricular radius, to the ventricular wall thickness [27]. So with LV remodeling and an increase in ventricular volumes and a subsequent increase in ventricular radius, a larger force is required from each individual myocyte to produce enough pressure in the ventricles, thus wall tension is seen as a function of both internal pressure and vessel radius. Also with ventricular remodeling, cardiac mass can increase, with associated changes resulting in ventricular wall thickness [28]. Any such thickness increase would result from remodeling at the cellular/extracellular matrix level by several processes including myocyte hypertrophy, cell slippage, and interstitial growth. However, such a wall thickness increase does not adequately compensate for the increase in wall stress resulting from cardiac chamber

dilation [29] with an increasing metabolic stress. Thus, ventricular remodeling is maladaptive, despite any incremental increase in ventricular wall thickness.

1.3 Mitral Regurgitation as a Consequence of Ventricular Remodeling

Increased LV size and chamber sphericity are major determinants of functional mitral regurgitation (MR); a condition which depending on its severity can have a major impact on reducing LV stroke output which is already impaired in heart failure. As heart failure progresses, remodeling of the left ventricle causes the papillary muscles (which support the mitral valve leaflets) to stretch out of shape and the valve annulus to enlarge, causing the valve to leak leading to mitral regurgitation. Mitral regurgitation (MR) is associated with a poor prognosis [30-33]. Recent interest has focused on “functional” or secondary MR in which the valve leaflets are anatomically normal but do not fully coapt because of annular dilation and restricted leaflet motion secondary to increased left ventricular (LV) size and sphericity [34-35]. According to the American Heart Association, around 95,000 people undergo heart valve surgeries in the US annually. Additionally we estimate (i.e., prevalence of CHF minus fraction with diastolic dysfunction, quantity halved) that there are nearly 2,000,000 U.S. patients with CHF and mitral regurgitation, and we assume that most have not been treated surgically because the risks of the current procedure are deemed too high. The high risk of postcardiotomy cardiogenic shock is one of the limiting factors of the open heart procedures in patients with moderate to advanced heart failure.

2. CONCEPTUAL MODELS OF HEART FAILURE

In the last few decades several clinical models have been developed in an attempt to describe and investigate the underlying mechanisms associated with the progression of heart disease. These include but are not limited to a cardiorenal model, a hemodynamic model, and a neurohormonal model. Though these models explain some aspects and/or symptoms in heart failure patients; none of these models explain the relentless "disease progression" that occurs.

2.1 Summary of Traditional Models of Heart Failure

Initially, CHF was seen as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow also known as the “cardiorenal model” [36]. Better quantification of hemodynamic parameters by clinicians led to an understanding that heart failure was associated with a reduced cardiac output and excessive peripheral vasoconstriction and led to the development of the “cardiocirculatory” or “hemodynamic” model [36] for heart failure. Thus, although the cardiorenal models provided the rational basis for the use of diuretics to control the volume status of patients with heart failure, and the cardiocirculatory model provided the rational basis for the use of inotropes and intravenous vasodilators to augment cardiac output, these therapeutic strategies have not prevented heart failure from progressing, nor have they led to prolonged life for patients with moderate to severe heart failure [36, 37].

The advent of ACE (angiotensin-converting enzyme) inhibitors and beta blockers has dramatically changed the way in which we conceptualize heart failure. Various studies and clinical trials have provided data and have led to both experimental model systems and clinical trials which suggest that both types of therapy may prevent the progression of pump dysfunction that characterizes the natural history of heart failure and may halt or even reverse the progressive cardiac dilatation that occurs as heart failure progresses. These observations have led to a point of view that heart failure should be viewed as a "neurohormonal model" in which heart failure progresses as a result of the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation [38]. Although the aforementioned models explain some of the mechanistic aspects and disease symptoms in the heart failure patients, they fail to provide a compelling explanation for the relentless "disease progression" toward ultimate total failure.

2.2 The Biomechanical Model of Heart Failure

The "biomechanical model" as developed by Mann and Bristow [12] explains the resistance to optimal therapy in end stage patients. There is increasing evidence of an important relationship between myocardial systolic dysfunction and cardiac remodeling in the development and progression of heart failure. This evidence suggests that heart failure can be described via a biomechanical model. A key aspect of the biomechanical model is the explanation of the resistance to optimal therapy in end stage patients. One

important departure of the biomechanical model from the neurohormonal model is that *the biomechanical model predicts that at some point heart failure will progress independently of the neurohormonal status of the patients*. Thus, when the deleterious changes in cardiac function and cardiac remodeling are sufficiently advanced, they become self-sustaining and hence are capable of driving disease progression independently of the neurohormonal status of the patient. This may help to explain, at least in part, why conventional neurohormonal strategies lose effectiveness in end-stage heart failure [39] as well as why many device-based therapies that concurrently affect LV pump performance and LV remodeling (e.g., cardiac resynchronization) are beneficial [12], often in ways that extend beyond the therapeutic intent of the design.

Though the biomechanical model provides a new insight into the way the problem is approached, it does not obviate the importance of the cardiorenal and hemodynamic models, or neurohormonal activation in the onset of heart failure. Rather it extends the insights provided by focusing the treatment of heart failure on the downstream biological consequences of neurohormonal activation rather than on the neurohormonal activation itself. From this perspective, evidence suggests that future therapies should be targeted more at alleviating the adverse biological consequences of neurohormonal activation, along with the treatment of the patient symptoms with diuretics and digitalis.

3. MECHANICS AND MECHANOBIOLOGY IN CHF

The heart is essentially a biomechanical pump and the important pillars of biomechanics i.e. force (i.e., stress) and motion (i.e., strain) play a fundamental role in the mechanobiology and development of physiological and pathological states. The understanding of the influence of mechanical stimuli on biological processes such as growth and remodeling is at a very early stage and their application in unraveling the mechanisms of disease process needs to be explored more innovatively and is crucial to understanding cardiovascular diseases and treatments.

It is well established that mechanical stimuli (e.g., stress or strain) are important epigenetic factors in cardiovascular development, adaptation, and disease [40-42]. Mechanical cues are known to play an important role in cardiogenesis, morphogenesis [42], and stem cell fate in general [43]. In the vasculature, it appears that perturbed loading conditions heighten the turnover of cells (proliferation and apoptosis) and matrix (synthesis and degradation) in altered configurations, thus resulting in altered geometries, properties, and biologic function [44]. Just as similar mechanisms appear to be operative in hypertension, aneurysms, and micro-gravity induced changes, it is likely that they are operative in cardiac disease [45]. Myocytes are very sensitive to perturbations in strain and respond with altered gene expression [46, 47]. Cellular and subcellular investigations have established that altered hemodynamic loading leads to growth and remodeling of myocytes and extra-cellular matrix [48-51]. Characteristics of

CHF include but are not limited to loss of myocyte shortening capability [52, 53], calcium dysregulation [54, 55], and unspecified myocyte apoptosis [56, 57]. Myofibrillar organization [58], sarcomere alignment [59], and cell migration [60] are all known to be mediated by mechanical factors. Stem cell differentiation and function are also known to be regulated by mechanical signals [43]. And there is precedence of cardiovascular therapy based on controlled induction of remodeling processes by strategic manipulation of mechanical factors [61].

Dyskinesis or aberrant motion of the myocardium during contraction is likely important in all diseases of the heart that involve remodeling of the myocardium. Abnormal cardiac kinematics is often considered as a symptom of heart failure when in actuality it may be a primary cause of the aberrant growth and remodeling. Cardiac muscle fiber alignment can be highly disorganized in the failing heart and disrupted by fibrosis. The afflicted region is highly dyskinetic exhibiting abnormal motion and mechanics [62]. Clearly, borderzone myocardium is viable [63] yet overloaded to the extent that it is dyskinetic, i.e., lengthens when it should shorten. It is likely that overloading leads to aberrant remodeling because (see review by Kherani [64]) offloading leads to: normalization of genes that regulate calcium handling [65], tumor necrosis factor [66] and cytoskeleton proteins [67]; regression of fibrosis and cellular hypertrophy [68, 69], and improved in-vitro contractile function [70]. Too much offloading is suspected to result in heart atrophy [64]. In treating aberrant strain patterns it is possible that the growth and remodeling will stop being abnormal and start being restorative. Eliminating

hypokinesis, for example, may reduce apoptosis, enhance myocyte development from native stem cells [43], and lead to ventricular recovery. Moreover, reverse remodeling has been reported in some patients receiving pump type left ventricular assist device (LVAD) implants, suggesting that mechanically induced reverse remodeling is possible if the appropriate conditions are established [71]. Herein it is proposed that by minimizing or eliminating aberrant strain patterns and strategically manipulating the mechanical environment, it is possible that normal growth and remodeling processes can be directed toward cardiac restoration and rehabilitation. Just as mechanical stimuli lead to adverse remodeling, appropriate mechanical stimuli may lead to recovery.

The role of mechanical therapy for treating heart disease is just beginning to be investigated. Given the significant role of stress/strain in cardiovascular disease; there is a need for devices designed to mediate the strain field and mechanical environment about the myocardium.

4. PRESENT TREATMENT OPTIONS FOR CHF

There are multiple classes of solutions for treating heart failure: pharmaceuticals, stem cells, electrical devices, mechanical devices, and surgical reconstruction. Each of these is successful at their target action (i.e., beta-blockade, ACE inhibition, electrical pacing, cardiac assist, etc); yet heart failure remains a cause of tremendous morbidity and healthcare burden. Pharmacological therapy is improving, yet many patients still reach end-stage failure and there are too few donor hearts available. A significant publication [72] of the Randomized Evaluation of Mechanical Assistance for the Treatment of CHF (REMATCH) trial states: "Patients with mild-to moderate heart failure [73] and, recently, some with more severe disease [74] have been shown to benefit from drug therapy. Nevertheless, the survival and the quality of life of patients with severe heart failure remain limited. Cardiac transplantation is the only treatment that provides substantial individual benefit, but with fewer than 3,000 donor hearts available worldwide per year, its impact is epidemiologically trivial [75]." To mitigate the disparity between the number of available donor hearts and the number of patients in need of a heart transplant (estimated at 300,000; [76]), the transplant waiting list has stringent guidelines. Consequently, most patients who are in need of a transplant are not qualified to be placed on the waiting list. Thus, there is great need for treatment options that can restore function to failing hearts.

4.1 Device Based Therapies

Current therapies for New York Heart Association (NYHA) Class II-IV patients, such as medical management with renin angiotensin/aldosterone system antagonists, beta-blockers, coronary artery bypass grafting (CABG), mitral valve repair and bi-ventricular pacemakers have limitations and none specifically address cardiac remodeling, which is a fundamental pathophysiologic mechanism of heart failure [77-81].

Mechanical heart assist devices can be classified into active devices that provide pumping energy, and passive devices that modulate the shape of the heart. The active devices are subdivided into blood pumps (like the DeBakey, Jarvik, Heart Mate), counter pulsation assist devices (aortic balloon pumps), and direct cardiac compression devices or DCCDs (Anstadt cup). The passive devices (CorCap, Heartnet, Myosplint, etc.) directly interact with the heart to change shape or limit growth.

4.2 Active Circulatory Assist Devices

There are numerous histories of artificial hearts and heart assist devices [4, 82, 83]. We focus on direct cardiac compression devices (DCCD) and diastolic support devices. The other therapies i.e., drugs, biventricular pacing, stem cell therapies, blood contacting assist devices, surgical manipulations, or passive stents and constraints, etc., typically off-load the heart and thus only modulate the strain pattern indirectly (e.g., through

greater ejection fraction). Only DCCDs can directly induce a particular strain pattern. However, prior DCCDs have been developed for enhancing ejection fraction or for ease of implantation rather than for strain modulation. All, in fact, induce aberrant strain patterns during contraction. The Anstadt cup and Cardio-Support System invert curvature in long axis planes yet preserve curvature in the short axis planes. The AbioBooster, DCC Patch, Hewson device, and Parravicini device pull on the interventricular sulci and push on the freewall such that the curvature will increase at the sulci and decrease on the freewalls. The Heart Booster inverts curvature in short axis planes, yet preserves curvature in the long axis planes. Since they were not designed to eliminate aberrant motions, it should not be surprising that prior DCCDs induce aberrant strain patterns. Presently the passive support devices, e.g. CorCap (ACORN Cardiovascular, St. Paul, Minnesota), purely work in the area of modulating the wall stress, but do not provide any systolic actuation or modulation of strain pattern.

Even though long-term assist enhances survival and quality of life, we can and must do better. In particular, some patients will experience signs of recovery (ventricular recovery) while mechanical assist is provided (see Rose and Frazier [71] for an overview). Combination of drug treatment and mechanical assist is even more promising [84]. Ventricular recovery is needed and is possible. Fortunately, many researchers are addressing ventricular recovery with different approaches (e.g., surgical, drug, and gene therapy, stem cells and/or tissue engineering. It is hypothesized that stress and strain pattern modulation plays a central role in myocardial growth, remodeling, and recovery.

If pharmacotherapy or traditional assist devices do not eliminate aberrant motion and forces (through indirect control of strain via such mechanisms as afterload reduction); then a device that does modulate stress and strain is clinically needed. Given that stress and strain are an important stimulus of myocardial growth and remodeling there is a need for a device eliminates dyskinetic or hypokinetic motions in the heart and modulates the wall stress to prevent LV dilation and sphericalization.

4.3 Passive Cardiac Support and Constraint Devices

Progressive LV remodeling is considered to be the one of most fundamental aspects of heart failure progression. At this point, two devices, CorCap (Acorn Cardiovascular) and HeartNet (Paracor Surgical Inc.) are in human clinical trials; this highlights the need for new technologies targeting LV remodeling with passive ventricular restraint devices. The CorCap Cardiac Support Device (CSD) is a mesh device that is implanted around the heart to reduce wall stress and the first therapy specifically designed to address LV remodeling. CorCap is closest to market today and has established, through preclinical and clinical studies, the concept of LV remodeling as a device therapy target. Below are some details from CorCap preclinical and clinical studies.

In a dog model of heart failure, animals that received the CorCap CSD demonstrated a significant decrease in left ventricular end diastolic volume (LVEDV, $p < 0.05$) and an increase in left ventricular ejection fraction (LVEF, $p < 0.05$) [85]. In a dog model of heart failure, animals that received the CorCap CSD showed improved cardiomyocyte

contraction and relaxation, down-regulation of stretch response proteins, and increased affinity of the pump for calcium [86]. In an ovine model of heart failure, the CorCap CSD implant maintained or reduced heart size and increased LVEF, fractional shortening and peak positive dP/dt [87]. In sheep with heart failure produced by ligation of coronary arteries, thus causing only mild dilation, consistent findings of reduced ventricular size and improved ventricular function were also reported [88].

Early clinical studies have shown that the CSD is safe and associated with improvements in LV structure and function and patient symptoms. The CorCap was studied in the largest prospective randomized multi-centered trial of a surgical device ever completed. From a total of 300 recruited patients, a subgroup of 193 patients were enrolled in the mitral valve repair or replacement stratum of the Acorn Clinical Trial; 102 patients were randomized to the mitral valve surgery alone group (control) and 91 patients were randomized to mitral valve surgery with implantation of the CorCap cardiac support device. Patients were followed for a median duration of 22.9 months. The study demonstrated both safety and effectiveness of the CorCap in patients with advanced heart failure and remodeled ventricles. Patients treated with the CorCap Cardiac Support Device had significant reductions in LV end diastolic volume (average difference 18.8 mL; $p = 0.005$) and LV end systolic volume (average difference 15.6 mL; $p = 0.013$) compared with the control group. Sphericity index was significantly increased in the treatment group (average difference 0.045 units; $p = 0.018$). These changes were maintained over three years of follow-up. The improvements in LV size and shape were

observed when the CorCap was implanted concomitantly with mitral value surgery or by itself.

Evidence from studies of cardiomyoplasty, suggest that passive mechanical constraint may halt or even reverse remodeling of the dilating heart. Moreover, passive cardiac constraint has been shown to reduce cardiac enlargement and functional deterioration. Results from studies employing current cardiac support devices (CSD) have shown promise and advanced understanding of mediating mechanical factors associated with the progression of heart failure. Present CSD, e.g. CorCap and Heart-net, are designed to provide mechanical constraint and support of an enlarged myocardium; they are not adjustable following implant and are not designed to pro-actively treat the concomitant reduction in cardiac output associated with hypertrophy. Moreover, these devices are designed to fibrose to the heart surface to stabilize the device-heart interaction. The ability to adjust the device following implant provides a proactive means to constrain and gradually reduce hypertrophy in the diseased heart. The ability to provide active assist ensures cardiac output can be maintained at nominal levels during treatment. Collectively, these qualities provide a means for stimulating cardiac remodeling events under conditions that are restorative toward full cardiac rehabilitation.

Existing cardiac assist devices do not address the idea that the mechanical environment can be pathologic, and thereby provide erroneous signals that in turn stimulate aberrant or pathologic remodeling in otherwise healthy tissues. Device based therapies that better target the pathologic mechanical environment may stimulate development processes, i.e.

growth and remodeling processes that are restorative in nature and thereby ultimately, facilitate the recovery of mechanical organs.

5. CARDIAC RECOVERY AND REHABILITATION: SHIFTING THE PARADIGM OF DEVICE BASED THERAPIES FOR CHF

Though scientific journals and undergraduate textbooks offer insurmountable evidence that mechanical factors influence growth and remodeling of biologic tissues, one need not turn to such literature to be convinced that this is indeed the case. For thousands of years it has been understood that a physical conditioning regimen could be employed to increase muscle mass and tone, as well as improve cardiopulmonary efficiency. This perception persists as evidenced by modern understanding of the importance of maintaining a healthy lifestyle, wherein personal physical fitness has been popularized. Thus, to establish cause and effect between mechanical factors and the growth and development of biologic tissue one need only to carry an appreciable mass for some finite time and evaluate the subsequent improvement in one's ability to do so. The load bearing tissues will remodel, given appropriate nutrition, resulting in an improved capacity to bear a load. Note also modern understanding of the importance of physical therapy targeting rehabilitation following musculoskeletal injury or surgery. For example, following surgical repair in the knee capsule, patients undergo a regimen of rehabilitative physical therapy wherein the aim is to restore full range of motion of the joint and increase strength in the muscle tissue surrounding the knee. Following such therapy, patients are expected to resume a quality of life similar to that maintained prior to injury. Generally, it is expected that muscular injuries can be treated via restorative medicine wherein complete recovery of the patient is common.

Ironically, though it is arguably self-evident that mechanical factors influence the growth, development and remodeling of biologic tissues, application of this concept is conspicuously sparse in the clinical setting – with the exception of the aforementioned "common-sense" approach to musculoskeletal therapy. Evidence that broader application is warranted, is easily obtained by those willing to pursue it. One example involves the development of autologous vein grafts which can be cultivated by axially loading a native vessel in vivo. Typically, a vessel in the leg is targeted. Under anomalous strain, the vein remodels, extending in length in an attempt to relieve the hyper-stressed condition. After some finite time, a section of the remodeled vessel, now of excess length, is excised and deployed as an autologous graft elsewhere in the body e.g. in the coronary portion of the arterial tree.

Interestingly, given all of the preceding evidence, mechanical therapies targeting recovery and rehabilitation for the myocardium do not exist in the clinical setting and are considered innovative in the research setting – in spite of the intuitive nature of the therapy. The heart is essentially a muscle not altogether too different from any other muscle. Cardiomyocytes are certainly unique, in aggregate they represent a unique "form" of muscle tissue, but remain in essence – muscle tissue; a tissue that is in essence load-bearing and that readily remodels in response to mechanical loading conditions. Athletes condition their myocardiums to pump more efficiently by increasing oxygen and nutrient rich blood demand through progressively more demanding workouts. In time, the athlete's heart evolves into a well-toned muscular pump. But what happens

when the health of this pump is compromised? Though this organ is essentially a biomechanical device comprised of mechanotransducing cells and tissues, the potential benefits of mediating mechanical factors is notoriously neglected in therapy. For example, in the treatment of patients suffering from CHF, pharmacological therapies, circulatory assist therapies, and transplant comprise present therapeutic approaches. While transplant is highly effective, the lack of available donor organs renders this option epidemiologically ineffective. Pharmacological solutions have proven tenuously effective at best as the benefits diminish with time. Assist therapies serve primarily to compensate for the loss of mechanical work, but do so without consideration of the impact on the already pathologic mechanical environment. The side effects of assist devices on mechanically induced growth and remodeling of the myocardium is essentially ignored – subverted in favor of effects on cardiac output. Note that ventricular assist devices are in fact, mechanical therapies distinguished by their ability to increase ejection fraction, i.e. sustain blood flow. Evidence from the application of these devices reinforces the idea that mechanical loading mediates growth and remodeling of biologic tissue – in this case, the heart muscle. Unfortunately, as these devices are not designed to provide physical therapy, or rehabilitation, the remodeling is predominantly aberrant, i.e. the effectiveness of the unassisted heart continues to deteriorate.

5.1 A Novel Device Based Rehabilitation Therapy for the Treatment of CHF

Herein it is proposed that damaged heart muscle could be rehabilitated by employing principles similar to those invoked in theories of musculoskeletal rehabilitation. The damaged heart muscle functions in a state of dyskinesis (pathologic motion), wherein anomalous strain patterns proliferate inducing aberrant growth and remodeling. Existing assist therapies, while improving cardiac throughput, are detrimental in that they exacerbate the existing dyskinesis. Herein it is proposed (though not studied) that restoration of normal physiologic strain patterns, i.e. normal motion, could induce restorative growth and remodeling. It is important to note that a device designed for this purpose would, in effect, also provide ventricular assist, and thereby improve cardiac throughput – as a natural consequence of restoring normal physiologic motion. Though clinical metrics such as "ejection fraction" would be immediately improved, the real benefit, the objective, would be rehabilitation of the myocardium. Restorative medicine, cardiac therapy that results in the rehabilitation of the heart muscle in a manner similar to rehabilitation of other load bearing muscle e.g. quadriceps, would represent a dramatic change in the treatment of CHF, wherein patients may, in fact, emerge in a state of health indistinguishable from that prior to failure.

Constraint and systematic reduction of an enlarging diseased heart without compromising cardiac output or imposing aberrant strain patterns will enable cardiac remodeling processes that are rehabilitative and restorative with respect to normal

physiologic function. Note that non-adjustable passive CSDs are designed to resist chronic dilation of end-diastolic volume, as well as reduce ventricular wall stress and myocardial stretch. In best case scenarios, passive CSDs may induce reverse remodeling toward normal size and function. The limiting factor in this process is the relative geometry of the device as compared to the diseased myocardium. Reverse remodeling events occur in response to the variations in the mechanical environment imposed by the device. Remodeling is an adaptive behavior, and once equilibrium with the device imposed mechanical conditions is achieved restorative remodeling will wane. Consequently, in order to achieve full rehabilitation of the myocardium it is important to be able to intervene in the remodeling process via an adjustable device wherein the mechanical conditions required to sustain restorative remodeling can be maintained until normal size, shape, and function are achieved by natural growth and remodeling processes.

The device being developed is a minimally-invasive device that is deployed into the pericardial space surrounding the heart for the purpose of modulating the mechanics of a failing heart via both active assist and passive support to achieve heart recovery by guidance of intrinsic growth and remodeling processes. The aim of this technology is to provide the mechanical environment necessary for growth and remodeling that is restorative in nature and potentially rehabilitative. Hypertrophy of the myocardium is characteristic of advanced disease. An important and devastating consequence of hypertrophy is the substantial loss of pumping efficiency. The technology described

herein would provide a means for guided intervention whereby normal growth and remodeling processes are directed toward a gradual reduction in size. Active synchronous assist capabilities will maintain critical cardiac performance, e.g. cardiac output and stroke work, for managing acute heart failure. Specifically, this is a device based technology that will (1) provide adjustable passive cardiac support and constraint designed to facilitate the gradual reduction in size of hypertrophied diseased hearts, thereby improving pumping efficiency; (2) provide active synchronous cardiac assist designed to maintain optimum cardiac performance, i.e. stroke volume, cardiac output, ejection fraction, stroke work, etc. and kinematics conducive restorative remodeling processes; and (3) be deployable via minimally invasive surgical procedures.

This approach is revolutionary and innovative in three important aspects:

- Combination of active and passive device: The proposed treatment of heart failure represents a shift in the paradigm of regenerative medicine, whereby kinematics is employed to achieve heart recovery in patients that would otherwise be treated with a heart replacement procedure (unlikely given that there are only 2000 hearts available per year) or receive no substantive treatment at all. A real need exists today for the patient population in Class III & IV heart failure stage who need both short term assist restoring cardiac output and hemodynamic stability with a transition to medium or long term support of active assist and passive support combination therapy. Though different devices exist today with specific indications

for medium/long term support, *the proposed minimally invasive implantable device will be the first device which has a dual component of active assist and passive support-applicable for medium to long term assist and support leading to reverse remodeling over a period of time.*

- Customization of the therapy: The active and the passive modes of the device can be optimized depending upon which clinical indication is being treated. The active and the passive two component design of the device separately modulate the end-diastolic (ED) and end-systolic (ES) configurations. The device can be operated in multiple modes to be able to separately modulate ED and ES volumes, as both will change as the recovery of the patient's heart progresses. This is also a innovation which present passive devices like Acorn's Corcap and Paracor's Heartnet do not possess.

- Minimally invasive & minimal risk of infection and coagulation: The proposed device is a major advancement of heart assist technology that minimizes invasiveness, infection, and coagulation and most importantly this device allows customization of therapy based on the patients' response to the treatment strategy. Heart replacement is highly invasive and induces great trauma on the patient and complications from anti-rejection medication. The present technology incorporates design principles conducive to leading edge minimally invasive techniques. The implications of developing this technology will likely be far-reaching, extending

beyond the proposed application. This technology is an excellent candidate for so called combination therapies which combine mechanical, electrical, pharmaceutical, and/or stem cell therapies.

5.2 Postcardiotomy Cardiogenic Shock and Mitral Regurgitation

Postcardiotomy cardiogenic shock (PCCS) is defined as the inability to wean successfully off cardiopulmonary bypass (CPB) despite maximal inotropic support and intra-aortic balloon pump (IABP) support. The risk of cardiogenic shock can be mitigated with the application of mechanical assistance. The most common use of mechanical assist is in the postcardiotomy shock setting [89-94]. If hemodynamic stability is not achieved, an assist device is considered. Many other cardiac surgical procedures have benefited from the use of a ventricular assist device (VAD) for postcardiotomy shock [95-97]. Technically challenging procedures, such as the Ross Operation and left ventricular remodeling procedures, complications from an acute MI, such as ruptured papillary muscle (with acute severe MR) and postinfarction ventricular septal defect (VSD), have traditionally been labeled as high-risk surgeries that may result in postcardiotomy shock states.

PCCS results in substantial morbidity and mortality. Despite intra-aortic balloon pump and inotropic support, some patients with PCCS continue to have a refractory low cardiac output. Treatment includes the use of ventricular assist devices (VAD) to support the patient until myocardial recovery occurs sufficiently to support end-organ protection.

Despite recent improvements in surgical techniques, anesthesia, CPB, and VAD design, operative mortality for this group of patients remains quite high, 50% to 70% in some reports. For these patients, more effective ventricular assistance is imperative to prevent death.

Because MR is a frequent complication of the chamber dilation associated with CHF, there is a significant number of Americans (we estimate 2,000,000) with CHF who would or could benefit greatly from valve repair if the risks of surgery were reduced. With regard to post cardiotomy recovery, two types of devices, cardiac assist and cardiac support, have been found to be beneficial. Although the leading cardiac support device (Acorn's CorCap) was denied approval by the FDA (Food and Drug Administration), it showed significant benefit (see Section B.4, clinical studies) for CHF patients having surgery for MR repair. A primary reason for denial of Acorn's PMA (pre-market approval) was that they sought approval for use of CorCap in the general CHF patient population—rather than just in patients who are already getting surgery for MR repair. For the general patient, FDA considered the risks of surgery to be greater than the benefit of CorCap placement. Heart failure management consists of multiple stages ranging from postcardiotomy short term assist to medium/long term support towards destination therapy or reverse remodeling. The bigger challenge towards successful management of heart failure is to design effective therapeutic protocols, as the separation between indications for recovery, bridge to transplantation and permanent use becomes less distinct. Thus, a simple, easy to implant, minimally-invasive device which can provide short term assist at postcardiotomy, and then transition to medium to long term

support enabling reverse remodeling could be of significant benefit to the postcardiotomy patient population.

6. COMPARISON WITH EXISTING DEVICE BASED THERAPIES

The technology presently being developed will have a significant competitive advantage over existing and alternate technologies in the treatment of CHF. This includes advantages over (1) active assist devices (e.g. MYO-VAD), which are non-adjustable, and also generally invert the curvature of the heart causing aberrant motion (2) blood-contacting devices (e.g. Thoratec's HeartMate LVAD) that can cause clotting and do not aid in reversing enlargement and (3) cardiac support devices (e.g. ACORN) which are non-adjustable and incapable of providing circulatory assist in the event constraint compromises cardiac output. The versatility of the device is illustrated in Table 1.

The device described herein is a major advancement of heart assist technology that minimizes invasiveness, infection, and coagulation. Heart replacement is highly invasive and induces great trauma on the patient and complications from anti-rejection medication. Current, blood-contacting assist technologies are greater risk for blood trauma, clotting activation, and sepsis. Blood-contacting assist technologies cannot be started and stopped because of clot formation. The proposed technology is an excellent candidate for combination therapies which combine mechanical, electrical, pharmaceutical, and/or stem cell therapies. Stem cells will benefit from improved mechanical stimuli. Prior devices in the class of direct cardiac compression devices (such as the Anstadt cup and cardiac support system) are more invasive and induce aberrant motions because of non-uniform application of forces (push on some areas and

TABLE 1: Device Comparison. In this comparison the versatility of the device being developed herein is evident. More importantly, note that the therapeutic target of this device is to stimulate growth and remodeling processes that are potentially restorative and rehabilitative in nature.

Device	**Mode**
Counter-Pulsation Devices: IABP	Bridge to Recovery – Short Term Hemodynamic Support: **POST-CARDIOTOMY**
Left Ventricular Assist Devices (LVAD)	Bridge to Transplant & Destination Therapy – Short, Medium, Long Term Assist: **ASSIST**
Cardiac Support Devices	Long Term Reduction of Wall Stress: **SUPPORT** (CorCap, Heartnet)
Device Under Development (Combination of Active Assist and Passive Support)	Short to Medium Term: **POST-CARDIOTOMY + ASSIST + SUPPORT** Maintain Cardiac Output, Increase Stroke Work, Modulate End Diastolic and End Systolic Volume Leading to Reverse Remodeling

pull on others). As will be discussed later, the proposed technology enhances without inhibiting normal cardiac motion.

6.1 Advantage over Intra-Aortic Balloon Pumps

Intra-aortic balloon pumps, or counterpulsation assist devices, are simple technologies inserted percutaneously provide active circulatory assist. These devices are blood contacting and therefore bring the associated risks. Moreover, they have a limited ability to modulate heart motion and the end-diastolic (ED) and end-systolic (ES) configurations. They add motion to the heart by sucking on the vasculature or deflating during the heart's systolic contraction. The rebound of the arteries and circulatory demands, however, limit the ability of aortic balloon pumps to decrease the transmural pressure felt by the heart wall. Arterial pressure must remain a significant fraction of mean arterial pressure to maintain organ perfusion. In contrast, this device affects the transmural pressure gradient by raising the external pressure rather than lowering the internal blood pressure.

6.2 Advantage over Left Ventricular Assist Devices

For the left ventricular assist devices, there are multiple challenges in surgery, device operation and postoperative care due to the infection and coagulation risks associated with devices that touch blood. But over the last decade there have been supportive data

towards destination therapy, it is exciting that some patients in end-stage failure recovered completely when given a mechanical assist device while on the transplant waiting list. This demonstrates that reverse remodeling and heart recovery are possible. The present technology is designed to make it possible in every patient with heart failure and is a great enhancement over the blood pumps because it is implanted in a minimally invasive fashion, there is no sewing to vessels or the heart, no contact with blood, and there is direct control of mechanical factors (ED configuration and ES configuration) that are likely to be most important for recovery. Thus this technology is a heart assist technology than circulatory assist technology.

6.3 Advantage over Present Cardiac Support Devices

Of the passive ventricular restraints in clinical trials are the CorCap device and Paracor's Heartnet. The CorCap is the leading device with a positive record of animal studies, clinical studies, and device sales in Europe. Their regulatory approval in the US has been difficult presently conducting a 50 patient confirmatory trial for PMA submission, but they are the first such device in this class to be near approval. The CorCap can be implanted in a minimally invasive fashion, but it is limited in its ability to restore the heart to normal, as it is not adjustable. Once inserted, it can limit the heart enlargement, but its size cannot be adjusted to continually reduce the ED configuration. To be most effective, the CorCap needs to be implanted prior to end-stage failure to limit the growth. Deciding which patients need device intervention and which patients will

recover on their own is difficult to determine in the early stages of failure. With the device described herein, intervention can be accomplished after the development of end-stage failure because ED configuration can be continuously adjusted. In addition, passive devices have limited ability to modulate heart motion because they cannot supply pumping power. For example, the CorCap cannot be undersized too much because it may limit heart filling and muscle stretch to the point that muscle contraction is too weak (i.e., an already shortened muscle cannot shorten much more). With our technology, we can supply systolic assist to normalize ejection while reducing the ED configuration. The device is not designed to fibrose to the myocardium thus allowing future intervention which is not an option in CorCap and Heartnet as they are implanted as a destination therapy.

7. DEVELOPMENT OF A DEVICE THAT PROVIDES ADJUSTABLE CARDIAC SUPPORT AND ACTIVE SYNCHRONOUS ASSIST

One of the major maladaptive changes after a major heart attack or cardiac event is an initial decline in pumping capacity of the heart leading to activation of variety of compensatory mechanisms, and subsequently a phenomenon known as cardiac or left ventricular remodeling, i.e. a geometrical change in the architecture of the left ventricle. Evidence suggests that mechanical factors are critical, and to control two important mechanical parameters, cardiac size and cardiac output.

7.1 Device Actions and Features

Given the prominent role of geometric and mechanical factors in driving the remodeling associated with disease progression, an implantable device has been designed to directly modulate heart size and motion; so to investigate the effectiveness of mechanical therapy to guide reverse-remodeling. Pump type LVAD implants have lead to reverse remodeling [71]. Yet, these devices do not modulate heart size and motion directly, rather they communicate with heart indirectly via contact with the blood. The device of this study, in contrast, surrounds the heart, contacts the epicardial surface of the heart, and thus acts on the heart directly, without blood contact. The following two modes of operation or device mediated actions (A1, A2) were sought and assessed in an acute ovine study:

A1) adjustable cardiac support or passive constraint to reduce heart size and

A2) synchronous active assist to increase heart motion or stroke volume when it has depressed motion.

Moreover, to enable our research goals of testing the effectiveness of the above actions to reverse-remodel the heart, we sought and assessed the following three inactions or device features (F1,F2,F3):

F1) does not impede heart function when it is inactive and

F2) does not invert heart curvature (nor induce similar, abnormal motions) when it is activated

F3) does not dislodge, extrude or expel the heart when it is activated

These features are necessary for chronic experiments to assess heart remodeling—i.e., the next phase of studies.

There is a recent report of a device capable of adjustable cardiac support [98], and there are reports of a direct cardiac compression device [99] for providing synchronous active assist. Nevertheless, there are no known implantable devices that provide actions A1-A2, i.e. this report is the first for a combination device that can perform both actions A1 and A2.

7.2 Device Construction

The device implanted in this acute, ovine study had six identical chambers composed of a nitrile, airtight bladder surrounded by a nylon mesh to constrain bladder expansion and to attach adjacent bladders together via 1/8” width stitches of braided nylon thread. The device is shown in Figure 1, as placed on the heart and viewed through a sternotomy. Each chamber had an identical helical orientation, but shifted 60 degrees so to form a complete circumference and form a cup-shaped structure. Polyurethane tubing (0.25” d) was employed as the conduit for fluid transport to and from the bladders. The end of the tubing within the bladders was spiral cut to prevent the nitrile film from collapsing onto to the tube end during the diastolic phase of assist when vacuum was applied to remove air in the chambers. The other tube ends were coalesced together into one driveline (0.375” d). Although separate in construction, tubing connections made the six-chambers contiguous with the same pressure source. The chambers were also attached to a nitinol scaffold which provided structural stability and served as a reference electrode for acquisition of the electrocardiogram (ECG) signal used to trigger the device. The sense electrode was sewn to the heart apex. This epicardial electrode configuration provided an on-axis, robust ECG signal with a maximally polarized QRS complex.

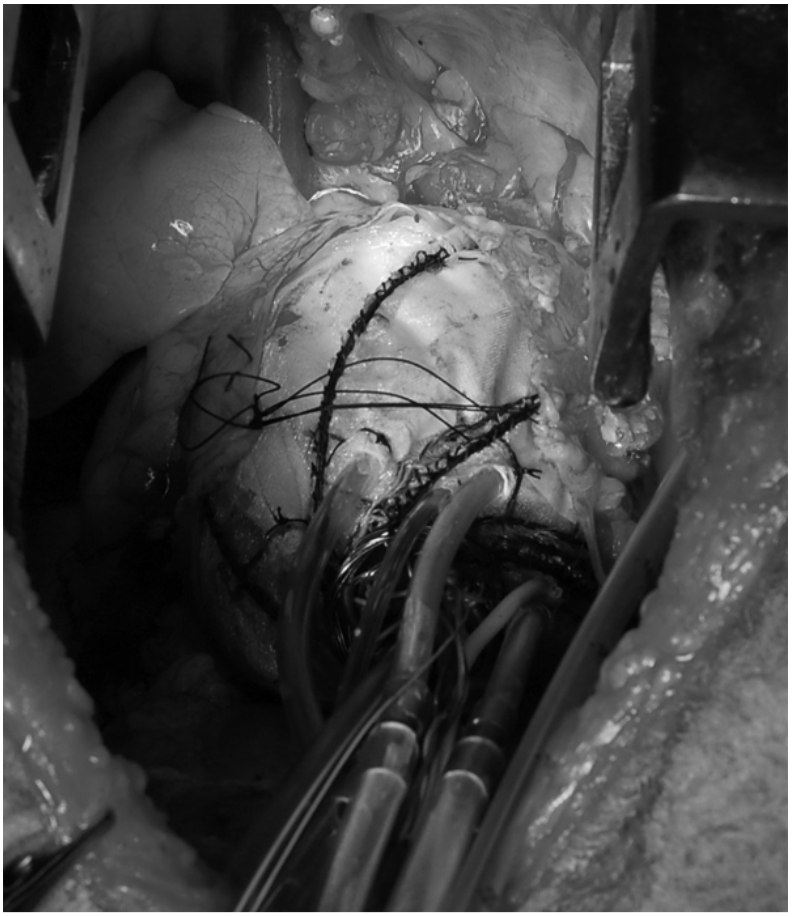


FIGURE 1: Dual Function Device. This device consisted of chambers which were filled with air to provide support or assist. In support mode a static pressure was applied. In assist mode, air was shuttled into the chambers during systole, and removed by vacuum during diastole. The device was implanted via sternotomy.

7.3 Device Control and Monitoring

The ECG was routed to a BNC-2110 connector block which in turn was connected to a USB-6251 DAQ Board (National Instruments Corporation, Austin TX). A custom LabView (National Instruments Corporation, Austin TX) VI was developed and used to monitor device pressure, acquire the ECG, and trigger the device. The front panel user interface is shown in Figures 2. The schematic is given in Figure 3. The ECG signal from the device is routed to a virtual low pass filter. A threshold algorithm then triggers off of the R-wave of the ECG. The program provides independent control of device pressurization and evacuation gate times. The trigger activates two virtual gates, one for the pressure signal; the other for the vacuum signal. The gate times can be adjusted as necessary to provide the desired magnitude of assist or to function as a percentage of the corrected QT interval at some fixed magnitude of assist. The device pressure was obtained with a Millar pressure catheter transducer (Millar Instruments Inc., Houston, TX) placed within one of the device chambers.

The device pressure is adjusted using a custom pneumatic system (Figure 4). Two reservoirs are employed. One reservoir is connected to a constant pressure source; the other reservoir is connected to a constant vacuum source. A T-fitting is used to couple the two sources to the device lines. Solenoid valves determine whether the pressure line is sent to the device or alternatively the vacuum. As a precaution the vacuum solenoid valve is open in the default state and the pressure solenoid valve is closed in the default state. When a trigger is generated a voltage is output to a custom built solid state relay

system that activates the appropriate solenoid valves (Figure 5). Thus, the gate times can be adjusted to vary the magnitude of assist provided by the device.

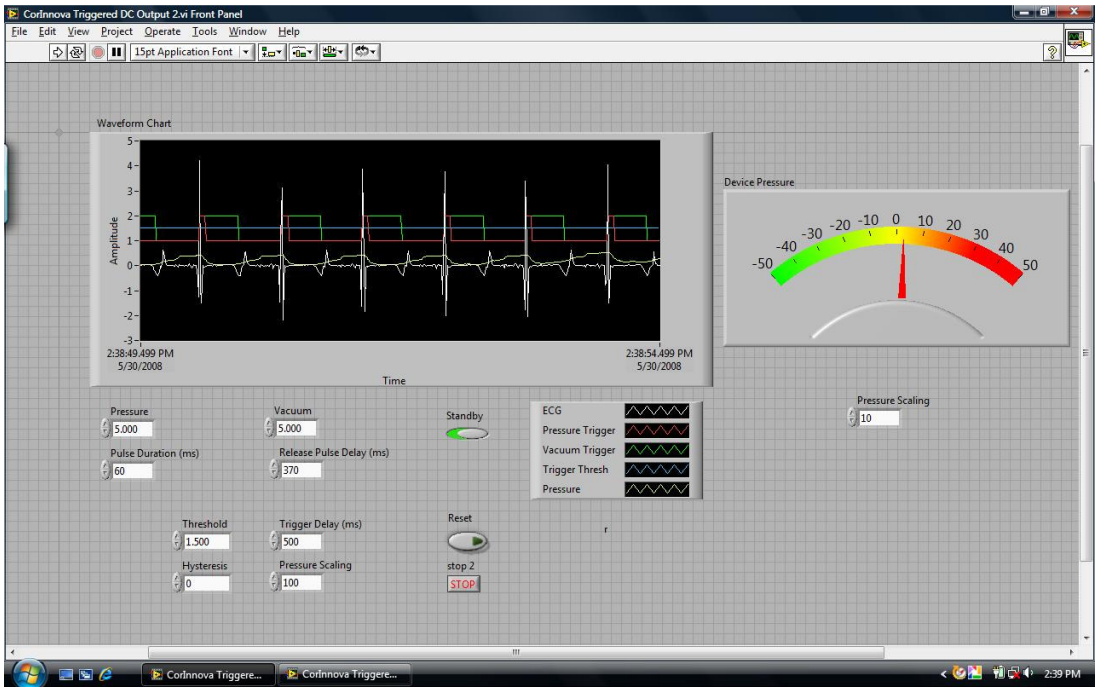


FIGURE 2: Control and Monitoring User Interface. The main display of the custom LabView application provides real-time monitoring of the ECG, Device Pressure, Gate Times, and Trigger Threshold.

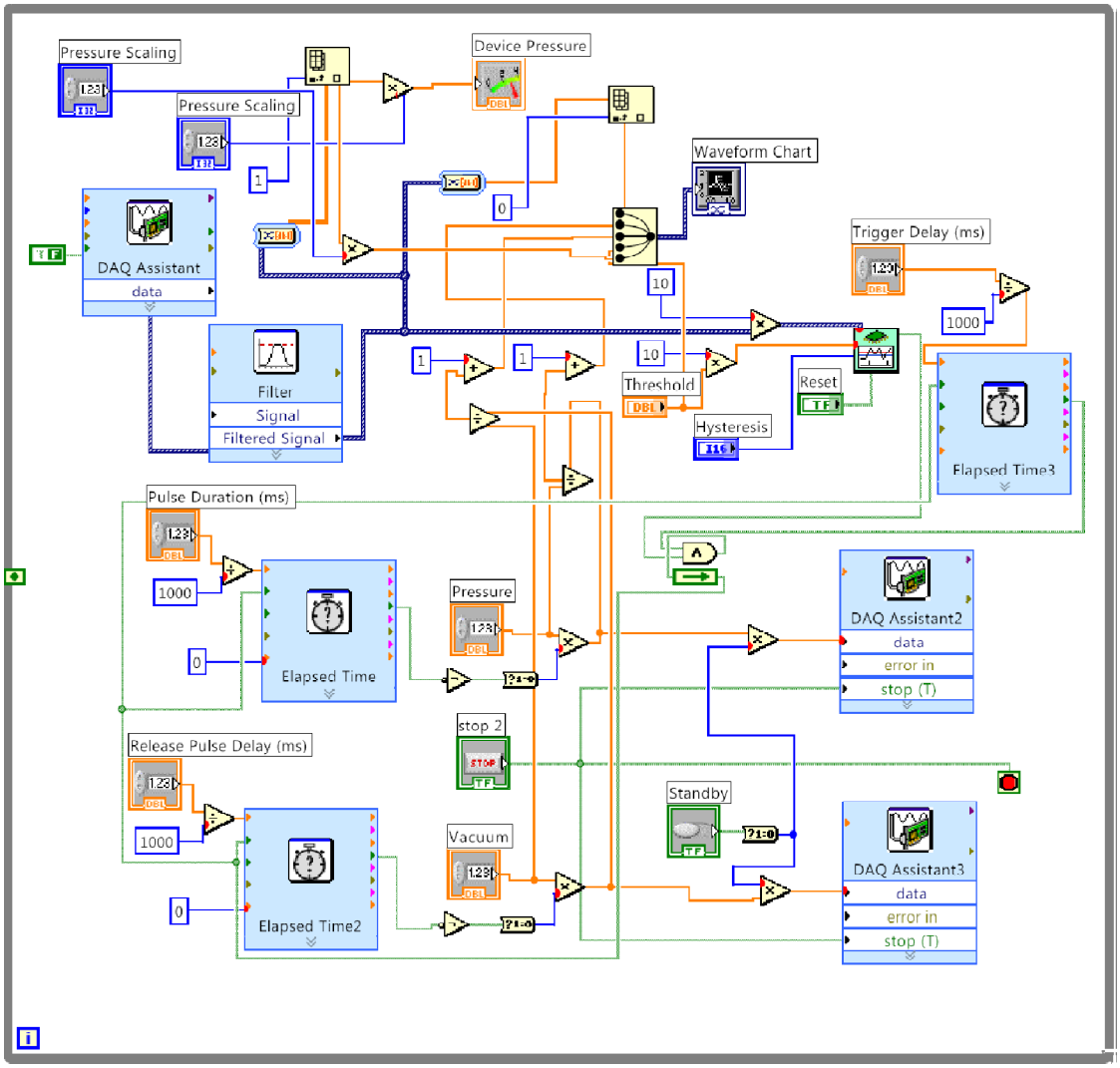


FIGURE 3: Schematic of the LabView Application. A custom LabView application was developed to control and monitor the device. The ECG signal from the device is routed to a low pass filter. A threshold algorithm then triggers off of the R-wave. This activates two gates, one for pressure signal; the other for the vacuum signal. The gate times can be adjusted as necessary to provide the desired magnitude of assist or to function as a percentage of the corrected QT interval at some fixed magnitude of assist.

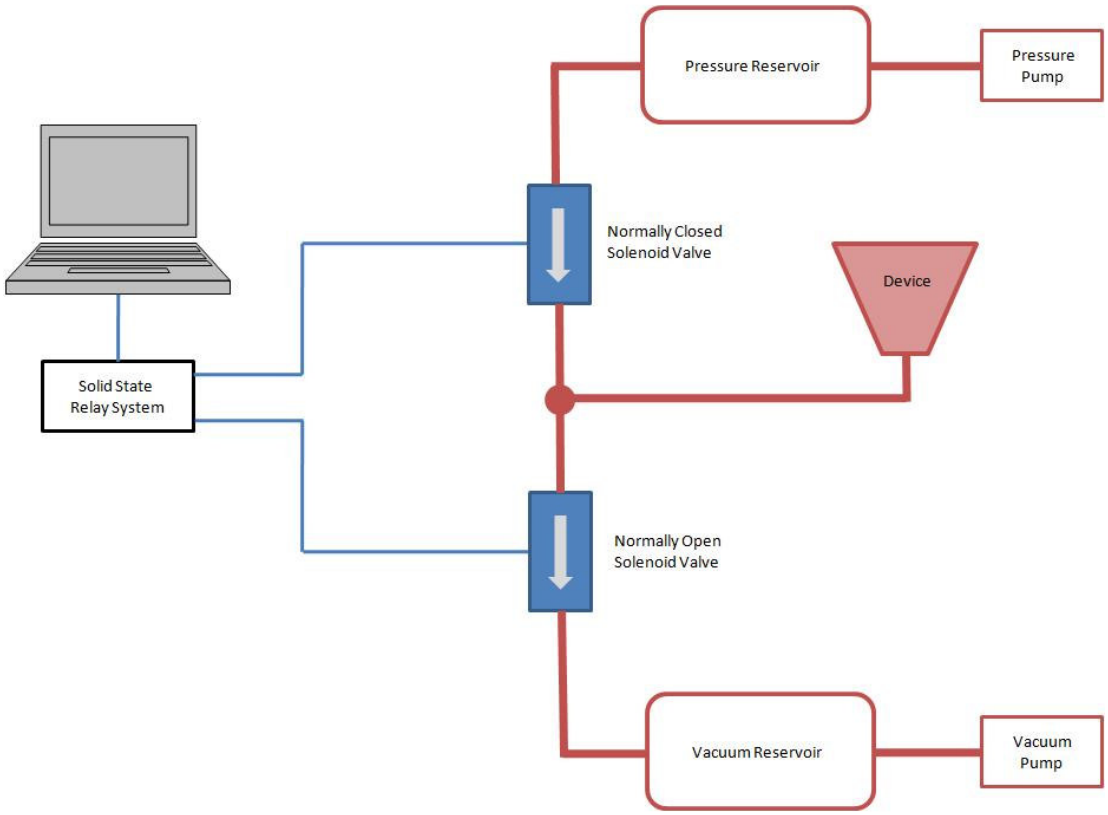


FIGURE 4: Pneumatic System Schematic. This schematic illustrates how fluid (air) is transported to and from the device. The device is connected to continuous pressure and vacuum sources. Independently controlled solenoid valves determine which source is actually applied to the device at a given time. The solenoid valves are activated by signals generated by the LabView application and routed through a custom solid state relay system.

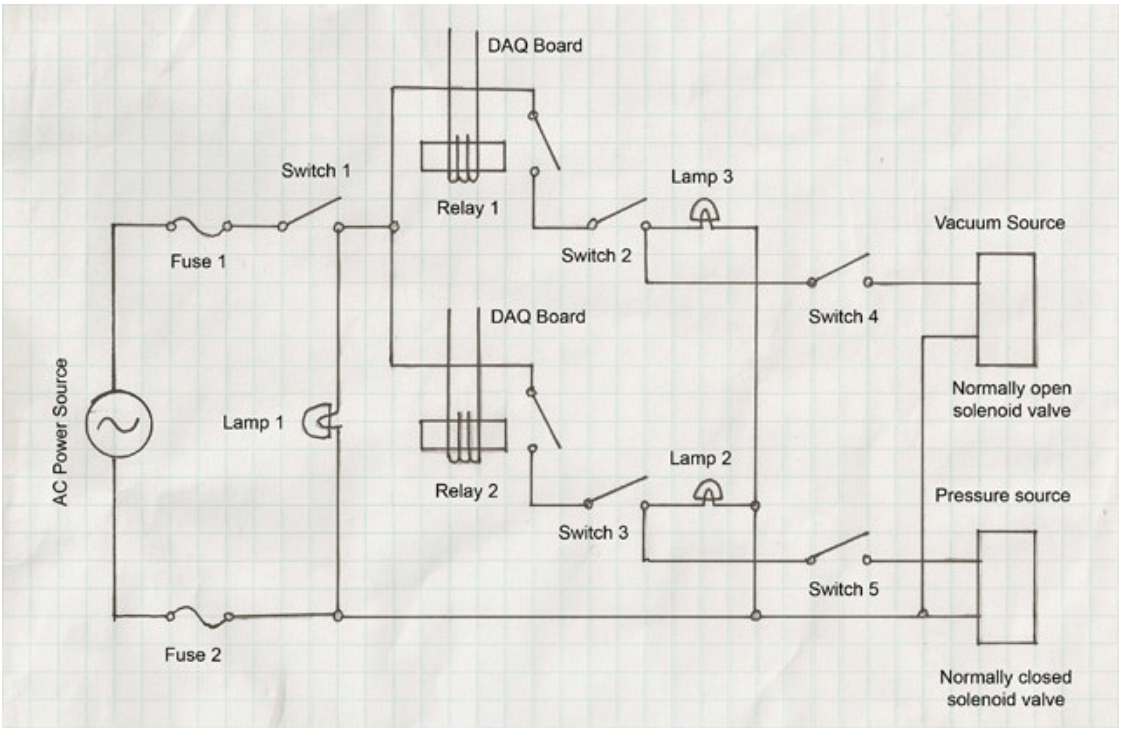


FIGURE 5: Solid State Relay System Schematic. This schematic of the custom relay system illustrates how the AC source is routed to the appropriate solenoid valve using solid state relays. Lamp 1 simply indicates the AC is present at the relays. Lamps 2 and 3 indicate the AC source is being routed to switches S4 and S5. This provides a means to verify appropriate triggering before actually activating the device via closing the Switches 4 and 5.

8. ASSESSMENT OF AN IMPLANTABLE DEVICE THAT PROVIDES ADJUSTABLE CARDIAC SUPPORT AND ACTIVE SYNCHRONOUS ASSIST IN AN ACUTE HEART FAILURE MODEL

8.1 Delivery and Assessment of Action A1

Adjustable cardiac support or passive constraint was accomplished by applying a static pressure on the driver end of the device driveline. Although we applied a constant or fixed pressure, this action is termed *adjustable* cardiac support because the pressure or amount of support can be adjusted post-implantation. We applied two separate, static pressures: 1) open to atmospheric pressure, and 2) 10cmH2O (or 7.5mmHg) above atmospheric pressure. Device pressure was monitored via the LabView setup; and although the pressure was held static at the driver end of the driveline, the pressure in the device chambers varied with heart contraction and relaxation. With caval occlusion, the end diastolic pressure-volume relationship (EDPVR) for both of the above states was determined and then compared to assess the effectiveness of action A1 to shift the EDPVR upward or leftward (i.e., toward a smaller heart size).

8.2 Delivery and Assessment of Action A2

Synchronous active assist was accomplished by oscillating the driving pressure of the device in synchrony with heart contraction. The LabView program detected the ECG

trigger and sent a line voltage signal to a custom designed relay system which shut off the solenoid valve to the vacuum pump and opened the solenoid valve to a pressure tank regulated to about 1,400 mmHg (approx. 20 psi). After a user specified delay, the LabView program cut off the voltage to the solenoid valve to the pressure tank. The appropriate delay was determined by starting at a zero and increasing it by a few milliseconds after a few cardiac cycles, until the systolic pressure in the device reached the desired amount. The amount of time that the pressure tank valve was open was significantly less than the length of systole. For example, a few milliseconds of a 1,400 mmHg pulse at the driver end became, at the device end, a pulse of 30 mmHg that lasted for hundreds of milliseconds. After a user specified delay (that was obtained from measuring the QT interval on the ECG), the LabView program opened the solenoid valve to the vacuum pump. Hence, during systole the vacuum line was closed and the line to the pressure tank was opened briefly at the start of systole, filling the device with air and thereby applying direct cardiac compression. After a QT delay from the R trigger, the vacuum line was opened and the air in the device was evacuated during diastole—allowing the heart to fill. To assess the ability of the device to provide synchronous cardiac assist for a failing heart, we applied 0 mmHg, 30 mmHg, and 60 mmHg of systolic assist for two cardiac states: 1) normal or baseline contractility, and 2) low contractility or esmolol induced, acute heart failure. For the normal cardiac state an active assist of 30mmHg was applied for approximately 5-10 cardiac cycles, after which the active assist was shut off for approximately 5-10 cardiac cycles. The same procedure was used for the esmolol induced failure state, first with an active assist of 30mmHg and

subsequently with an active assist of 60mmHg. PV (pressure-volume) loop analysis was used to assess cardiac function during the varying amounts of assist.

8.3 Design and Assessment of F1

The device was made of thin-film bladders, fabric like material, and wires that formed an open frame so that it was collapsible when depressurized. The design constraint of collapsibility when depressurized was sought so that the device itself did not impede cardiac function. To assess this feature, PV loop analysis was done prior to implantation (prior to opening the chest) and after implantation (after chest closed). Pre-implant and post-implant cardiac functions were subsequently compared.

8.4 Design and Assessment of F2

The outer half of the device chambers formed a continuous, inextensible outer shell of nylon whereas the inner half was in direct contact with the heart surface rather than fully distended. Consequently, the device was designed to apply uniform pressure to the entire epicardial heart surface, as uniform pressure was likely to preserve cardiac curvature—i.e., it was unlikely to invert the ventricular wall or cause similar aberrant motions. To assess the heart shape during device activation, the heart silhouette was observed in fluoroscopy videos taken during maximal device activation. The air-heart interface was easily identified with x-ray imaging.

8.5 Design and Assessment of F3

The chambers of the device were tapered with minimal space near the apex and maximal space near the base. Consequently, when the device was activated it took on a cup-like shape as opposed to a ball-like shape—the latter being the expected shape for an inflated object that does not have chamber partitions. The advantage of a cup-like activated shape is that the heart is likely to be retained in the device rather than expelled from the device. This is so because there is no free air in the chest to fill the space between an expelled heart and the cup cavity. Rather, the heart and device were expected to be pneumatically coupled and coaxially fixed without the need of suturing to the heart. To assess this feature, the motion of the heart silhouette relative to the wire frame on the device was observed in fluoroscopy videos.

8.6 Surgical Procedure

The care and use of the sheep in this acute implant study and terminal procedure was conducted at the Texas A&M University College of Veterinary Medicine in accordance with an active animal use protocol approved by the Institutional Animal Care and Use Committee of the Texas A&M University System. Adult sheep, which weighed approximately 70 kg, were premedicated with an anti-anxiety drug (Xylazine 0.075 mg/lb) and an anticholinergic (glycopyrrolate 0.01 mg/kg). Both drugs were given intramuscularly. After sedation a 16 g catheter was placed in the left jugular vein and

anesthesia was induced with ketamine (4.4 mg/kg) and diazepam (0.11 mg/g) mixed together and given intravenously (IV) to effect. After induction and endotracheal intubation, the animal was maintained on inhalant anesthesia using a combination of isoflurane in oxygen. The animal was clipped and prepped for a sternotomy procedure, The 16g jugular catheter was replaced with an 8 French quad-lumen catheter to allow multiple IV access, and an orogastric tube was placed to prevent bloating. An arterial catheter was placed in the left dorsal pedal artery to allow for direct blood pressure monitoring. The animal was placed in dorsal recumbency for the remainder of the study. Intraoperative IV fluids and mechanical ventilation were initiated. Using a Power Lab physiological monitoring unit; heart rate, blood pressure, central venous pressure, oxygen saturation, ECG, and respirations were monitored throughout the procedure. A lidocaine CRI (constant rate of infusion) was started to prevent arrhythmias and buprenorphine (0.02-0.05 mg/kg) was administered for pain. A Millar PV Catheter was placed through a left carotid artery cut-down and positioned by use of fluoroscopy. A sternotomy was performed and the device was placed over the heart apex. The xiphoid process was removed, and the device drivelines and chest tube were routed caudal to the sternum. The sternum was closed with wire and the fascia was closed tightly with suture to create a pneumatic seal. Free air in the chest was evacuated.

8.7 Data Acquisition

Using data acquired via the PV catheter, and the accompanying PVAN software (Millar Instruments Inc., Houston TX), cardiac function was evaluated. Pressure-volume (PV) relationships were determined for three cardiac states: normal, vena cava occlusion, and esmolol induced failure. Measures of heart rate (HR), maximum pressure (Pmax), minimum pressure (Pmin), maximum volume (Vmax), minimum volume (Vmin), end-diastolic pressure (Ped), end-diastolic volume (Ved), end- systolic pressure (Pes), end-systolic volume (Ves), stroke volume (SV), ejection fraction (EF), cardiac output (CO), and stroke work (SW) were obtained. The aforementioned values were calculated for each PV loop acquired. A minimum of six loops were acquired for each case. Mean values and standard deviations were calculated for each case using the PVAN software package. These values were then used to determine statistical significance via a t-test with $p=0.05$. To assess diastolic mechanics, the end diastolic pressure-volume relationship (EDPVR) was measured by use of a balloon catheter inflated in the caudal cava to reduce the pre-load on the heart. To model acute heart failure, an overdose of esmolol was administered. This included four boluses of 33mg each for a volumetric sub-total of 13.2ml (0.5-1.0mg/kg), and a constant rate of infusion (CRI) of 0.5-2.0 mg/kg/min for a volumetric sub-total of 15.2ml, and thus a total volume of 28.4ml esmolol administered.

8.8 Results

Action A1: Adjustable Cardiac Support or Passive Constraint to Reduce Heart Size

To assess the passive assist capabilities a balloon catheter was inflated in the vena cava to vary the preload. Figure 6A shows the PV loops during onset of caval occlusion with device driveline open to atmosphere, and lower-left panel shows the PV loops during onset of caval occlusion with the device driveline held at 7.5mmHg. The comparison of the EDPVR for the 0mmHg versus 7.5mmHg cases is presented in Figure 6B and shows that the EDPVR shifted upward with the 7.5mmHg passive support. This upward shift in the EDPVR indicates a decrease in the size of the left ventricle relative to filling pressure, i.e. for the same filling pressure the volume is lower.

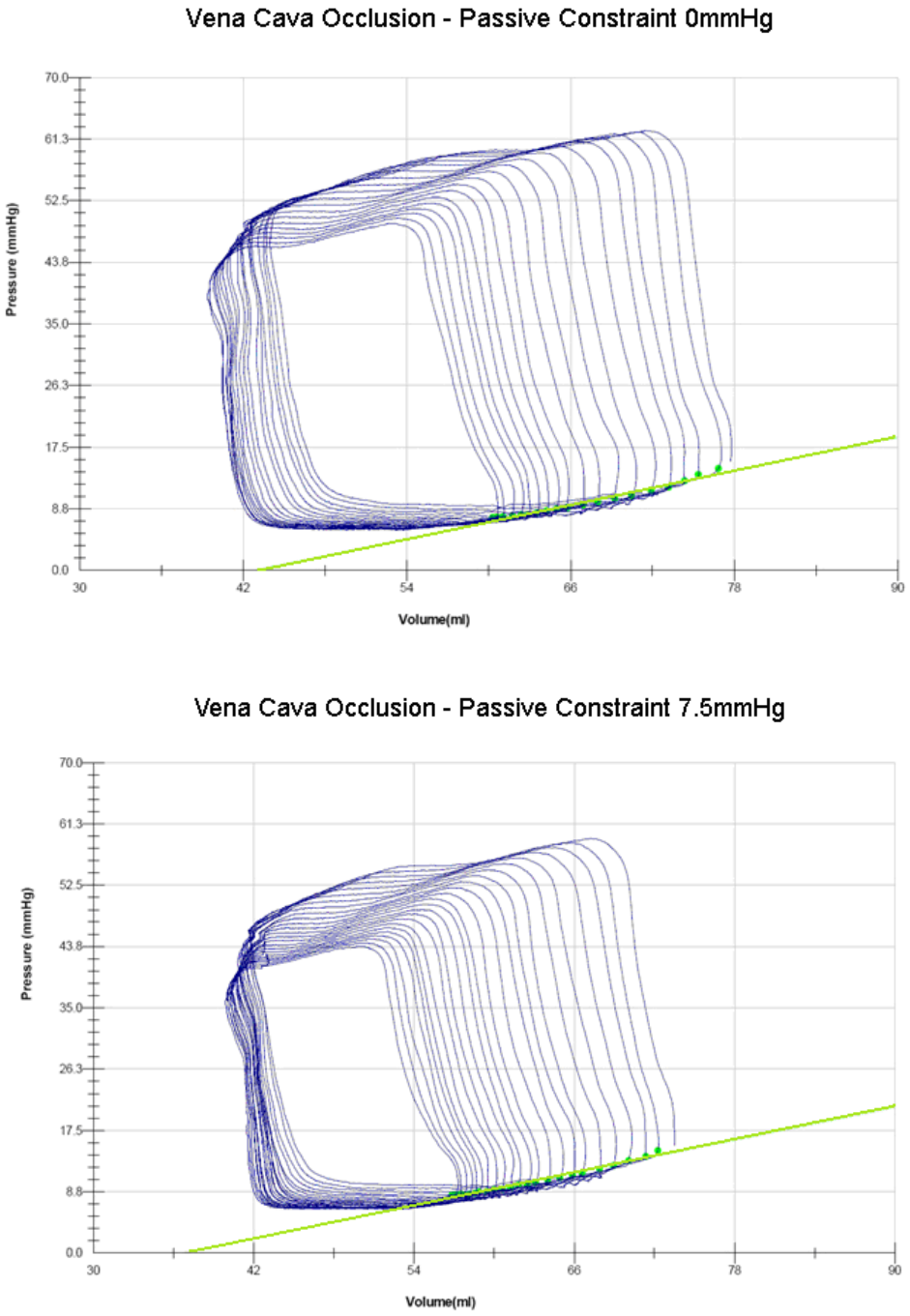


FIGURE 6A: PV Loops - Vena Cava Occlusion. PV loops acquired in the left ventricle during vena cava occlusion with a passive constraint of 0mmHg. (Left Bottom) PV loops of left ventricle during vena cava occlusion with a passive constraint of 7.5mmHg.

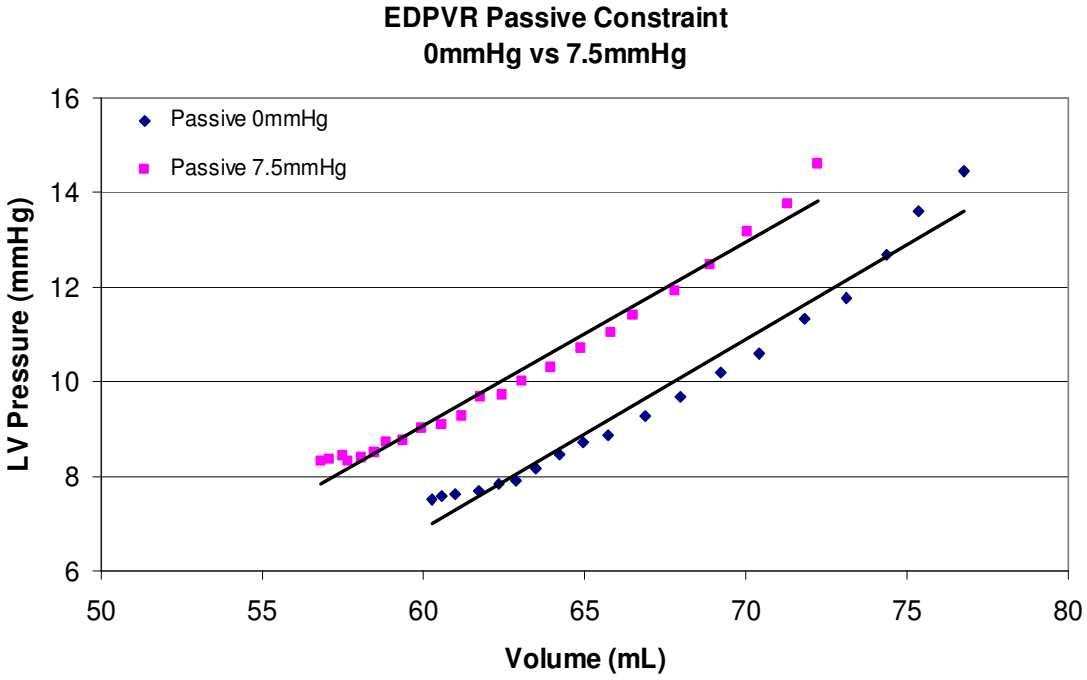


FIGURE 6B: Shifting the EDPVR with Passive Support. Plots of the end-diastolic pressure-volume relationships with and without poassive support, during gradual reduction of pre-load accomplished via vena cava occlusion with a balloon catheter.

Action A2: Synchronous Active Assist to Increase Heart Motion or Stroke Volume

High dose esmolol infusion reduced SV by 39%, EF by 39%, CO by 42% and SW by 52% (Figures 7A and 7B). Application of 30mmHg active assist provided substantial restoration of cardiac performance as EF, CO, and SW increased significantly by 27%, 33% and 62%, respectively (p=0.05). Stroke volume is determined by the change in volume between the vertical isovolumic segments. For normal contractility, stroke volume increased by approximately 11% when the active assist was applied; in the esmolol induced failure model, stroke volume increased by approximately 35%. Application of 60mmHg active assist resulted in significant increases in SV, EF, and CO of 49%, 44%, and 49%, respectively (p=0.05). Increase in SW was dramatic, over 85% as compared with the esmolol baseline (Figure 8A). Note that the levels of CO and SW achieved with 60mmHg assist were similar to the healthy baseline measures, i.e. differences were statistically significant (Figure 8B).

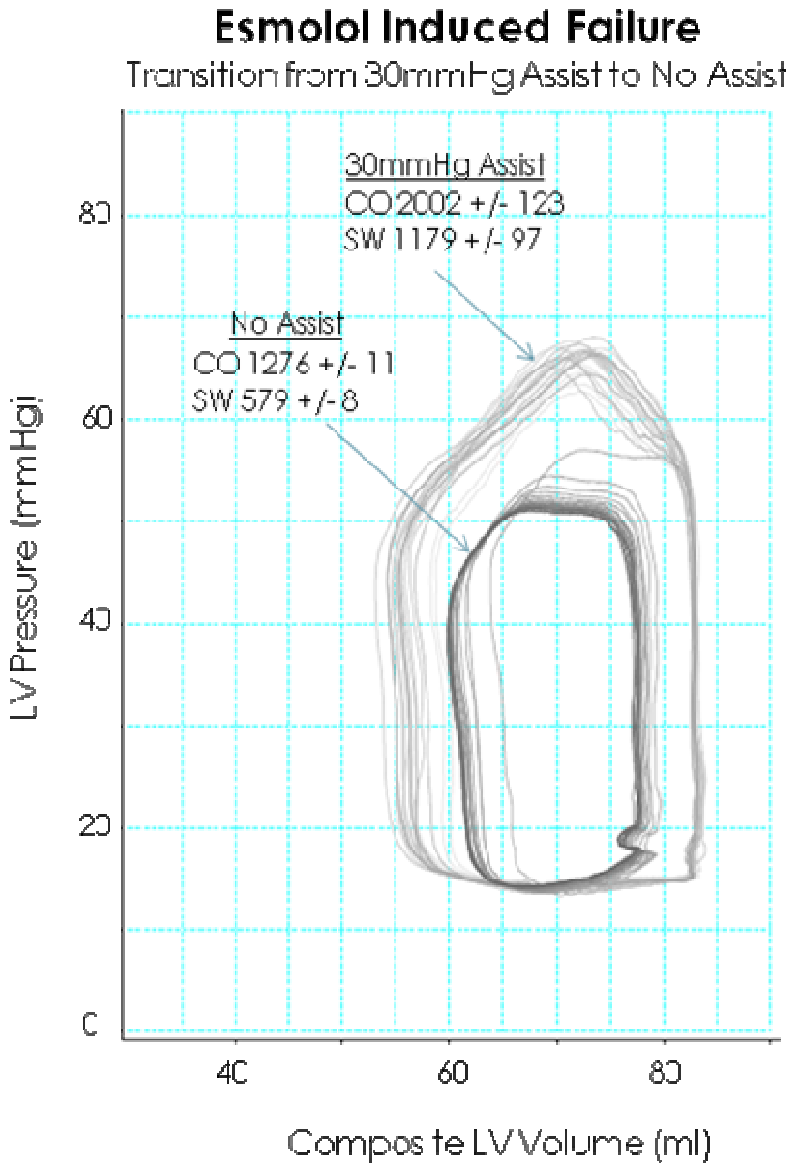


FIGURE 7A: Esmolol Induced Failure – 30mmHg Assist. Pressure-Volume loops of the transition from 30mmHg assist to "no assist" in the esmolol induced failure model. Here it is evident that assist significantly improved cardiac metrics e.g. SV, SW, etc.

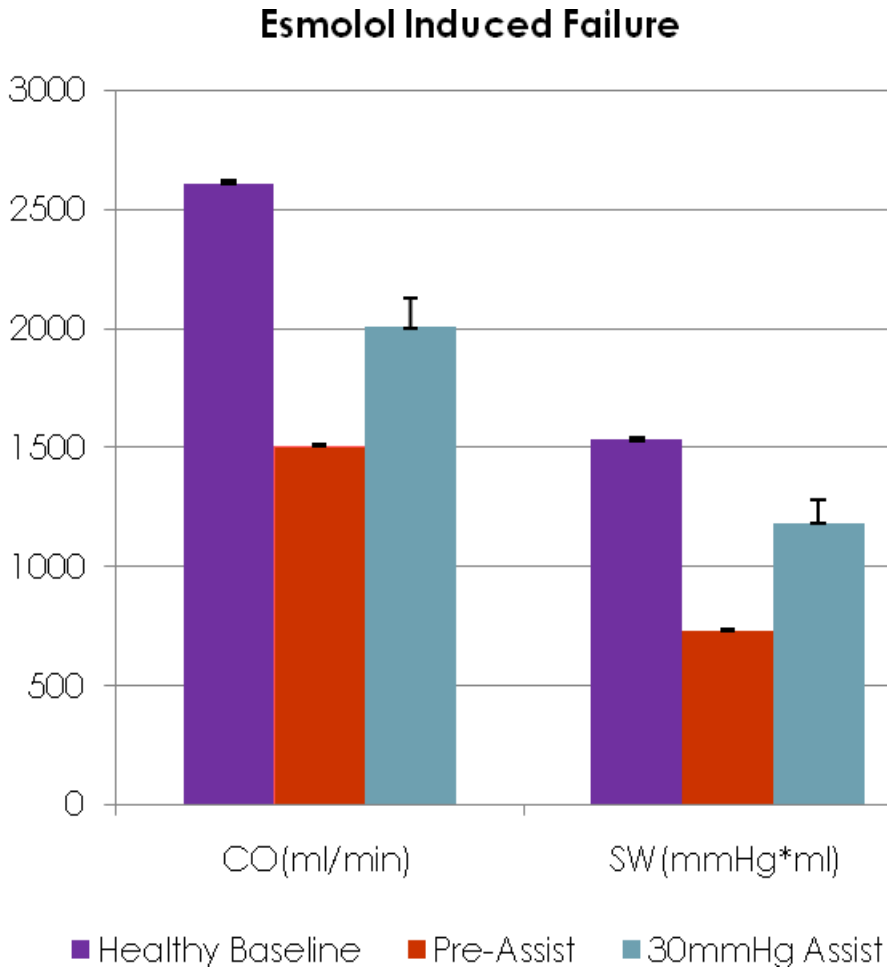


FIGURE 7B: Esmolol Model CO and SW – 30mmHg Assist. Comparison of Healthy Baseline, Esmolol Pre-Assist, and Esmolol with 30mmHg Assist in the esmolol induced failure model. Note that assist resulted in significant increases in SW and CO, though levels remained lower than the healthy baseline.

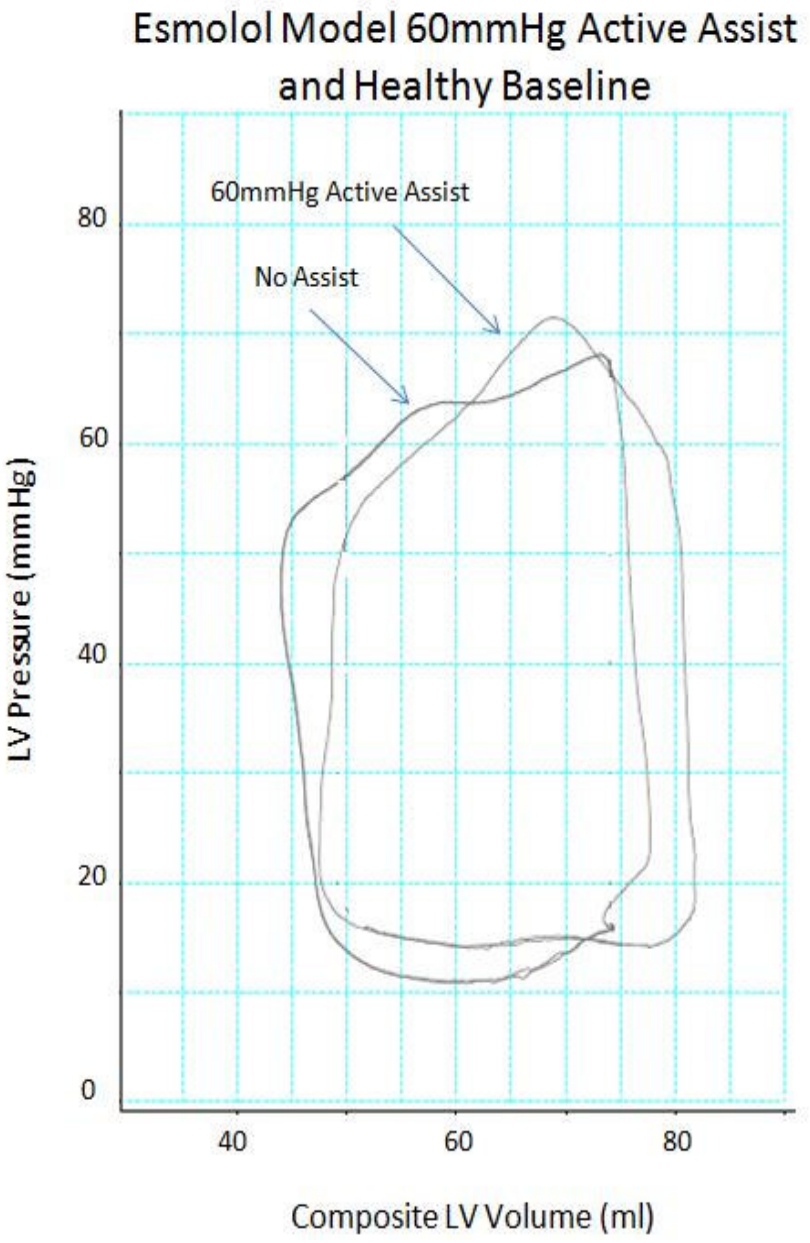


FIGURE 8A: Esmolol Induced Failure – 60mmHg Assist. Pressure-volume loop plots from 60mmHg assist of the esmolol model and the healthy baseline.

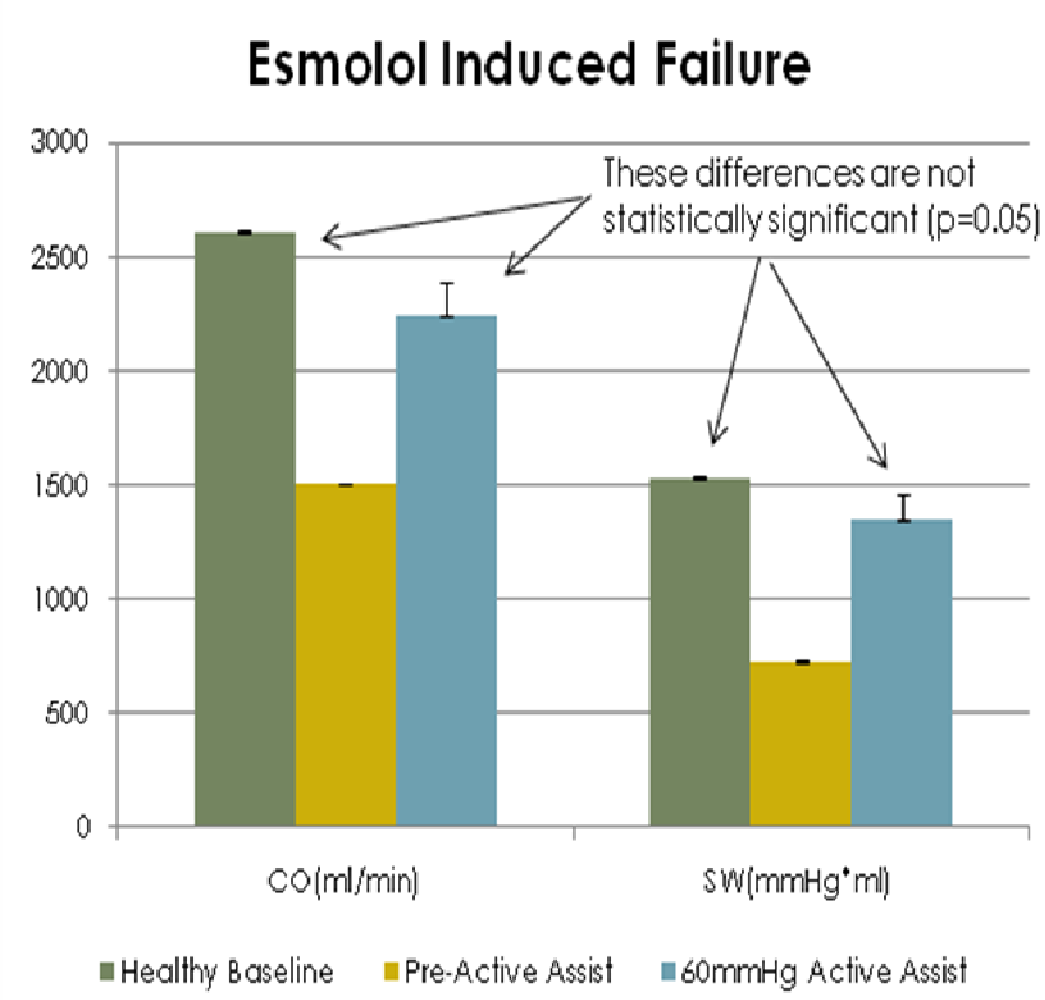


FIGURE 8B: Esmolol Model CO and SW – 60mmHg Assist. In this comparison of SW and CO levels, it is evident that 60mmHg Assist provides significant gains in the esmolol failure model, achieving performance levels that were statistically similar to those observed in the healthy model.

Feature F1: The Device Does Not Impede Heart Function When It Is Inactive

PV loops obtained pre- and post-deployment are shown in Figure 9. SV, EF, CO, and SW were statistically similar pre- and post-deployment. CVP (central venous pressure), wedge pressure, and AoP (aortic pressure) were also unaffected by device placement. Thus, sternotomy, device placement, and closing the chest did not have a significant impact on cardiac function. Although it is of no therapeutic value, it is scientifically relevant to measure the cardiovascular response to synchronous active assist on a normal, healthy heart. Prior to esmolol infusion to induce heart failure, i.e. in the normal contractility state, activation of the device during systole (with 30 mmHg of assist pressure) SW increased over 30% ($p=0.05$). Significant increases in CO (13%), SV (11%), and EF (11%) were also observed (Figure 10).

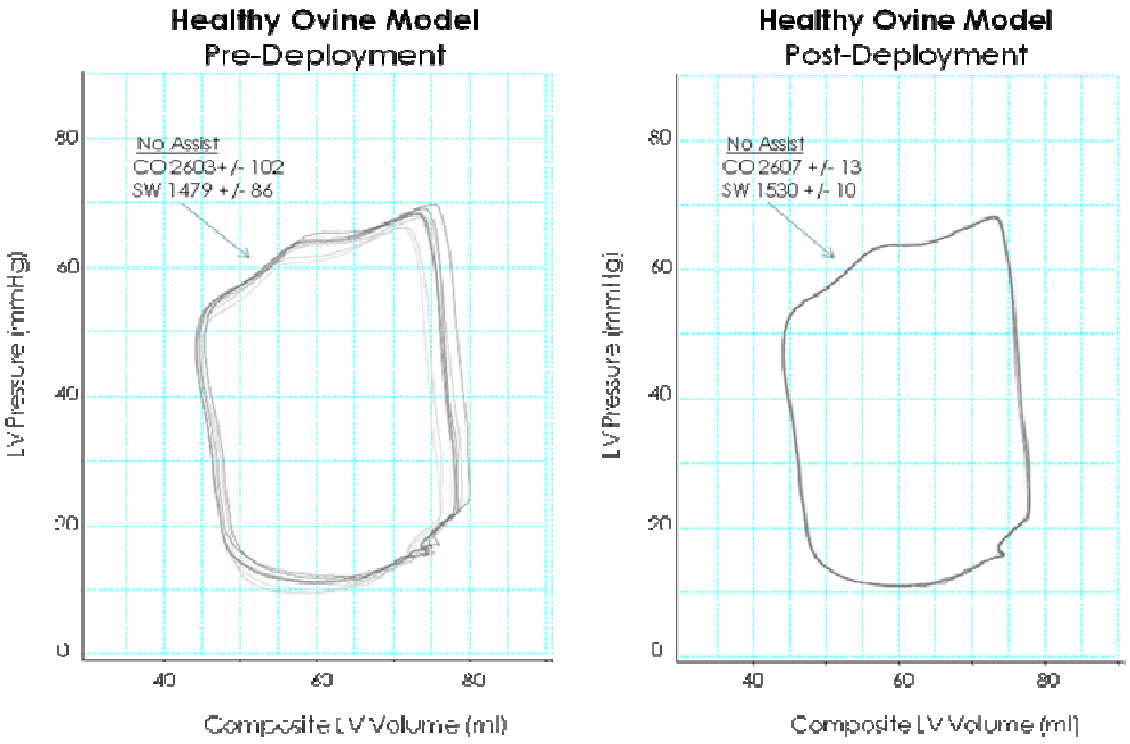


FIGURE 9: **PV Loops Pre- and Post- Deployment**. Note that the deployment of the device had no significant effects on cardiac function and performance.

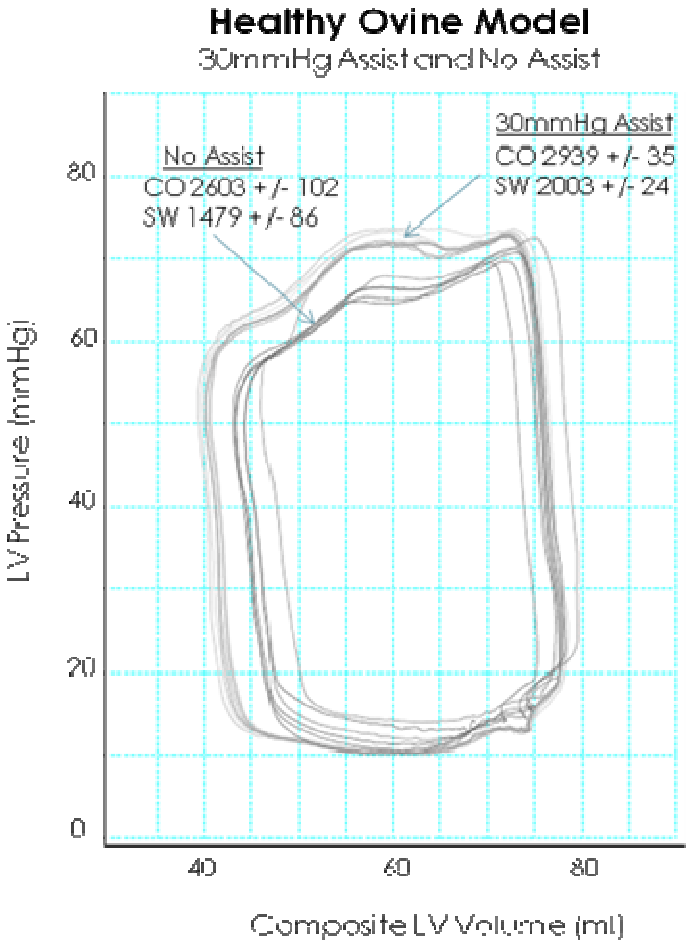


FIGURE 10: **Assisting the Healthy Heart**. Application of 30mmHg active assist to a healthy heart. Note that though SV, EF, CO, and SW were significantly increased (p=0.05), assist did not substantially alter the PV relationship.

Feature F2: The Device Does Not Invert Heart Curvature When Activated

Inspection of images obtained via fluoroscopy demonstrates that the device does not invert the curvature of the heart when activated. Images were acquired continuously at a rate of 15 frames per second over several cardiac cycles. Figure 11 displays fluoroscopic images acquired during end-diastole (ED) and end-systole (ES). During systole the device is maximally loaded with air that is easily discernible in the images; and consequently, the free wall is also apparent. Although the size is reduced from ED to ES, the heart shape remained the same in the images—i.e., no curvature inversion or gross changes in cardiac shape during systolic activation.

Feature F3: The Device Does Not Dislodge, Extrude or Expel the Heart When Activated

Fluoroscopic imaging was used to verify the proper placement and motion of the heart and device. The heart remained in the device throughout the study. Figure 11 provides images acquired during systole and diastole. These images affirm proper device placement and operation is maintained during maximal activation.

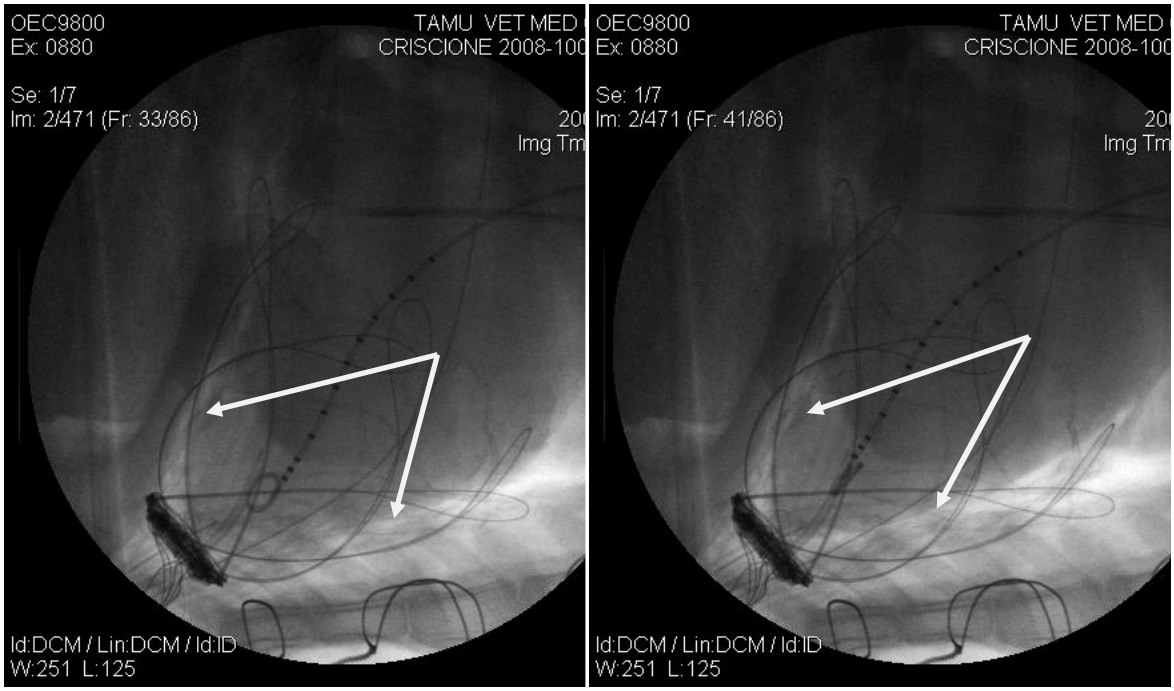


FIGURE 11: Flouroscopic Imaging of Active Assist. Left – diastole, fluid from the device is evacuated. Right – systole, the device is maximally filled. Note the free wall is not inverted during maximum assist and that the heart is not dislodged or expelled during assist.

8.9 Discussion

This investigation was motivated by the premise that mechanical stimuli are critical factors for guiding the growth, remodeling, and maintenance of mechanical organs. It is common understanding that physical therapy is essential to recovery from injury in the musculoskeletal system. In this sense it is well understood that mechanical stimuli are critical for proper function of a mechanical organ system. Cardiogenesis is known to be guided by mechanical factors. The role of mechanical factors in morphogenesis has also been well documented. Patwari and Lee [42] provide a review of this related to the cardiovascular system in particular. At the cellular level, myofibrillar organization [58], sarcomere alignment [59], and cell migration [60] are all known to be mediated by mechanical factors. Mechanical factors are also known to play an important role in the behavior of stem cells, suggesting that understanding and control of the mechanical environment may be critical to the realization of the potential for stem cell therapies [43]. The device described herein is capable of manipulating important mechanical factors that may ultimately influence cardiac performance, growth and remodeling processes, and regenerative therapies. It is proposed that a device such as that reported here may advance investigations of therapeutic options that target cardiac rehabilitation, restoration, and/or regeneration.

Considering the strong role of LV remodeling in promoting a maladaptive cardiac geometry, preventing or reversing remodeling has emerged as important target in the

treatment of CHF [6]. While there is strong evidence that Cardiac Support Devices (CSD) inhibit enlargement, evidence suggesting restorative or rehabilitative remodeling is mostly missing and limited to case reports of “reverse remodeling” following treatment of an underlying disease (e.g., valve defect or metabolic disease) or after placement of a left ventricular assist device in patients awaiting transplant. Nevertheless, contractile proteins are in a constant state of flux with absorption and formation occurring simultaneously — at rates about equal to half of the heart muscle mass per week. The myocardium is continuously reconstituting itself by processes that are guided by physiologic demand and the mechanical environment in which the heart must function.

It is hypothesized that with passive constraint and systematic reduction of an enlarging diseased heart, natural growth and remodeling processes can be directed such that they are restorative and thereby therapeutic intervention is rehabilitative. Active assist capabilities will ensure clinical cardiac performance metrics (e.g. cardiac output, ejection fraction, stroke work, etc.) are not compromised during the treatment regimen. Note that non-adjustable passive CSDs are designed to resist chronic dilation of end-diastolic volume, as well as reduce ventricular wall stress and myocardial stretch. In best case scenarios, passive CSDs may induce reverse remodeling toward normal size and function. The limiting factor in this process is the relative geometry of the device as compared to the diseased myocardium. Reverse remodeling events occur in response to the variations in the mechanical environment imposed by the device. Remodeling is an

adaptive behavior, and once equilibrium with the device imposed mechanical conditions is achieved restorative remodeling will wane. Consequently, in order to achieve full rehabilitation of the myocardium it is important to be able to intervene in the remodeling process via an adjustable device wherein the mechanical conditions required to sustain restorative remodeling can be maintained until normal size, shape, and function are achieved by natural growth and remodeling processes. A recent report [98] shows promise for such therapy in an ovine model.

Regenerative therapies incorporating stem cells or more sophisticated engineered tissue constructs have demonstrated potential but have yet to be fully developed. Benefits observed in stem cell studies have been controversial, e.g. there is a general lack of evidence that implanted stem cells are actually integrating with the native tissue as functional cardiomyocytes [100-103]. Stem cells are typically transplanted into the diseased myocardium where fiber alignment is highly disorganized and disrupted by fibrotic tissue. In the dyskinetic myocardium, the mechanical and environmental cues required to guide alignment and migration of transplanted cells are severely compromised. The device described herein, provides the means to restore motion that may be critical to establishing the appropriate physiologic mechanical environment required to optimize cell and tissue transplant therapies.

It is acknowledged that the primary limitation of this study is that the data are from only one animal. Nevertheless, we are not making conclusions about reliability, safety, or

efficacy; rather we are reporting that it is possible to deliver actions A1 and A2 with a device that also has features F1-F3. Only one successful experiment is needed to establish proof-of-concept, albeit multiple animal experiments with proper control groups are needed to assess reliability, safety, and efficacy of the mechanical therapy. Another limitation is that our imaging was restricted to a single 2-D long-axis view, and thus our assessment of curvature inversion is limited to this single image plane. This limitation, however, does not restrict our ability to assess feature F3 because our imaging was sufficient for visualizing the heart apex location relative to the device apex.

8.10 Conclusion

The technology described herein has potential to serve as (1) a means of investigating the effects of the mechanical environment on cardiac physiology, and (2) a therapeutic device for the treatment of congestive heart failure. As an experimental apparatus it is versatile, incorporating adjustable passive constraint and synchronous active assist capabilities. These properties provide for a wide range of mechanical effects to be examined. As a therapeutic device, it is possible that a diseased hypertrophied heart can be gradually returned to normal size with restoration of function – rehabilitation. The principles guiding this approach involve simply creating the conditions under which natural growth and remodeling processes are guided in a therapeutic manner. The versatility of the device gives the practitioner or researcher options and allows for controlled, disease specific, flexible intervention. While the technology performed well

given the nature of the study, the value and utility is vested in the idea that mechanical factors are important stimuli in normal and pathologic physiology – particularly with tissues and organs that are essentially mechanical in nature.

8.11 Additional Observations

The device is triggered by the ECG signal which is obtained by probes built into the device. The built ECG probes give a more stable signal, as movement of the animal does not affect the signal in the way it can affect signals obtained by probes placed on the skin. Though triggering worked very well the device in its' present incarnation is vacuum limited, i.e. vacuum fluid (gas) transport is relatively slow. Thus, the system is very sensitive to gate times and may be unusable at higher heart rates. In this study heart the heart rate varied from 68 to 78 beats per minute. The device functioned well at these frequencies. One notable device failure is analyzed below and is representative of the known potential problems with this system. In this case, tachycardia caused the pressure gate to open before the device was completely depressurized (Figure 12). The problem was resolved by momentarily shutting down the system (and extending the vacuum gate time). Though this was a relatively simple solution, it required (1) manual adjustment and thus, (2) that the device performance be monitored continuously. One potential software solution would be to disable the pressure gate until the device pressure falls below an established threshold – in essence, this may involve the device being disabled for a given cardiac cycle, however this would be preferable to hyper-pressurization.

Another interesting observation concerned the modes by which stroke work was increased when the device was activated. In all cases the activation of the device resulted in an increase in the maximum ventricular pressure which contributed partially to increased stroke work. Ventricular volume is the other factor that may provide for increased stroke work. Note that, in the healthy heart increases in stroke work were associated with a decrease in the minimum volume, i.e. greater ejection. However, when the pre-load was reduced, increased stroke work was associated with an increase in maximum volume, i.e. greater filling. When contractility is reduced, increased stroke work is associated with greater filling and greater ejection (Figure 13).

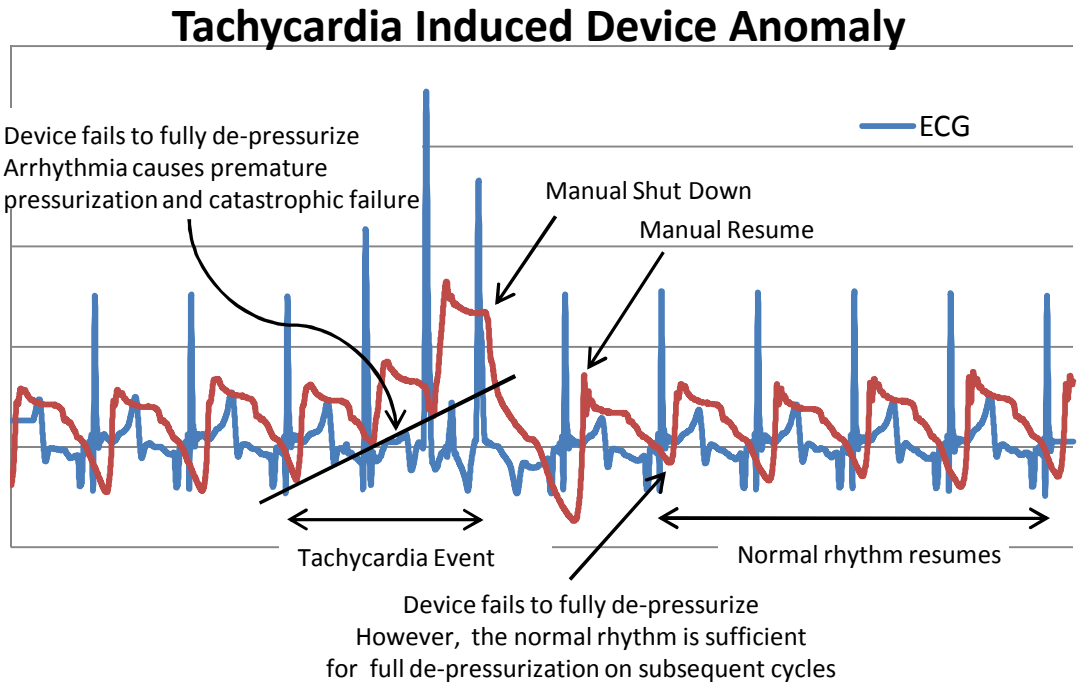


FIGURE 12: Tachycardia Induced Device Anomaly. Tachycardia coupled with slow vacuum performance caused the device to over pressurize. The vacuum limited nature of the system is evident in the distinct differences in the rise and fall times of the device pressure waveform. Software modification will prevent this type of failure from occurring by disabling the pressure gate when the device pressure is above a prescribed threshold.

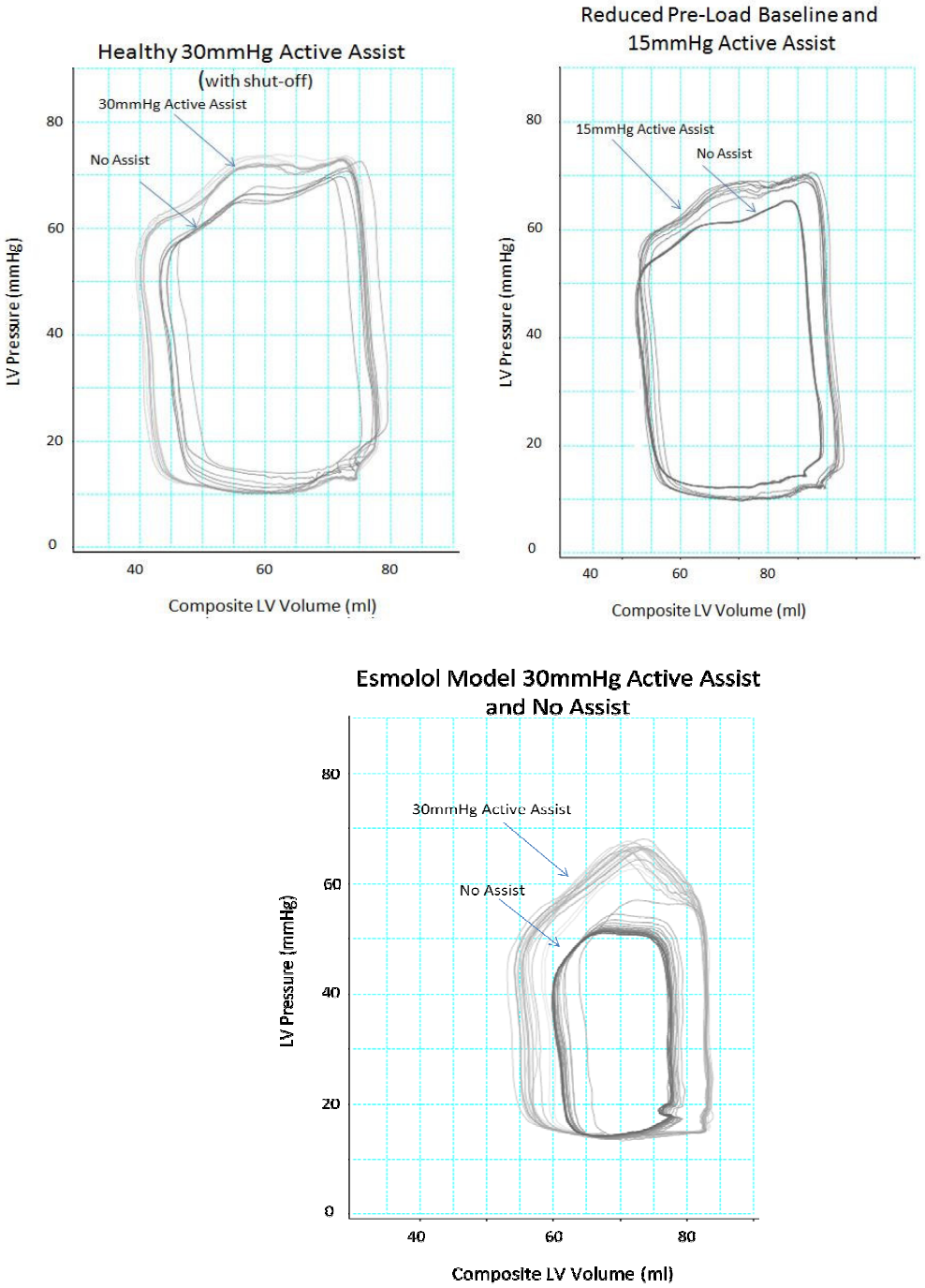


FIGURE 13: Modes of Increasing Stroke Work. (Top Left) Assist results in increased SW predominantly via increased Pmax and descreased Vmin. (Top Right) Assist results in increased SW predominantly via increased Pmax and increased Vmax. (Bottom) Assist results in increased SW via increased Pmax, as well as, increased Vmax and decreased Vmin.

9. DEVELOPMENT OF A *MINIMALLY INVASIVE* DEVICE CAPABLE OF *SIMULTANEOUS* ADJUSTABLE CARDIAC SUPPORT AND ACTIVE SYNCHRONOUS ASSIST

9.1 Device Actions and Features

The device described herein represents a substantial advancement over that described in section 8 above. The ultimate goal remains the development of a novel device and therapy targeting cardiac rehabilitation through physical therapy, facilitated via artful management of the local mechanical environment. The major advancements achieved in this design iteration are (1) device deployment via minimally invasive procedures and (2) capability to provide simultaneous support and assist. The following two modes of operation or device mediated actions were sought and assessed in an acute ovine study. These modes of operation may be implemented independently or simultaneously. They are as follows:

A1) adjustable cardiac support or passive constraint to reduce heart size

A2) synchronous active assist to increase heart motion or stroke volume, stroke work, ejection fraction, and/or cardiac output

Moreover, to enable our research goals of testing the effectiveness of the above actions to reverse-remodel the heart, we sought and assessed the following four inactions or device features:

F1) delivered and deployed via minimally invasive surgical procedures

F2) does not impede heart function when it is inactive

F3) does not invert heart curvature (nor induce similar, abnormal motions) when it is activated

F4) does not dislodge, extrude or expel the heart when it is activated

These features are necessary for chronic experiments to assess heart remodeling—i.e., the next phase of studies.

The device and deployment system are designed for less invasive implantation through a 1-2" sub-xiphoid incision in sheep (mini left thoracotomy in humans). The device is non-blood contacting, resides in the pericardial space and provides assist and support through direct cardiac contact or compression. Cardiac support capabilities are designed to be progressively actuated over a period of months, whereas assist capabilities are designed to temporarily restore cardiac output in the event of cardiogenic shock.

There is a recent report of a device capable of adjustable cardiac support [98], and there are reports of a direct cardiac compression device [99] for providing synchronous active assist. Nevertheless, we could not find any implantable devices that provide actions A1-A2, either independently or simultaneously, and hence, we developed the device of this study. To our knowledge, this report is the first for a combination device that is delivered via minimally invasive procedures and can perform both actions A1 and A2 independently or simultaneously.

9.2 Device Construction

The device was designed with an inner passive layer containing six chambers and an outer active layer containing six chambers. The chambers were composed of a thin nylon film. Each chamber had an identical helical orientation, but shifted 60 degrees so to form a complete circumference and form a cup-shaped structure. The inner and outer layers were offset such that the seams between the chambers did not overlap. Polyurethane tubing (0.25" d) was employed as the conduit for fluid transport to and from the chambers. The end of the tubing within the bladders was spiral cut to prevent the nylon film from collapsing onto to the tube end during the diastolic phase of assist when vacuum was applied to remove air in the chambers. The other tube ends were coalesced together into one driveline (0.375" d). Although separate in construction, tubing connections made the six-chambers of a given (inner passive or outer active) layer contiguous with the same pressure source (Figure 14). The device pressure was monitored continuously via use of a Millar pressure catheter transducer (Millar Instruments Inc., Houston, TX) placed within one of the inner passive chambers. The chambers were also attached to a nitinol scaffold which provided structural stability and served as a reference electrode for acquisition of the ECG signal used to trigger the device. The sense electrode was sewn to the heart apex. This epicardial electrode configuration provided an on-axis, robust ECG signal with a maximally polarized QRS complex. The ECG was routed to a BNC-2110 connector block which in turn was connected to a USB-6251 DAQ Board (National Instruments Corporation, Austin TX).

FIGURE 14: Minimally Invasive Simultaneous Function Device. A prototype of the minimally invasive device capable of simultaneous passive support and active assist, deployed about an excised ovine heart that is preserved and wrapped in thin latex for handling.

A modified version of the custom LabView (National Instruments Corporation, Austin TX) program described in section 7.2 was used to monitor device pressure, acquire the ECG, and trigger the device (Figure 15). The primary modification incorporated a safety algorithm designed to prevent the device from over-pressurization, e.g. in the event of tachycardia. Briefly, a threshold is set for the device pressure. If the pressure is not below the threshold the device is not triggered and the vacuum is continued until sufficient fluid is removed from the device. This prevents fluid from accumulating in the device such that pressure continues to rise or remains abnormally high during diastole thereby inhibiting ventricular filling.

The pneumatic system was also modified following the previous study (Figure 16). A network of capacitors was added to provide more flexibility in the manner in which fluid (air) could be transported into the device. This provides an additional safety measure as the device is no longer directly exposed to the high pressure source, as in the previous design. The capacitor network allows for variable capacitance. The pressure in the reservoir was tuned with the capacitor network to achieve the desired transport profile.

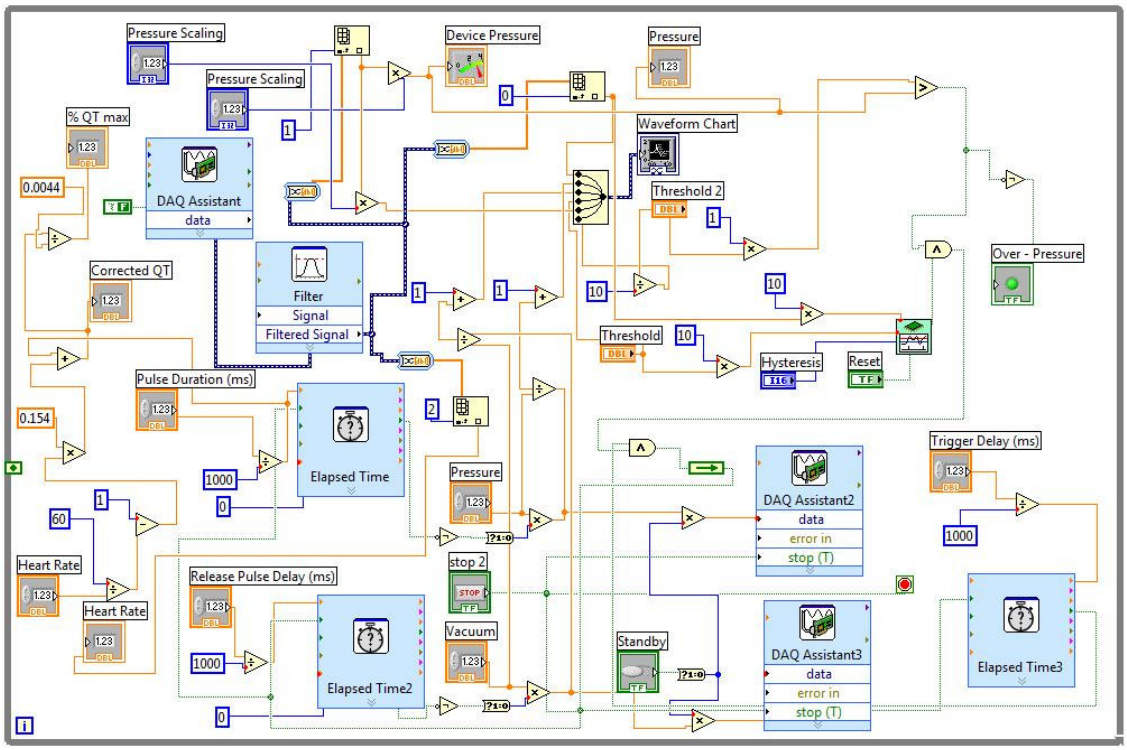


FIGURE 15: Schematic of the Modified LabView Application. The specific modifications included the use of device pressure to disable triggering to prevent device over-pressurization and the implementation of corrected QT intervals to determine gate times.

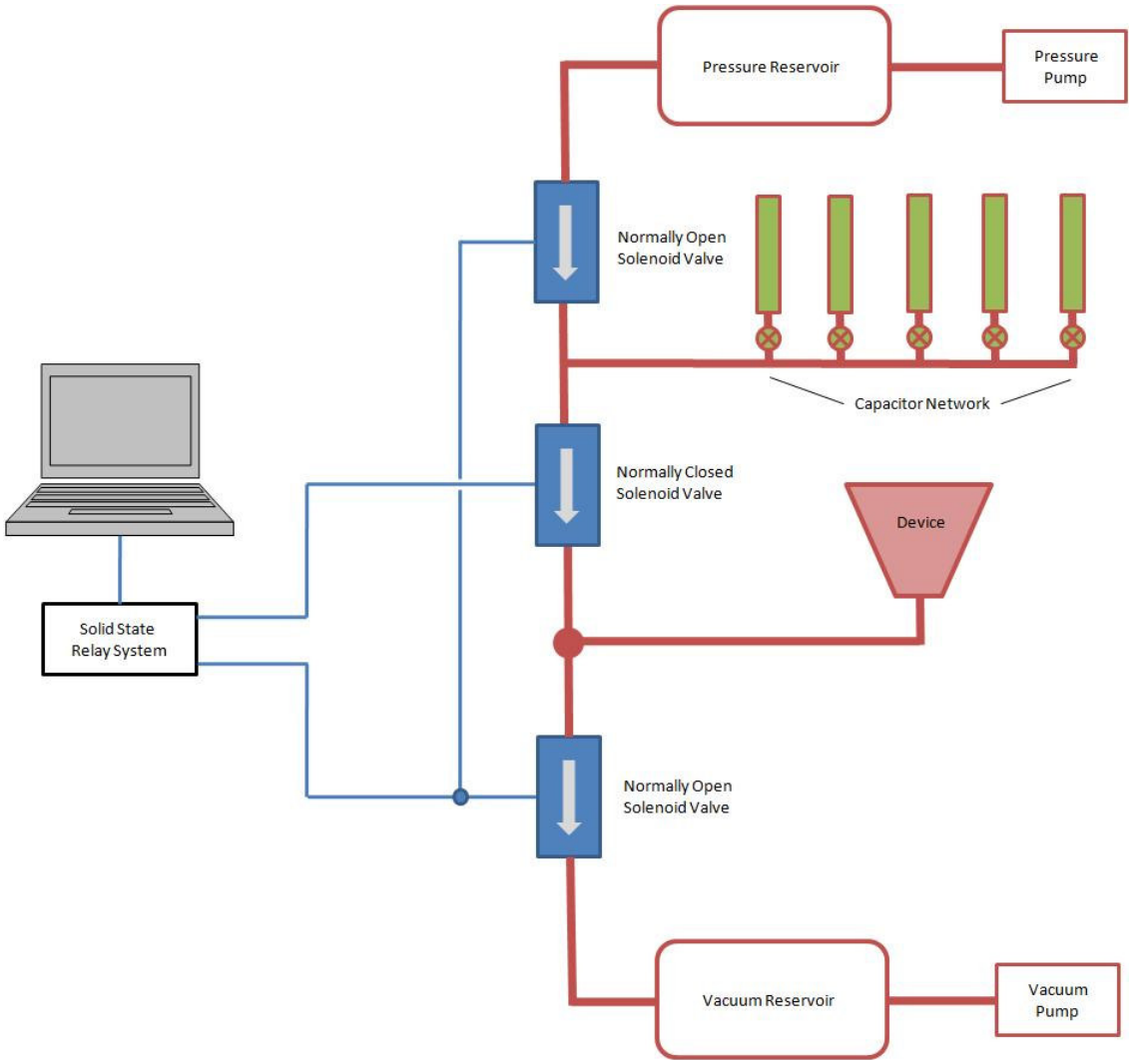


FIGURE 16. Schematic of the Modified Pneumatic System. Note the addition of the capacitor network. This network allowed more control over the manner in which fluid (air) was transported into the device and prevented the device from being directly exposed to a constant pressure source.

10. ASSESSMENT OF A *MINIMALLY INVASIVE* DEVICE CAPABLE OF *SIMULTANEOUS* ADJUSTABLE CARDIAC SUPPORT AND ACTIVE SYNCHRONOUS ASSIST IN AN ACUTE HEART FAILURE MODEL

10.1 Delivery and Assessment of Action A1

Changes in the filling pressure of the left ventricle, known as preload, move the end-diastolic point, the lower right-hand corner of the PV loop. These points can often be approximated in a linear fashion and are collectively known as the end-diastolic pressure-volume relationship (EDPVR), which represents the passive filling mechanics of the left ventricle. Adjustable cardiac support or passive constraint was accomplished by filling the passive chambers of the device with a fixed volume of saline. Although we applied a fixed volume, this action is termed *adjustable* cardiac support because the volume of fluid or amount of support can be adjusted post-implantation. We tested two separate cases: 1) 0mL saline, and 2) 40mL saline. With caval occlusion using a balloon catheter, the EDPVR for both of the above states was determined and then compared to assess the effectiveness of action A1 to shift the EDPVR upward or leftward (i.e., toward a smaller heart size).

10.2 Delivery and Assessment of Action A2

Synchronous active assist was accomplished by oscillating the driving pressure of the device in synchrony with heart contraction. With the modified pneumatic system, during diastole valves were opened to expose the device to the vacuum source, and the capacitor network to the pressure source. During systole the pressure and vacuum source valves were closed and the capacitor valve was opened to fill the device. The appropriate gate times were correlated with the QT interval. Device pressure was varied by adjusting the capacitor network and pressure source. To assess the ability of the device to provide synchronous cardiac assist for a failing heart, we applied 0 and 20 mmHg of systolic assist for two cardiac states: 1) normal or baseline contractility, and 2) low contractility or esmolol induced, acute heart failure. For the normal cardiac state an active assist of 20mmHg was applied for approximately 5-10 cardiac cycles, after which the active assist was shut off for approximately 5-10 cardiac cycles. The same procedure was used for the esmolol induced failure state, first with an active assist of 20mmHg. PV loop analysis was used to assess cardiac function during the varying amounts of assist.

10.3 Design and Assessment of F1

Implantation is designed to be accomplished by using guide wires attached to a deployment tube containing the device, seen in Figure 17 (Top). Fixed suture loops are sewn to the base of the device. The guide wires are then passed through the suture loops

and the device is preloaded into the deployment tube. Once the guide wires are properly placed inside the pericardial space, the device can be pushed out of the deployment tube following the guide wires into the correct position. In order to get the guide wires placed properly, the tip of each wire is sutured together to form a scoop or spoon shape, seen in Figure 17 (Bottom). The scoop is inserted into the pericardial opening at which time the suture holding the nitinol guide wires together is released allowing them to recoil into the correct position.

10.4 Design and Assessment of F2

The device was made of thin nylon film bladders and nitinol wires that formed an open frame so that it was collapsible when depressurized. The design constraint of collapsibility when depressurized was sought so that the device itself did not impede cardiac function. To assess this feature, PV loop analysis was done prior to implantation (prior to opening the chest) and after implantation (after chest closed). Cardiac function pre- and post- implant was subsequently compared.

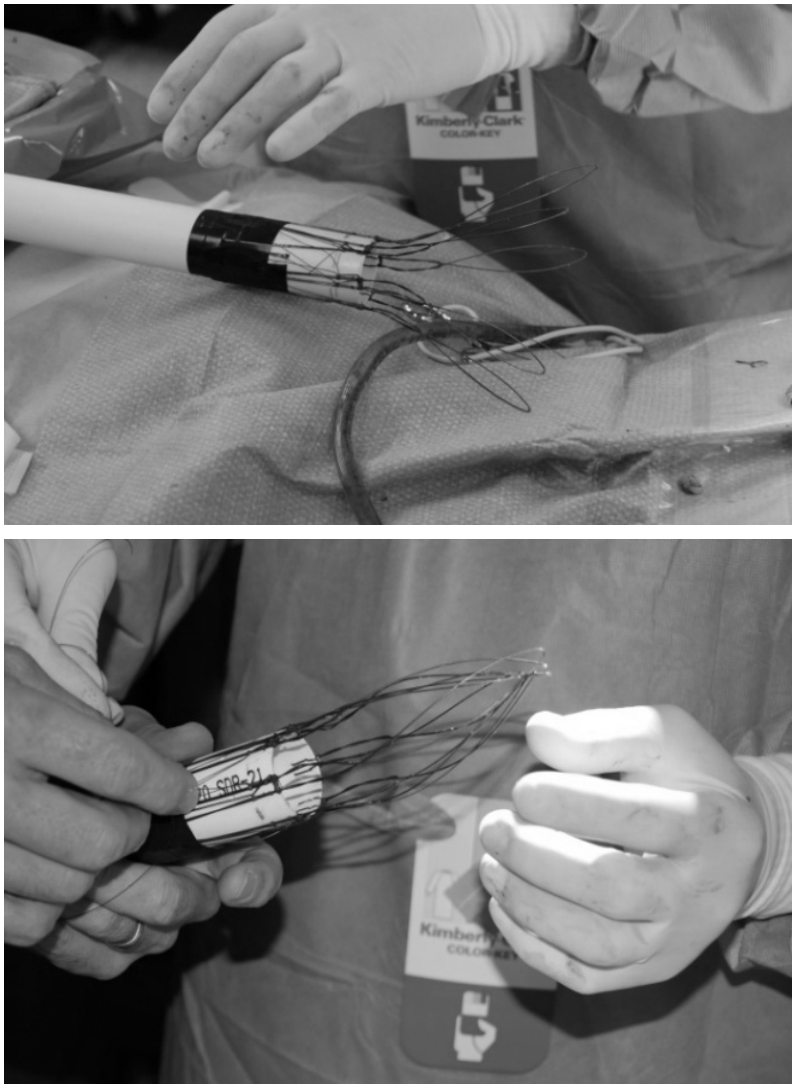


FIGURE 17: Delivery and Deployment Device. (Top) Picture of guide wires attached to deployment tube. (Bottom) Picture of guide wires sutured together to form scoop shape to aid in device placement.

10.5 Design and Assessment of F3

The outer half of the device chambers formed a continuous, inextensible outer shell of nylon whereas the inner half was in direct contact with the heart surface rather than fully distended. Consequently, the device was designed to apply uniform pressure to the entire epicardial heart surface, as uniform pressure was likely to preserve cardiac curvature—i.e., it was unlikely to invert the ventricular wall or cause similar aberrant motions. To assess the heart shape during device activation, the heart silhouette was observed in fluoroscopy videos taken during maximal device activation. The air-heart interface was easily identified with x-ray imaging.

10.6 Design and Assessment of F4

The chambers of the device were tapered with minimal space near the apex and maximal space near the base. Consequently, when the device was activated it took on a cup-like shape as opposed to a ball-like shape—the latter being the expected shape for an inflated object that does not have chamber partitions. The advantage of a cup-like activated shape is that the heart is likely to be retained in the device rather than expelled from the device. This is so because there is no free air in the chest to fill the space between an expelled heart and the cup cavity. Rather, the heart and device were expected to be pneumatically coupled and coaxially fixed without the need of suturing to the heart. To

assess this feature, the motion of the heart silhouette relative to the wire frame on the device was observed in fluoroscopy videos.

10.7 Surgical Procedure

The care and use of the sheep in this acute implant study and terminal procedure was conducted at the Texas A&M University College of Veterinary Medicine in accordance with an active animal use protocol approved by the Institutional Animal Care and Use Committee of the Texas A&M University System. The adult sheep, which weighed approximately 70 kg, was premedicated with an anti-anxiety drug (Xylazine 0.075 mg/lb) and an anticholinergic (Glycopyrrolate 0.01 mg/kg). Both drugs were given intramuscularly. After sedation a 16 g catheter was placed in the left jugular vein and anesthesia was induced with Ketamine (4.4 mg/kg) and Diazepam (0.11 mg/g) mixed together and given intravenously (IV) to effect. After induction, the animal was placed sternal and an endotracheal tube of appropriate size was placed and the animal connected to the anesthesia machine. Anesthesia was maintained with isoflurane gas at a concentration of 2-4% throughout the procedure. The animal was clipped and prepped for surgery, 16g jugular catheter was replaced with an 8 French quad-lumen catheter to allow multiple IV access, and an orogastric tube was placed to prevent bloating. An arterial catheter was placed in the left dorsal pedal artery to allow for direct blood pressure monitoring. The animal was placed in dorsal recumbuncy for the remainder of the study. Supporative IV fluids and mechanical ventilation were started. Using a

Power Lab physiological monitoring unit; heart rate, blood pressure, central venous pressure, oxygen saturation, ECG, and respirations were monitored throughout the procedure. A lidocaine CRI was started to prevent arrhythmias and Buprenorphine (0.02-0.05 mg/kg) was administered for pain. A Millar PV Catheter was placed through a left carotid artery cut-down and positioned by use of fluoroscopy. This conductance catheter was calibrated by injecting hypertonic saline into the left ventricle. To determine the parallel conductance contribution of the ventricle wall, the total conductance with the hypertonic saline is plotted versus the conductance of blood. The intersection of these plots represents the parallel conductance. After placement of the catheter, a sub-xiphoid incision was made, and extended up the sternum to increase exposure for device implantation. Implantation was accomplished by direct insertion of the device into the pericardial sac using the guide wires and deployment tube as described in section 10.3. The drive line was routed to the back of the sheep and exteriorized.

10.8 Results

Data was acquired and processed as described in section 8.7 above.

Action A1: Adjustable Cardiac Support or Passive Constraint to Reduce Heart Size

The vena cava occlusion was first done with the passive support chambers filled with 0mL of saline to establish a baseline EDPVR (Note: In the previous study, described in section 8, air was used in the passive chamber). After the heart recovered, the vena cava was occluded again but this time the passive component of the CSD was filled with 40 mL of saline. The end-diastolic points for each PV loop are plotted in the bottom of Figure 18. The plots of the EDPVR for the 0mL versus the 40mL show that the EDPVR shifted leftward. This shift in the EDPVR indicates a decrease in the size of the left ventricle relative to filling pressure, i.e. the ventricle maintains the same filling pressure at a smaller volume.

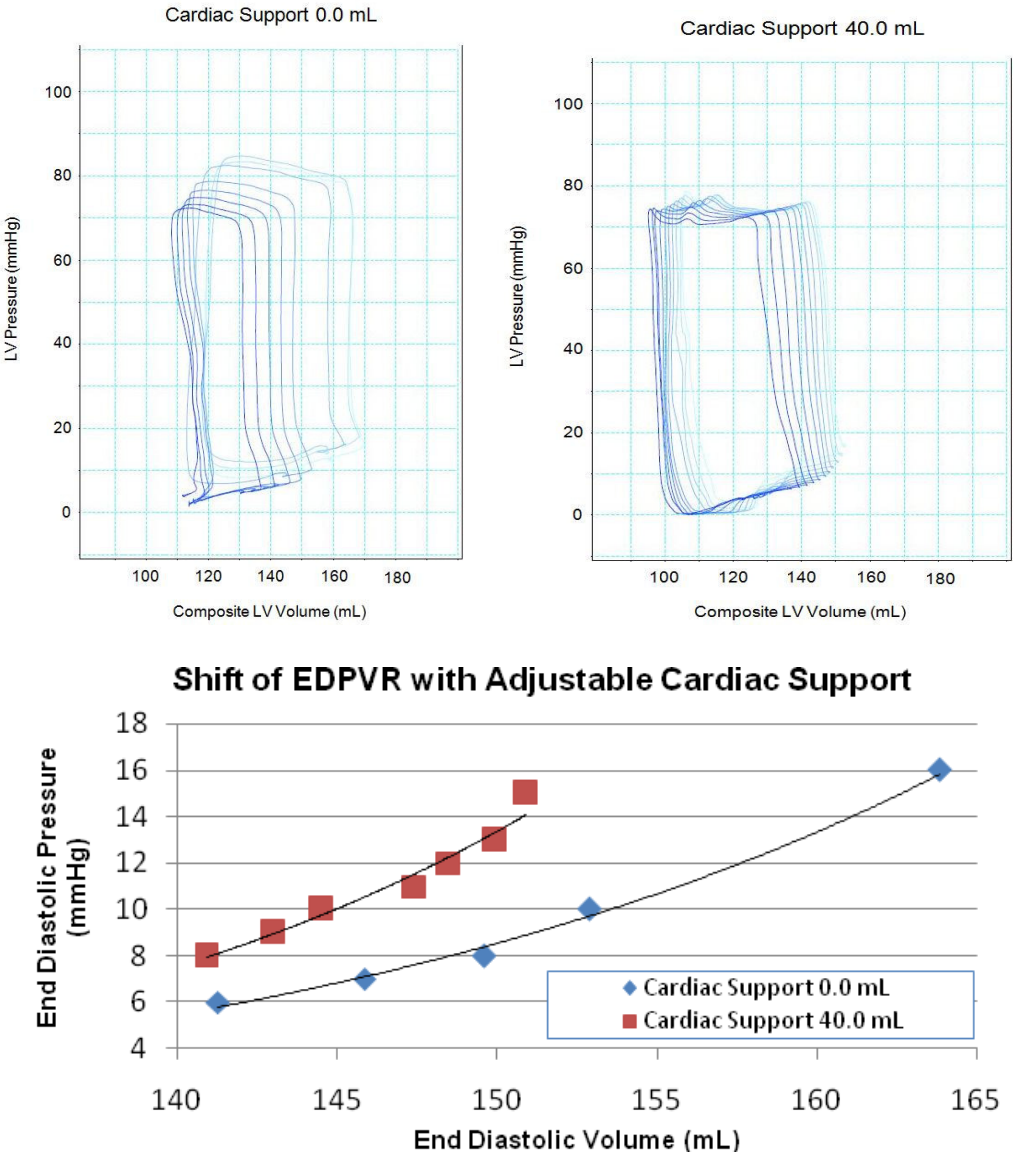


FIGURE 18: Shifting EDPVR Revisited. (Top Left) PV loops of the left ventricle during vena cava occlusion in the absence of passive support, i.e. cardiac support of 0.0 ml. (Top Right) PV loops of the left ventricle during vena cava occlusion with 40mL of passive support. (Bottom) Plots of the EDPVR for both the 0mL of support and 40mL of support.

Action A2: Synchronous Active Assist to Increase Heart Motion or Stroke Volume, Stroke Work, Ejection Fraction, and/or Cardiac Output

For the normal cardiac and the esmolol induced failure states, an active assist of 20mmHg was applied for approximately 5-10 cardiac cycles, after which the active assist was shut off for approximately 5-10 cardiac cycles. A comparison of the pressure-volume loops for both cases are in Figure 19. Notice that the PV loops for both states have a larger area with the active assist of 20mmHg. The area within the PV loop is stroke work, and it increased dramatically in the esmolol induced failure state. Figure 20 shows two critical measurements of cardiac performance for the normal cardiac state and esmolol induced heart failure state. For the normal cardiac state, an active assist of 20mmHg increased SV, EF, CO, and SW by 11.9%, 17.7%, 11.7%, and 20.5% respectively. For the esmolol induced heart failure state, high doses of esmolol infusion reduced SV by 30.7%, EF by 27.0%, CO by 29.3%, and SW by 49.9%. When the active assist of 20mmHg was applied to the esmolol induced heart failure state SV, EF, CO, and SW increased by 37.9%, 38.2%, 58.8%, and 49.9%, respectively.

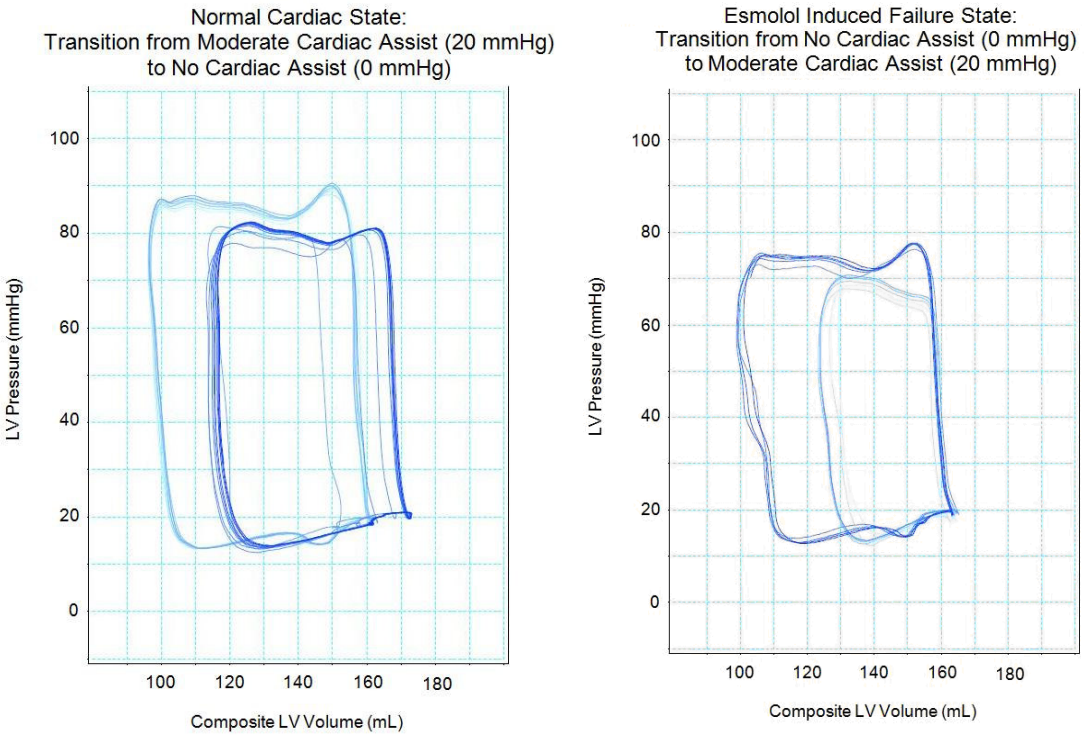


FIGURE 19: Assisting the Healthy Heart and Esmolol Failure Model. (Left) PV loops of left ventricle for the normal cardiac state with 20mmHg active assist transitioned to 0mmHg active assist. (Right) PV loops of the left ventricle for the esmolol induced failure state with 0mmHg active assist transitioned to 20mmHg active assist.

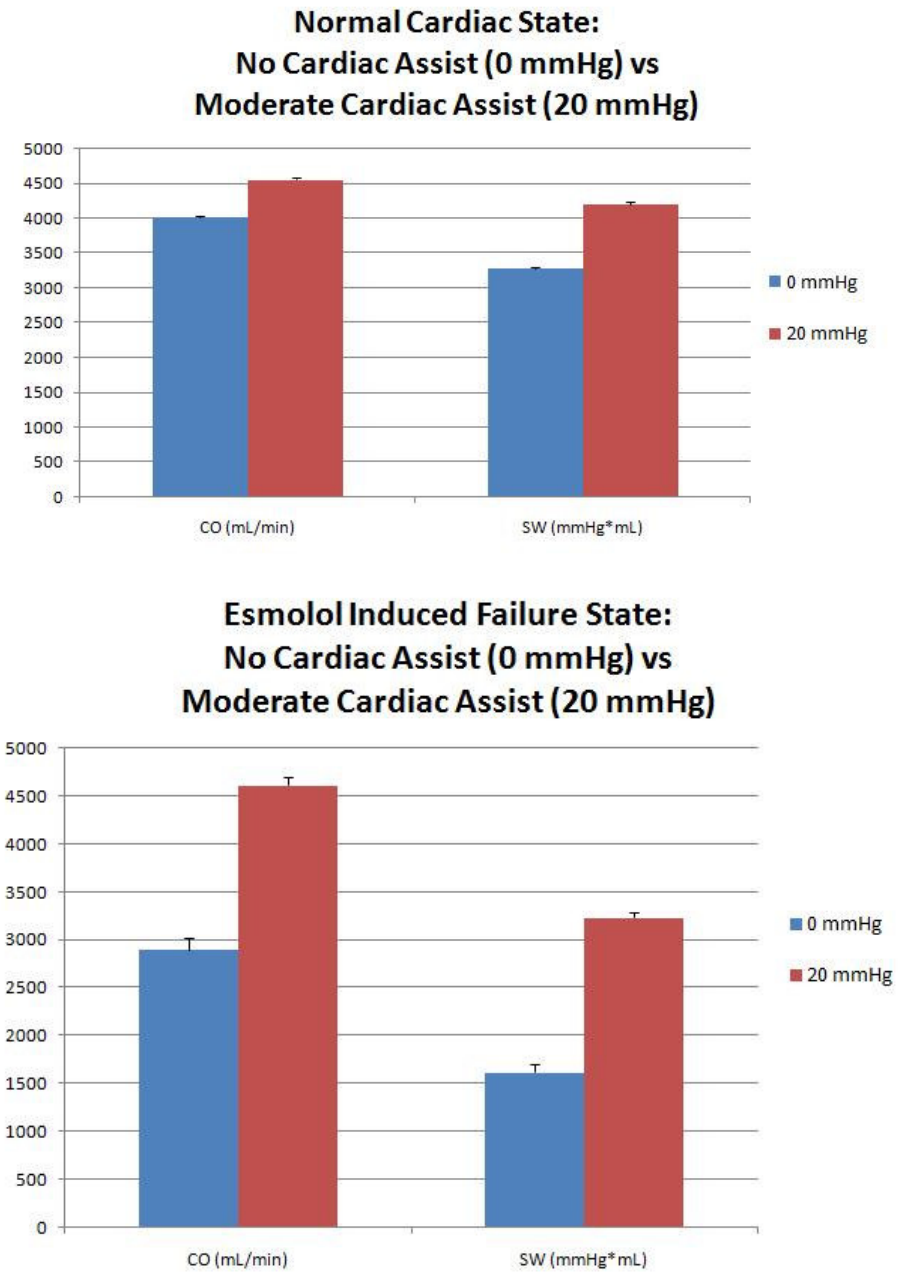


FIGURE 20: CO and SW in Healthy and Esmolol Models with Assist. Comparison of the cardiac output and stroke work for the normal cardiac state and esmolol induced failure state with and without assist. Notice the significant improvement in CO and doubling of SW for the esmolol induced heart failure state when an active assist of 20mmHg is applied.

Simultaneous Application of Actions A1 and A2

Fluoroscopic imaging was used to assess the simultaneous application of actions A1 and A2. Radio-opaque die was injected into the passive chambers. The working fluid in the active chambers is air which is easily discernible via fluoroscopy (Figure 21).

Feature F1: Delivery and Deployment via Minimally Invasive Surgical Procedures

The positioning of the guide wires was checked using fluoroscopy—the lateral boundaries of the heart are easily discernable, and a catheter in the coronary sinus indicates the lower boundary of the AV groove. With the guide wires positioned correctly the device was deployed out of the tube and along the guide wires. Once the device was fully deployed, the deployment tube and guide wires were removed from the pericardial space and the device implantation was complete. An image, using fluoroscopy, of the fully deployed device can be seen in Figure 21.

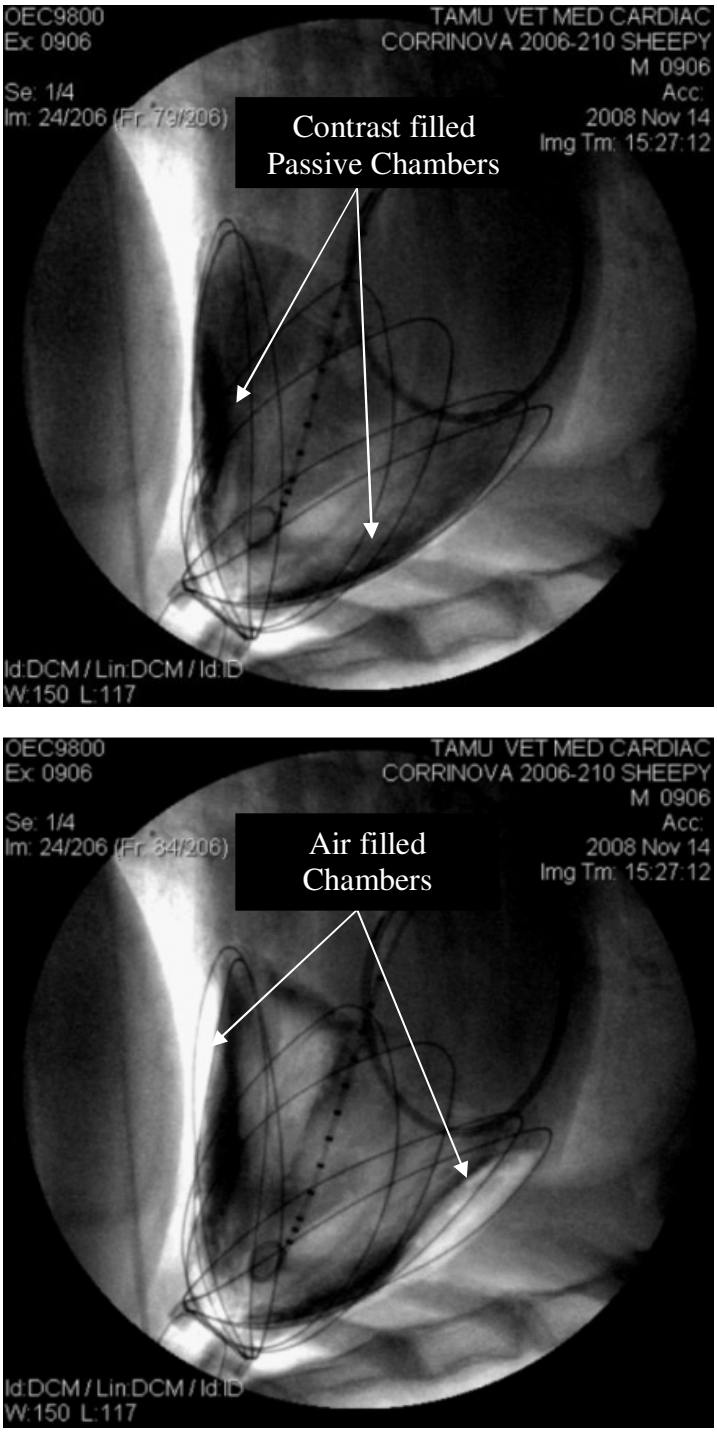


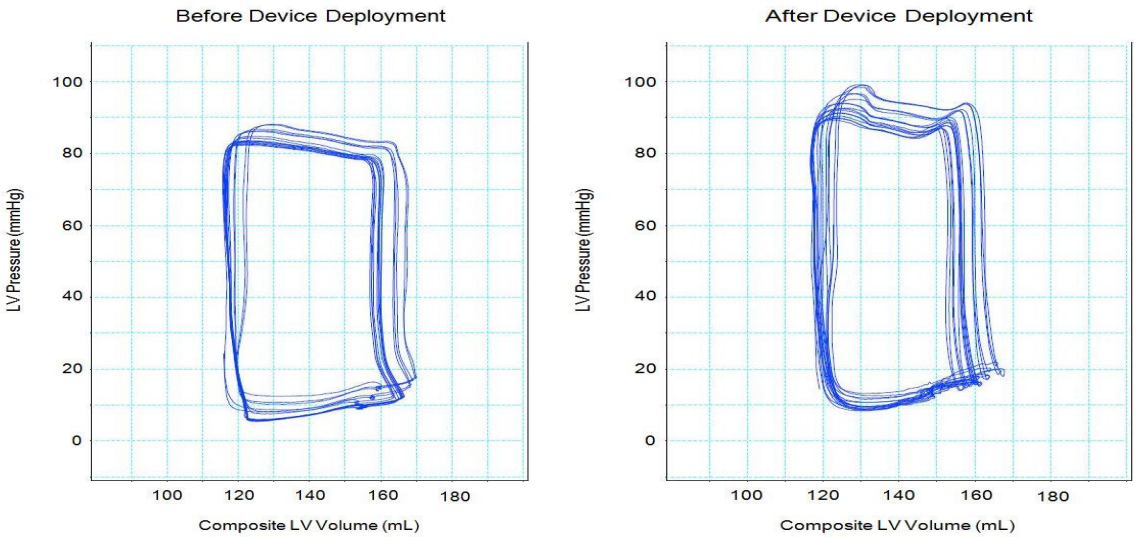
FIGURE 21: Fluoroscopic Imaging of the Simultaneous Function Device in Action. (Top) The passive chambers are filled with contrast-saline solution for imaging. The active chambers fully deflated. (Bottom) Fluoroscopic image of the fully deployed device with the active chambers partly inflated.

Feature F2: Device Does Not Impede Heart Function When Inactive

The PV loops acquired pre- and post- deployment are shown in (Fig 22). Stroke Volume (SV), Ejection Fraction (EF), Cardiac Output (CO), and Stroke Work (SW) were statistically similar. The heart rate increased by approximately 10% after device implantation; however, the heart rate was still well within the normal range. Figure 22 also provides a comparison of Cardiac Output (CO) and Stroke Work (SW) pre and post device deployment. Differences were not statistically significant.

F3: Device Does Not Invert Heart Curvature When Activated

Inspection of images obtained via fluoroscopy demonstrates that the device does not invert the curvature of the heart when activated. Images were acquired continuously at a rate of 15 frames per second over several cardiac cycles. Figure 21 displays fluoroscopic images acquired during end-diastole (ED) and end-systole (ES). During systole the device is maximally loaded with air that is easily discernible in the images; and consequently, the free wall is also apparent. Although the size is reduced from ED to ES, the heart shape remained the same in the images—i.e., there is no evidence of curvature inversion or gross changes in cardiac shape during systolic activation.



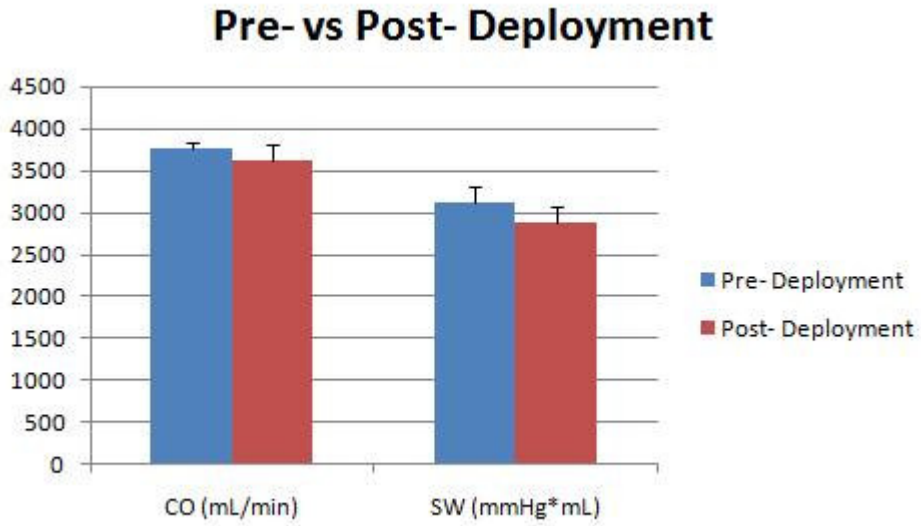


FIGURE 22: Simultaneous Function Device Pre- and Post-Deployment. (Top Left) and after device implantation (Top Right). Scales are the same, notice no significant change in the PV loops. (Bottom) Cardiac output (CO) and stroke work (SW), before and after deployment. Differences were not statistically significant. Error bars indicate the standard deviation.

F4: Device Does Not Dislodge, Extrude or Expel the Heart When Activated

The device takes on a rigid cup like shape (i.e., structurally supported cavity) when it is pressurized, and this naturally draws the heart into the device—such that suturing to the heart is not required. After air in the mediastinum is removed, the heart and device are pneumatically locked in a co-axial configuration. This feature was proven by fluoroscopy of device assist when actively pressurized during systole. The air filled bladders are easily visible on flouro, and it is evident that the heart is not displaced by device activation, rather the heart diameter decreases when bladders inflate (Figure 21).

Cardiac De-compression via Active Assist

The application of assist results in an immediate increase in stroke volume with concomitant decrease in both end-diastolic and end-systolic volumes, to new "assisted" equilibrium states. The upper tracing in Figure 23 is the volume channel from the PV catheter. The lower tracing is the device pressure. Note that the device pressure goes from 0mmHg during systole (before assist starts) to 20mmHg during systole after assist begins. The end-diastolic pressure in the device is constant at 15mmHg before assist begins and falls to 10mmHg after assist starts. The end diastolic pressure (EDP) is high in this case because of passive constraint; and the result here is that the active assist decompresses the LV, subsequently decreases EDP, and brings EDP back into the normal range. This phenomenon is cardiac decompression with cardiac assist.

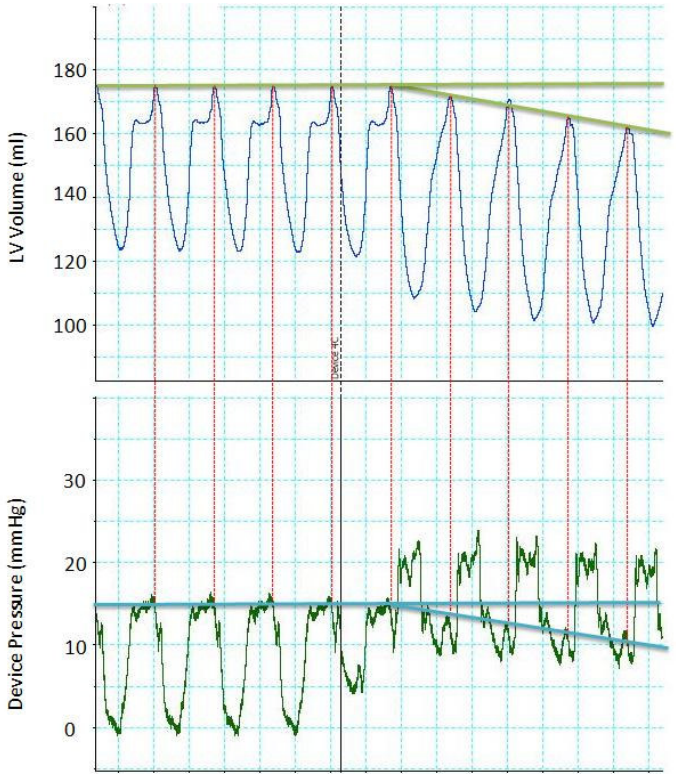


FIGURE 23: LV Volume vs. Device Pressure. This illustrates the transition from no assist to 20mmHg of assist. The upper tracing is the volume channel from the PV catheter. The lower tracing is the device pressure. Note that the device pressure goes from 0mmHg during systole (before assist starts) to 20mmHg during systole after assist begins. The end-diastolic pressure in the device is constant at 15mmHg before assist begins and falls to 10mmHg after assist starts.

Rose et al., 2001, examined the Randomized Evaluation of Mechanical Assistance for the Treatment, or "REMATCH" trial [72]. This was a major, multi-center (20), large trial (129 patients) designed to compare long-term cardiac assist treatments to pharmacological treatment in the areas of survival, serious adverse events, number of days of hospitalization and quality of life. The REMATCH trial states, "Patients with mild-to-moderate heart failure [73] and, recently, some with more severe disease [74] have been shown to benefit from drug therapy. Nevertheless, the survival and the quality of life of patients with severe heart failure remain limited. Cardiac transplantation is the only treatment that provides substantial individual benefit, but with fewer than 3,000 donor hearts available worldwide per year, its impact is epidemiologically trivial [75]." To mitigate the disparity between the number of available donor hearts and the number of patients in need of a heart transplant (estimated at 300,000) [76], the transplant waiting list has stringent guidelines. Consequently, most patients who are in need of a transplant are not qualified to be placed on the waiting list. Thus, there is great need for treatment options that can restore function to failing hearts. The REMATCH trial contributed to the recent action of the FDA to approve cardiac assist devices for use in end-stage heart failure patients who are not waiting for a transplant. Prior to this, cardiac assist devices were only approved as a bridge to transplantation. To our knowledge, none of the existing mechanical assist therapies are actually designed to treat pathologic mechanics such that cardiac recovery and rehabilitation is the targeted outcome.

The progression of CHF is typically initiated by some “index” cardiac event, e.g. acute myocardial infarction (AMI) due to obstruction of a coronary artery. Following an initial recovery period from AMI, there is symptomatic deterioration and evidence of progressive LV remodeling characterized globally by changes in LV chamber size and shape, and an ongoing loss of cardiomyocytes, myocyte hypertrophy and interstitial fibrosis [5]. Though pharmacotherapy can slow the progression of disease, ultimately the therapeutic options become limited to those that include or provide some form of mechanical assistance. Alternatively, though the mechanics can be neglected in the early stages of disease without immediate adverse clinical consequences, inevitably mechanical implications must be reconciled. It is well understood that the heart is a mechanical organ and therefore as it fails, there is a loss of mechanical performance that must be compensated by mechanical devices, i.e. the requisite mechanical work required to sustain life must be performed. It is also well understood that cardiac cells and tissues are mechanotransducers that rely on mechanical cues to perform their respective integrated roles. Abberant mechanical cues stimulate cell and tissue responses that are pathologic. To our knowledge existing device based therapies are designed to compensate for the loss of cardiac work, and essentially target symptoms of disease. This is critical to sustain life, however a strategy wherein device based interventions target the aberrant mechanical environment could provide a means for recovery and rehabilitation while simultaneously maintaining the conditions necessary to sustain life.

Many mechanical assist therapies (i.e., drugs, biventricular pacing, blood contacting assist devices, surgical manipulations, or passive stents and constraints etc.) off-load the heart and thus only modulate the strain pattern indirectly (e.g., through greater ejection fraction). DCCD are used to improve ejection of blood from the left ventricle, and thus, effectively offload the heart rather than directly modulate the strain pattern, e.g., the rigid cup shaped device of MyoVad (a.k.a. Myotech CSS - Biophan Technologies, Inc., Pittsford, NY). A major disadvantage of this type of device is that the process performed to eject blood inverts the curvature of the heart, which induces aberrant motion and hence an aberrant strain pattern. The inverted curvature leads to a flawed ventricular wall contour and results in regions of stress concentrations in the ventricle, which might lead to aneurysm formation, fibrosis, and impairment of the contractility and compliance of the ventricle. The resulting irregular contour of the endocardial surface of the left ventricle may lead to localized hemostasis or turbulence, which may in turn lead to thrombus formation and possible thromboembolism.

Curvature inversion can greatly increase ejection fraction. However, the curvature of the ventricles in a normal heart does not invert during systole, thus rendering such motions grossly abnormal. A healthy heart, moreover, will resist having its curvature inverted and Artrip et al. [104] shows that heart function needs to decline by 30% before the effect of "non-uniform direct cardiac compression" becomes noticeable. In short, the heart resists assist when a DCCD induces aberrant strains. The Vineberg device inverts curvature in long axis planes and short axis planes. The Anstadt cup [105] and Cardio-

Support System (Cardio Technologies Inc., Pine Brook, NJ) invert curvature in long axis planes yet preserve curvature in the short axis planes. The attachment is via vacuum on the apical end and the assist is via inflation of a membrane that lies between a rigid shell and the epicardial surfaces of the right ventricle (RV) and left ventricle (LV) (Williams and Artrip, 2001). The AbioBooster, [106] by Abiomed Inc. (Danvers, MA) and the devices of Parravicini [107] are sewn to the interventricular sulci; elastic sacks between the shell and the epicardial surface are inflated during systole. The DCC Patch, Heart Assist Tech Pty Ltd (NSW, Australia), and Parravicini devices pull on the interventricular sulci and push on the freewall such that the curvature will increase at the sulci and decrease on the freewalls. The Heart Booster [108] is composed of longitudinal tubes that have elliptical cross-sections with the major axis of the ellipse in the hoop direction and inverts curvature in short axis planes, yet preserves curvature in the long axis planes. Because they were not designed to eliminate aberrant motions, it should not be surprising that these existing DCCDs induce aberrant strain patterns. Given that strain is a primary stimulus of myocardial growth and remodeling, there is a need for a DCCD that eliminates dyskinetic or hypokinetic motions in the heart.

It is important to note that contraction strain depends on both the end-diastolic configuration (reference configuration) and the end-systolic configuration (current configuration). The strain field is a function of the gradient (with respect to reference position) of the mapping of material points from the reference configuration to the current configuration. The fact that a direct cardiac compression device fits the diastolic

configuration is inconsequential to achieving an appropriate contraction strain pattern because the end-systolic configuration is grossly aberrant. For example, passive direct compression cardiac devices (e.g., HeartNet and CorCap) are made of biocompatible mesh or nitinol and placed around the heart as an elastic, compressive reinforcement on the left ventricle to reduce deleterious wall tension during diastole (i.e., restrict end diastolic volume) and to resist shape change of the ventricle during the mechanical cardiac cycle. It is also important to note that these devices are not adjustable in vivo, fibrose to the myocardium, and therefore represent a one-shot approach to therapy.

To achieve a minimally invasive device, a soft-shelled DCCD has been constructed with inflatable, longitudinally oriented chambers that when deflated are collapsible. The device does not hinder cardiac performance when the device is deflated or deactivated. In addition, the deflated chambers are shaped and adjoined to form a structure that allows typical diastolic configurations. When pressurized the chambers push on the exterior of the heart in such a way as to induce a systolic configuration with normal curvatures. There is no need to attach the present invention to the heart because the heart is naturally drawn into the pressurized or activated device. Specifically, for the heart to leave the device (i.e., be extruded from the DCCD), the device curvature would need to invert, yet the device rigidity (when pressurized) resists curvature inversion. This is very useful because implantation time and complications due to attachment are minimized when this feature is present—i.e., when the activated shape of the device

cavity (i.e., the inner wall of the DCCD which touches the epicardial or outer boundary of the heart) is nearly end-systolic shape.

Two problems related to the inability of previous cardiac assist devices to promote cardiac regeneration and reverse the effects of congestive heart failure include 1) Previous cardiac assist devices being studied do not provide a physiological mechanical environment to the damaged tissue. 2) There may be an inability for resident cardiac stem cells to contribute significantly to the repair of cardiomyocytes. In fact, mechanical signals provide important cues that regulate stem cell behavior [43]. Establishing a normal mechanical environment may also be critical to the ultimate success of stem cell transplant therapies. Cardiac muscle fiber alignment can be highly disorganized in the failing heart and disrupted by fibrosis. Moreover, the afflicted region is highly dyskinetic exhibiting abnormal motion and mechanics. Transplantation of progenitors in the absence of cues to drive alignment with native heart tissue may not improve global heart function. Therapies based on the direct introduction of cardiomyocytes into the failing heart assume transplanted cells will align, differentiate, and functionally integrate into the host tissue in the absence of the cues that normally drive these processes [62]. In cardiogenesis, mechanics play an important role in the appropriate pathfinding, differentiation, and ultimate function of embryonic progenitors [42]. In disease, mechanics has also been shown to play an important role in morphogenesis. The prospect of inducing bona fide cardiac regeneration via cell cycle activation, cell transplantation, or stem cell mobilization is greater now than at any previous time [103].

One important obstacle to be overcome involves establishing the conditions, under which transplanted cells may integrate, differentiate and function in harmony with the native tissue.

While there is strong evidence that cardiac support devices e.g. CorCap, inhibit enlargement, evidence suggesting restorative or rehabilitative remodeling is mostly missing and limited to case reports of "reverse remodeling" following treatment of an underlying disease (e.g., valve defect or metabolic disease) or after placement of a left ventricular assist device in some patients awaiting transplant. Nevertheless, contractile proteins are in a constant state of flux, simultaneous absorption and formation at rates equal to approximately half of the heart muscle mass per week. Essentially, the myocardium is continuously reconstituting itself by processes that are guided by physiologic demand and the mechanical environment in which the heart must function. Variations in mechanical factors influence the growth and remodeling processes that are continuously at work within the myocardium. With use of an adjustable cardiac support device (ACSD) to continually shrink the heart over a period of several months (with 3-5% reduction every 3 weeks), it is possible that heart size can be returned to normal—regardless of the etiology. Reduction of heart size is highly significant because size and function are inversely in failing hearts. Restoration of normal size could alleviate failure.

With the exception of the device described by Ghanta in [98], current devices are not adjustable and, moreover, resist adjustment because of extensive fibrosis around the

heart. Though the Ghanta [98] device is adjustable in vivo, it is incapable of providing synchronous active assist, and requires tethering via continuous suture along the AV groove. With a novel design, we propose a CSD that can be adjusted in-situ over a period of weeks to months. We hypothesize, that this ACSD will enable proactive intervention whereby specific mechanical conditions can be generated and employed to direct growth and remodeling processes that are restorative and/or rehabilitative in nature, and thereby provide a substantial improvement over fixed CSD therapies. In addition to adjustable passive support, the device described herein has an active assist component that can increase stroke work as needed to provide enough cardiac output to keep vital organs functioning. Once the diseased heart is restored to normal size, the device (or a fixed CSD) can be used to prevent re-enlargement of the heart.

It is acknowledged that the primary limitation of this study is that the data is from only one animal. The purpose of this study was to establish proof-of-concept as it relates to device function. In addition, the purpose of this report is to provide a foundation for the immediate development of other device based therapies targeting pathologic mechanical factors, rather than merely compensating for loss of mechanical function, particularly when that function may be restored via physical rehabilitative therapy. Multiple animals experiments with proper control groups are needed to assess reliability, safety, and efficacy of this mechanical therapy. Another limitation is that our imaging was restricted to a single 2-D long-axis view, and thus our assessment of curvature inversion is limited to this single image plane. This limitation, however, does not restrict our ability to assess

feature F4 because our imaging was sufficient for visualizing the heart apex location relative to the device apex.

10.10 Conclusion

The technology described herein has potential to serve as (1) a means of investigating the effects of the mechanical environment on cardiac physiology, and (2) a therapeutic device for the treatment of congestive heart failure. To our knowledge it is the first device capable of providing adjustable passive support and synchronous active assist – simultaneously. Moreover, it is collapsible and can be delivered via minimally invasive surgical procedures. The versatility of the device provides for a wide range of proactive intervention possibilities. As a therapeutic device, it is possible that a diseased hypertrophied heart can be gradually returned to normal size with restoration of function – rehabilitation. The principles guiding this approach involve simply creating the conditions under which natural growth and remodeling processes are guided in a therapeutic manner. The versatility of the device gives the practitioner or researcher options and allows for controlled, disease specific, flexible intervention. While the technology performed well given the nature of the study, the value and utility is vested in the idea that mechanical factors are important stimuli in normal and pathologic physiology – particularly with tissues and organs that are essentially mechanical in nature.

11. DEVICE LIMITATIONS AND CAPABILITIES

The device described herein incorporates two basic mechanical functions, (1) load bearing and (2) fluid transport. The present design consists of two layers of six pressure chambers each. The chamber geometries of the outer active layer are necessarily different than those of the inner passive layer (Figure 24). To test the ability of the device to bear a pressure load five chambers of each design were used. The chambers were attached to a simple sphygmomanometer system in order to determine the magnitude of pressure at which the chamber fails either by burst or plastic deformation. Pressure was increased in increments of 10mmHg.

Deformation of the nylon material begins when pressure exceeds 130mmHg in the larger passive chambers (Table 2). Maximum operating pressure for the device is 60mmHg. Thus, the nylon material is sufficient and safe with respect to pressure induced failure. The pressurized diameter of the outer chambers is smaller than that of the inner chambers. Thus, at similar pressures, according to the Law of Laplace, the stresses in the nylon are lower in the outer chambers than in the inner chamber counterparts. Accordingly, the outer chambers tended to fail at the seams rather than by plastic deformation of the nylon (Table 3). Failure of the seams occurred at similar pressures and is not a concern given the operating pressure of the device. All panels are tested for leaks prior to incorporation into a device.

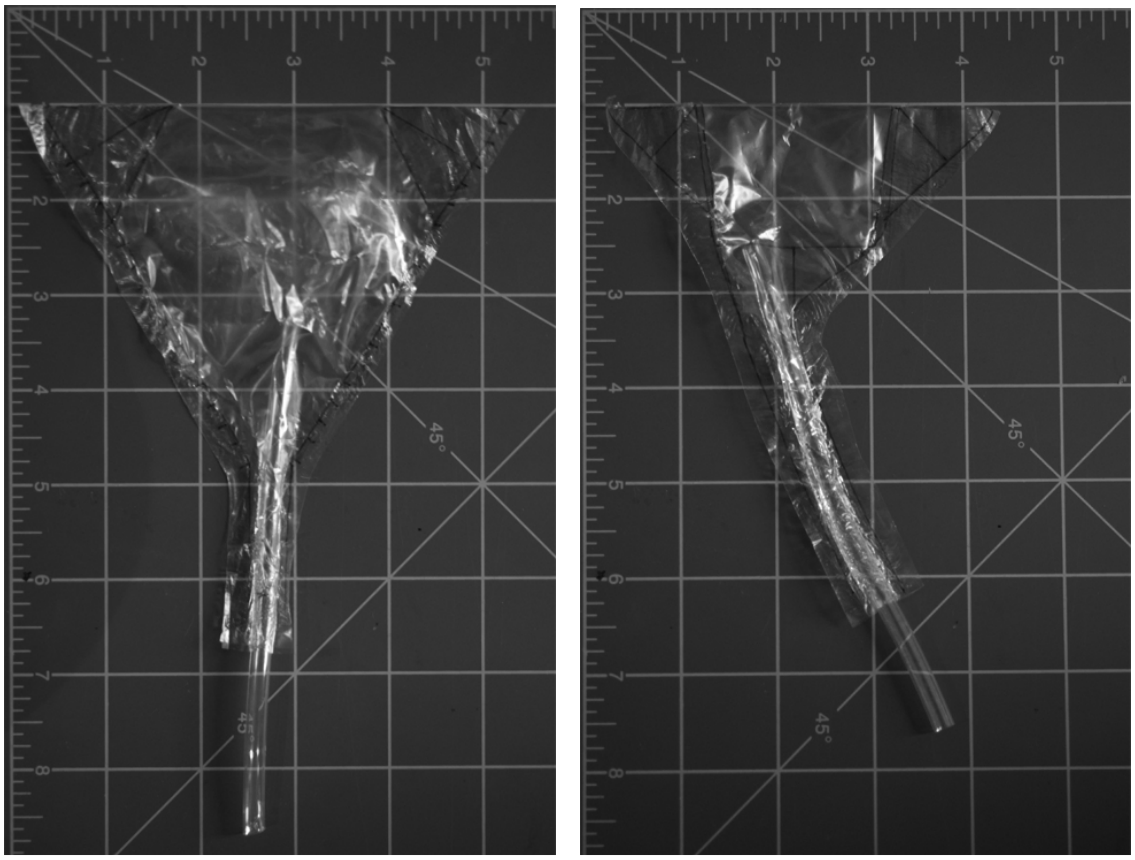


FIGURE 24: Active and Passive Device Chambers. Left – The larger passive chamber design. These chambers typically failed due to plastic deformation of the nylon. Right – The smaller active chamber design. These chambers typically failed at the seams. The geometry is more intricate thatn the larger passive chamber design and thus, creating the seal was more difficult. All chambers were tested to ensure the integrity of the seal prior to incorporation into the device.

TABLE 2: Inner Passive Chamber Pressure Capacity Test. The nylon material fails when pressures exceed 130mmHg. Seams generally held up well, i.e. bursts at the seams are likely due to manufacturing flaws.

Component	Outcome
PC1	Continuous Deformation at 140mmHg
PC2	Continuous Deformation at 150mmHg
PC3	Continuous Deformation at 140mmHg
PC4	Burst at seam at 130mmHg, signs of deformation present
PC5	Continuous Deformation at 140mmHg

TABLE 3: Outer Active Chamber Pressure Capacity Test. Slow leaks are suggestive of the difficulty in sealing the seams with this geometry. Deformation of the nylon material occurred at higher pressures as compared to the passive chambers, likely due to the smaller radius.

Component	Outcome
AC1	Burst at Seam at 140mmHg
AC2	Slow Leak, Burst at Seam at 150mmHg
AC3	Continuous Deformation at 150mmHg
AC4	Slow Leak at 100mmHg, Burst at Seam at 140mmHg
AC5	Slow Leak, Burst at Seam at 160mmHg

In order for the device to function properly it is imperative that fluid be shuttled in to and out of the device efficiently and reliably. It was empirically determined that the device is vacuum limited; the challenge of the fluid transport problem is one of evacuating the fluid from the device such that the heart may fill during diastole. The QT interval is measured from the start of the QRS complex and the end of the T wave in the ECG. For clinical purposes the corrected QT interval (QTc) as determined by Bazett's formula, is often used:

$$QTc = \frac{QT}{\sqrt{\frac{60}{heart\ rate}}}$$

Normal QTc intervals range from .3 to .45 seconds. Using this information, the corresponding "normal" QT intervals are plotted versus heart rate in Figure 25. Given the vacuum limited nature of the system the maximum QT values were used in an experiment designed to determine the maximum heart at which the device could operate reliably. A function generator was used to provide a sine wave to trigger device. The frequency was increased 15 cycles per minute, beginning at 60 cycles per minute. With each increase the device gates were adjusted according to the corresponding QT interval. The system was configured such that the device applied 30mmHg to a rigid mock heart setup. The device maintained reliable assist at simulated heart rates up to 135 BPM. At 150 BPM, performance varied as evidenced by increasing variance in applied. At 165 BPM, device performance was erratic (Figure 26). Thus, the assist function of the device appears limited in utility to heart rates near 135 BPM or below.

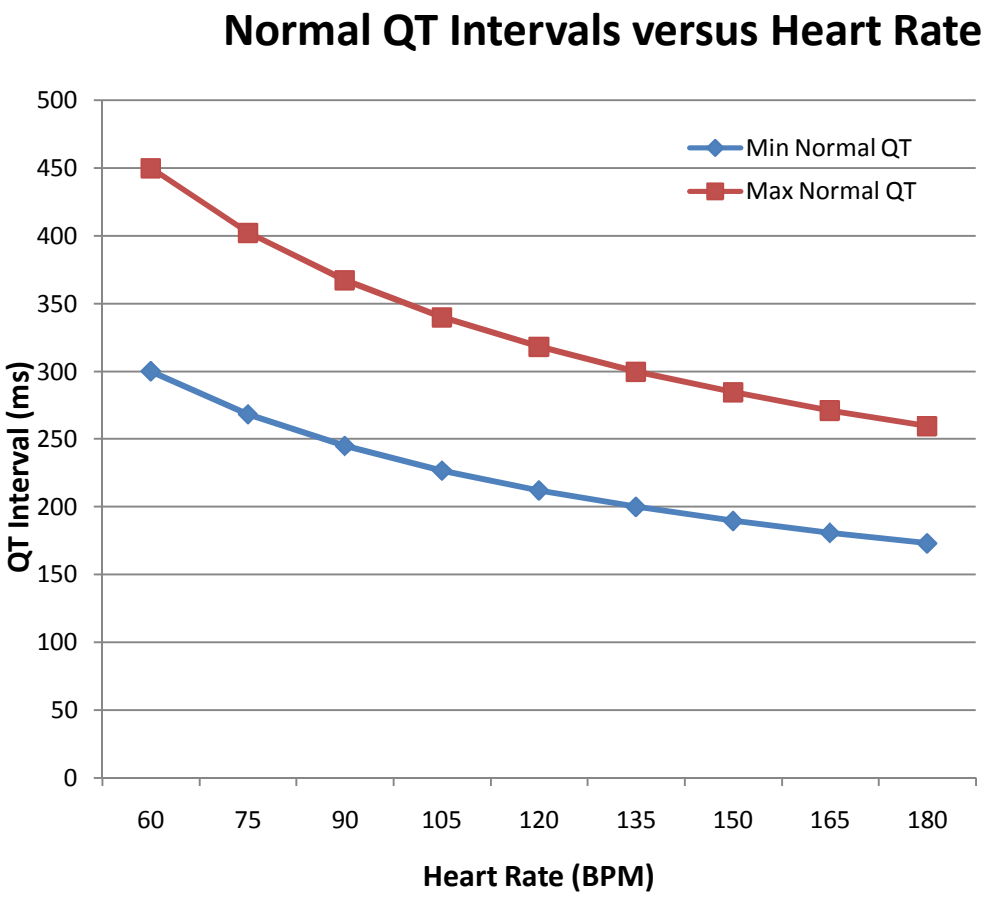


FIGURE 25: Normal QT Interval versus Heart Rate. The device range of operation is limited by the ability to transport fluid. Specifically, the challenge is removing all fluid during diastole, as the heart fills. Thus, as a worst case scenario, the device was tested at the maximum QT for each heart rate as indicated by the red curve above.

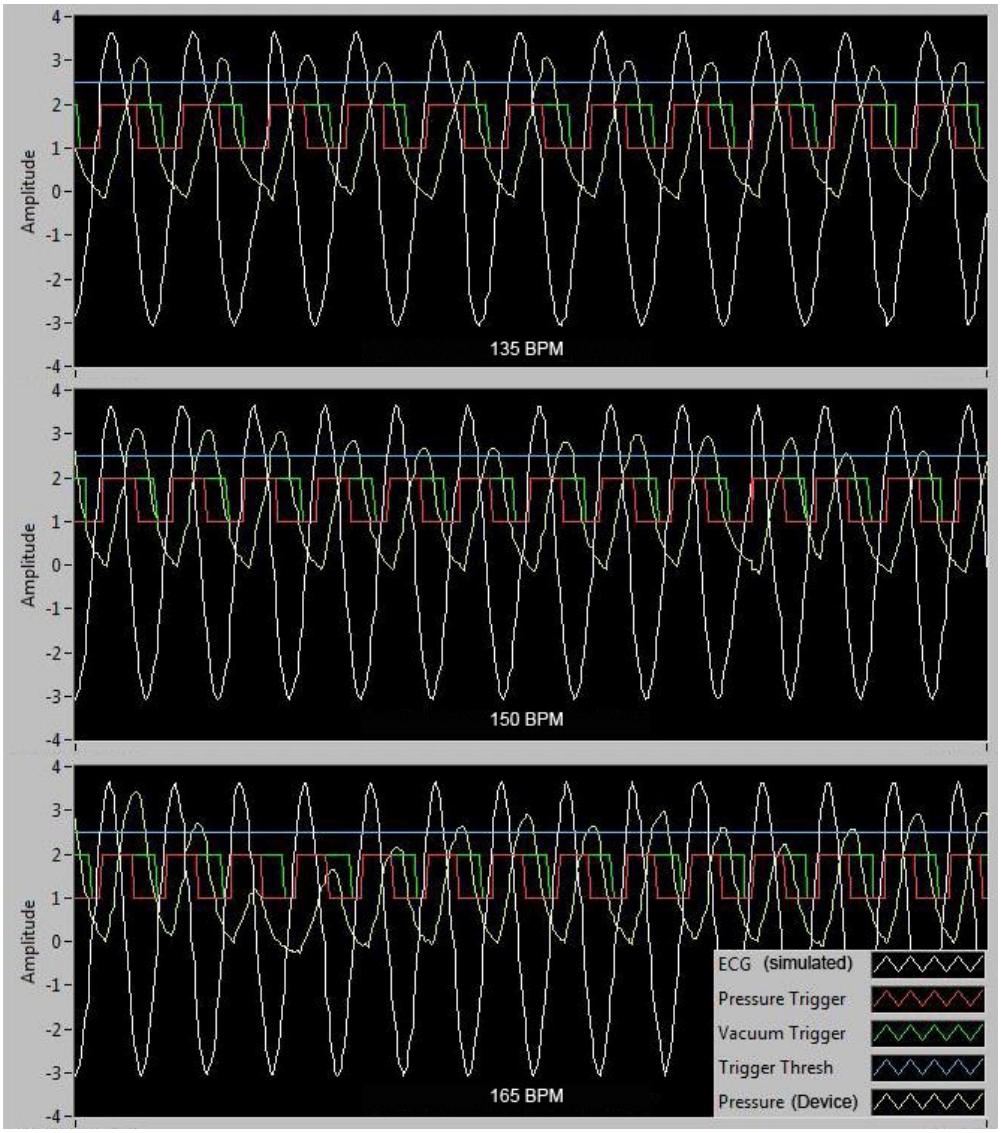


FIGURE 26: Device Operational Range Results. A function generator was used to produce the large sine wave that was used to trigger the device. All values were normalized in order to fit on the same display. To determine the actual pressure applied to the heart model in mmHg simply multiply the plotted pressure value by 10. Top **-** At heart rates near or below 135 BPM the device was capable of providing 30mmHg assist reliably. Middle - As heart rate increased to 150BPM and QTc subsequently decreased, performance began to deteriorate as evidenced by increasing variance in applied pressure. Bottom – By 165 BPM performance was totally unreliable.

12. MANIPULATING THE MECHANICAL ENVIRONMENT TO OPTIMIZE STEM CELL THERAPY

Stem cell therapy for the treatment of heart failure remains promising but is as yet not fully developed. Results of stem cell studies have collectively been inconclusive, and perhaps even controversial. Some crucial observations have not been reproducible and conclusions from similar findings have been conflicting [100-103]. Thus, though the concept is simple - cultivate progenitor cells outside the heart then transplant them into the heart and hope that they will eventually integrate into the intact myocardial tissue - the results have been ambiguous, marginal, or negative, suggesting that transplantation of progenitor cells into a failing heart will not necessarily lead to substantial clinical improvement [62].

Mammalian cardiogenesis requires many cell types – atrial and ventricular cardiomyocytes, conduction system and pacemaker cells, smooth muscle cells, valvular cells, endothelial cells, and endocardial cells. Multipotent progenitors in the early embryonic field can be classified into two groups, the Primary and Secondary Heart Field. The absence of molecular markers for primary heart field progenitors has thus far rendered isolation and characterization of these progenitors impossible. However purified secondary progenitors, i.e. myocardial, smooth muscle and endothelial progenitor cells have been isolated and characterized [62].

The present goal of stem cell therapy is cardiac regeneration. At present, this objective has not been met. To accomplish cardiac regeneration, generally three types of tissue generation are required (1) angiogenesis, (2) arteriogenesis, and (3) cardiomyogenesis. Given this fact, bone marrow derived cells are likely the best cell type to use in meeting the cardiac regeneration objective. In bone marrow one may find the endothelial progenitor cells (EPC), necessary for angiogenesis and arteriogenesis; and the mesenchymal precursor cells (MPC), necessary for arteriogenesis and cardiomyogenesis. Though promising, early reports have suggested implantation of this cell type is unreliable, e.g. at 18 hours post-delivery, only 1% of the cells remained in the heart. Skeletal myoblasts have been used to treat ischaemic cardiomyopathy but there have been problems with arrhythmias when using this cell type. While this problem decreases over time, the reason for this occurrence is not known. Proponents suggest that the cells are integrating into myocardial tissue whereas opponents propose that the cells have simply died. Presently, cell tracking studies are insufficient to answer this question definitively. Efforts have also targeted harvest and cultivation of resident cardiac stem cells. In this case autologous cells are obtained via biopsy and cultured ex vivo [100].

Cardiac muscle fiber alignment can be highly disorganized in the failing heart and disrupted by fibrosis. Moreover, the afflicted region is highly dyskinetic exhibiting abnormal motion and mechanics. Transplantation of progenitors in the absence of cues to drive alignment with native heart tissue may not improve global heart function.

Therapies based on the direct introduction of cardiomyocytes into the failing heart assume transplanted cells will align, differentiate, and functionally integrate into the host tissue in the absence of the cues that normally drive these processes [62]. In cardiogenesis, mechanics play an important role in the appropriate pathfinding, differentiation, and ultimate function of embryonic progenitors [42]. In disease, mechanics has also been shown to play an important role in morphogenesis.

The prospect of inducing bona fide cardiac regeneration via cell cycle activation, cell transplantation, or stem cell mobilization is greater now than at any previous time [103]. One important obstacle to be overcome involves establishing the conditions under which transplanted cells may integrate, differentiate and function in harmony with the native tissue. The cues required to drive the transplanted cells through the appropriate processes are largely mechanical in nature. Mechanical cues are transduced by cells which respond biochemically, initiating a variety of potential responses, i.e. proliferation, migration, contraction, alignment, etc. Herein it is proposed that the promise of stem cell therapy as a means of treating heart failure can be realized by mediating the local mechanical environment. Thus, a combination therapy incorporating a device based intervention designed to manipulate the mechanical environment about the heart with a stem cell based therapy is presented as superior alternative to either approach alone.

It is important to note that the “whole” of this specific combination approach will exceed the “sum of the parts”. Stem cell therapies, which have already demonstrated some

benefit, will likely show improved efficiency as important mechanical cues will now be present to guide stem cell processes. Device performance will also increase as the incorporation of healthy stem cells will accelerate the cardiac recovery and rehabilitation normally associated with this “physical therapy”. In combining these specific therapies, a synergistic response is produced as the benefits of either are maintained while promoting improved responses from each. Thus, it is also important to note that the device based intervention must be versatile, i.e. capable of producing a range of mechanical circumstances, enabling deliberate strategic intervention aimed at maximizing the synergistic response of the combination therapy.

13. MANIPULATING THE MECHANICAL ENVIRONMENT TO OPTIMIZE CARDIAC TISSUE GRAFT THERAPY

Similar to the proposed combination therapy with stem cells, the device described herein could provide a method of manipulating the cardiac mechanical environment to promote the integration and optimize the function of engineered tissue constructs designed for cardiac regenerative therapy. Following a myocardial infarction (MI), ischemia is prevalent characterized by damaged, dysfunctional, and/or fibrotic myocardial tissue. There is great interest in therapies designed to restore cardiac function and/or regenerate cardiac tissue. For example, various types of stem cells may be injected directly into the damaged region or into coronary arteries feeding the damaged region to help regenerate this damaged tissue into healthy cardiac tissue. There has been some success with this type of cardiac regeneration therapy; however, the potential success of stem cell therapy is limited by (1) the dyskinetic or hypokinetic motion of the damaged heart tissue – the ability of the cells to differentiate into functional cardiomyocytes integrated into the native tissue is compromised by the absence of the appropriate mechanical cues in the local diseased environment; and (2) for true regeneration to occur, multiple cell types must be delivered into the diseased region – in addition to the precursors to cardiomyocytes, cells capable of promoting angiogenesis, e.g. endothelial progenitor cells, and arteriogenesis may be required. Consequently there is increasing interest in developing more sophisticated engineered structures for transplant with cardiac regeneration as the therapeutic target. These constructs incorporate multiple cell types

and synthetic or biologic scaffolds to provide structural framework for the tissue graft. Engineering functional tissues in vitro provides advantages to current stem cell strategies, particularly in addressing limitation (2) described above. However, it is anticipated that the ability of the tissue engineered construct to integrate and function with the native tissue will be constrained by the local mechanical and environmental cues. The device described herein is capable of manipulating the mechanical environment such that the mechanical factors necessary for proper tissue integration and function can be modulated as necessary to optimize performance.

As stated previously, therapies based on the direct introduction of cardiomyocytes into the failing heart assume transplanted cells will align, differentiate, and functionally integrate into the host tissue in the absence of the cues that normally drive these processes. It unlikely that the transplantation of cardiac muscle progenitors or their differentiated progeny, will lead to substantial long term clinical improvement in the absence of cues to drive their appropriate linear alignment with the native heart tissue [62]. Moreover, cardiac regeneration may require many cell types – atrial and ventricular cardiomyocytes, conduction system and pacemaker cells, smooth muscle cells, valvular cells, endothelial cells, and endocardial cells.

According to a recent review by Zimmerman [109], there are two broad approaches to the use of stem cells in cardiovascular therapeutics – cell based therapies which entail the delivery of a volume or mass of cells to the tissue being targeted for treatment; and

tissue engineering which may involve generating sheets of tissue and ultimately whole organs. Several cell types are typically used as basic units to grow specific types of tissue. A structural framework or scaffolding is also necessary as a structural framework on which to build [100]. The resulting constructs may subsequently be assessed ex vivo, before implantation to support or replace a significant portion of a failing heart in vivo [110]. Tissue engineering-based myocardial repair approaches in animal models have been reported [111, 112]; and one year follow-up data from a human tissue engineering trial (MAGNUM-trial) has been published [113]. The construction of 3D synchronously contracting vascularized human cardiac tissue that exhibits typical structural and functional properties of early cardiac tissue has been reported. It is proposed that engineering vascularized cardiac tissue before implantation to the infarcted myocardium will enable improved graft survival and may result in an increased functional benefit [114]. Restoring or at least enhancing heart muscle function by grafting of tissue engineered myocardium seems foreseeable and may not only be applicable in older patients with heart failure but also in children with congenital defects. Ultimately, tissue engineering based myocardial regeneration may be an attractive alternative to heart transplantation and other surgical interventions to rebuild the heart [110].

Zimmerman [109] identifies several tissue engineering technologies that have been developed to treat heart failure. These include but are not limited to:

- A classical biomaterial approach, wherein biocompatible materials are chemically engineered for use as growth substrate for cells. This scaffold would ideally be designed to offer initial structural support, but be degraded over time. Several materials have been used, including polylactic acid (PLA) and polyglycolic acid (PGA) and mixtures thereof [115, 116]. Alternatively, alginates [117], polysaccharides derived from seaweed, and gelatin/collagen sponges [118, 119] have been employed.

- A cell entrapment approach, aiming at concentrating cells at a high density within a defined three-dimensional environment to facilitate spontaneous cell aggregation [120 – 122]; Spontaneous assembly of mostly spherical cell aggregates occurs if cardiomyocytes are cultured at high densities in bioreactor suspension cultures [123]. During the naturally occurring condensation process of hydrogel/cellmixtures muscle aggregates fuse to form a functional syncytium. This process can be optimized by imposing mechanical strain onto the resulting tissue constructs [121, 122, 124]. Importantly, hydrogel-based engineered heart tissues (EHTs) display several structural and functional properties of native myocardium and can further be optimized by growth factor conditioning, electrical stimulation, and addition of non-myocytes to the initial cell mixture [122, 125].

- A cell sheet engineering approach, aiming at stacking cell monolayers to generate tissue "sandwiches" [126]; The development of culture surface coatings containing poly(N-isopropylacrylamide), being either hydrophobic or hydrophilic depending on the

environmental temperature to facilitate cell attachment and detachment at high (37°C) and low (20°C) temperatures, respectively, has enabled the controlled release of monolayer cell cultures from its underlying substrate [127]. Stacking cell layers can eventually be utilized to generate complex three-dimensional tissue with a specific organ function [128]. The absence of vascularization does, however, restrict the size of individual cell sheet stacks to three to four layers [126]. This limitation may be overcome in vivo by a so called "polysurgery approach" that would, however, necessitate repeated access to the implantation site to sequentially stack cell sheet sandwiches in vivo after previous grafts have become properly vascularized [129]. In a modification of the original cell sheet engineering approach, spontaneous detachment of cell monolayers from uncoated or laminin coated culture dishes has been exploited to generate cardiac muscle constructs [130].

- Micro-tissue technology, being essentially a modification of the commonly used hanging-drop cell culture system [131]; Micro-tissues can be generated by aggregating cardiomyocytes in hanging-drop cultures [131, 132]. They demonstrate several features of a functional myocardial syncytium.

- An organ decellularization-recellularization approach. De-cellularized hearts provide an underlying extracellular matrix, perfusable vascular architecture, competent acellular valves, and intact chamber geometry for the development of bioartificial hearts. The constructs are re-seeded with cardiac or endothelial cells [133].

"An average myocardial infarction causes a loss of approximately 1 billion myocytes [134]. Subsequently, scar tissue forms and the remaining myocardium responds to the loss of contractile tissue by cardiomyocyte hypertrophy. The latter may transiently suffice to compensate for the loss in myocardial performance but will in the long-run perpetuate the myocardial damage, eventually leading to heart failure. If a defined defect can be clearly localized after a myocardial insult, engineered heart muscle may be placed on top of it, to locally support the failing heart and inhibit further deterioration…In an alternative approach, localized defects (e.g. aneurysms and transmural scars) may be surgically excised, using for example a Dor-procedure [135], and replaced with tissueengineered myocardium [136, 137]. This approach is expected to be superior to an epicardial application of tissue engineered myocardium, because it avoids potentially interfering effects of otherwise underlying non-contracting scar tissue. It may, however, especially if applied in the left ventricle, be complicated by (1) high systolic left ventricular pressures (requiring bioartificial grafts with high burst strength), (2) thrombus formation (requiring non-adhesive/non-thrombogenic tissue surfaces), and (3) arrhythmias (requiring seamlessly integrated and physiologically conducting grafts bridging the transmural defect)" [109].

The device described herein would provide a means to control the mechanical environment, providing support, constraint, and active assist. All of which would improve the likelihood of success particularly in procedures wherein the transmural scars are excised and replaced with tissue-engineered myocardium. Potential complications

associated with high left-ventricular pressures would likely be avoided altogether, and complications related to arrhythmias would likely be reduced as active assist could improve the mechanical cues required for proper tissue integration.

14. MANIPULATING THE MECHANICAL ENVIRONMENT TO MAINTAIN ORGAN VIABILITY FOR TRANSPLANT

For patients with end stage heart failure, heart transplant is the preeminent choice of treatment. Over the last decade, the incidence of end stage heart failure has been increasing due to the rising age of the population and survival rate of individuals experiencing myocardial infarction. Currently there are over 2,700 patients on the heart transplant waiting list (OPTN – Organ Procurement and Transplantation Network – as of Feb 2009) and many more patients that do not currently qualify for heart transplant but could benefit if more donor hearts were available. Progress has been made in the availability of donor hearts; however progress in the sustainability of those hearts has been lacking. The current four hour time frame for the viability of donor hearts is a major shortcoming, not only limiting the time necessary for the preparation of transplant surgery but also limiting the geographic location from which donor hearts can be transported.

Current methods of transporting and preserving hearts for transplant once the heart is removed include: flushing the heart clean of blood, placing the heart in a bag of storage solution, and packing the heart in an insulated container of ice. Using the current method of preservation and transportation, the donor hearts must be implanted within 6 hours of the donor's death (one hour for the procurement of the heart, four hours for transport, and one hour for transplant surgery) or the heart will no longer be viable. This process

attempts to slow the cell death and does little to sustain organ health. The time constraint often requires the presence of costly around-the-clock transplantation teams able to quickly utilize incoming donor hearts

There had been a long held belief that subjecting a harvested heart to low temperatures substantially lowers metabolic rates to negligible levels, thus depriving the heart of oxygen did not result in cellular damage. However, research has shown that subjecting a harvested heart to temperatures of four degrees Celsius only lowers metabolic rates up to ten percent [138]. Even at low metabolic rates, depriving the heart of oxygen results in the switch from aerobic metabolism to anaerobic metabolism further degrading tissue, as cardiomyocytes begin to consume themselves and release metabolic toxins. In addition to myocardial damage, oxygen deprivation may also cause coronary vascular endothelial and smooth muscle injury leading to coronary vasomotor dysfunction.

The need for sustaining the viability of donor hearts has resulted in several perfusion systems, which perfuse the heart with various oxygenated solutions in an attempt to provide the heart with nutrients necessary for survival. Perfusion systems have three advantages over current heart preservation techniques. 1) Perfusion with oxygenated solutions has the ability to prevent ischemia, anaerobic metabolism, and reperfusion injury. 2) Perfusion allows for a more effective delivery of oxygen and nutrients to myocardial cells. 3) Continuous perfusion can effectively clear the heart of metabolic waste products.

Many studies have shown that perfusion can substantially sustain a heart ex vivo compared to simple immersion [139, 140]. However, an ideal perfusate that would mimic physiological conditions is still up for debate. Several additives, temperatures, pressures, and pH levels have been examined and have been found to affect the hearts viability. Perfusion solution additives include albumin, potassium, calcium, magnesium, Lidocaine, glucose, insulin, and vasodialators. Albumin has been shown to decrease edema formation. Potassium and calcium, while optimal levels are unknown, are thought to improve viability during perfusion preservation. Magnesium protects myocardial mitochondria and is a cofactor in intracellular enzyme reactions. Lidocaine decreases ventricular fibrillation. Glucose and insulin complement each other and protect against myocardial injury as long as myocardial cells have sufficient oxygen and removal of metabolic byproducts. Vasodialators improve coronary flow during perfusion. Ideal perfusion temperatures have been found to be at or above 20° C, because the protective effects of metabolic substrates such as glucose and insulin are experienced. Ideal pH levels and pressures are still up for debate [139].

Current perfusion systems usually have the ability to regulate oxygenation, thermal conditions, and may or may not include electrical stimulus. However, the mechanical environment is dramatically altered. The mechanical cues necessary for proper cell physiology are absent. Aberrant mechanical factors can lead to myocardial degradation and cell death. Contractile proteins are in a constant state of flux with absorption and formation occurring simultaneously—with rates equal to approximately half of the heart

muscle mass per week. Essentially, the myocardium is continuously reconstituting itself by processes that are guided by physiologic demand and the mechanical environment in which the heart must function. Variations in mechanical factors influence the growth and remodeling processes that are continuously at work in the myocardium. It is therefore essential to provide a mechanical environment that is conducive to myocardial survival.

Ex vivo, the heart may not have the ability or nutrients required to perform the mechanical work necessary for myocardial survival. Therefore, pacing the heart alone will not produce the desired physiological motion needed for heart viability. Mechanical assist in the form of direct cardiac compression in a manner that promotes physiological strain patterns and motion is necessary to maintain viability.

A perfusion system that can provide a near physiological environment by applying mechanical assist, electrical stimulation, temperature regulation, and perfusion of oxygenated solutions is necessary for maintaining heart viability. Increasing the time of heart viability will not only expand the organ donor pool but it will also allow more time for histological compatibility testing and overall surgical preparedness, resulting in fewer wasted donor hearts, organ rejection, and surgical mistakes.

The device described herein could provide the means to reconstruct an in vivo physiological fluid and solid mechanical environment. Application of mechanical assist and electrical stimulation, regulation of temperature, and perfusion with a solution

composed of oxygen and nutrients are necessary for cardiac tissue survival and will provide a near physiological environment conducive to maintain viability of the harvested organ.

15. SUMMARY AND CONCLUDING REMARKS

The device presented herein could function well as a clinical device based therapy or a research tool, e.g. to investigate disease processes, and/or the effects of specific mechanical factors on cardiac growth and remodeling processes. The concluding remarks will focus on the clinical application, and in so doing should reveal the value as a research tool as well. Though initiated by some index cardiac event, e.g. myocardial infarction, and the subsequent compensatory neurohormonal mechanisms, aberrant growth and remodeling of the left ventricle eventually progresses independent of the neurohormonal status of the patient. Evidence suggests that mechanical factors are critical to healthy growth and remodeling of biologic tissues. As the diseased ventricle remodels, the local mechanical environment is altered and exhibits symptoms of disease, i.e. the mechanical environment itself becomes wrought with disease. Erroneous mechanical cues contribute to further aberrant growth and remodeling processes. A positive and deadly feedback loop emerges, stimulating spurious remodeling processes that ultimately render the vital organ incapable maintaining of homeostasis.

While it is important to recover the mechanical work that can no longer be provided by the organ itself, it is equally important to treat the pathologic mechanical environment. Present device based therapies are designed exclusively to (1) provide cardiac assist or alternatively, *recover mechanical work*, or (2) *mechanically* inhibit further detrimental growth and remodeling processes. In the each case, the focus on mechanics is myopic.

Recovering mechanical work with DCCDs is critical to sustain life, however, there is much more to consider. These devices impose a new set of mechanical stimuli and may do further damage to the mechanical environment, e.g. invert the curvature of the heart, effectively eliminating any possibility of cardiac recovery or rehabilitation. If we instead treat the diseased environment, i.e. restore the mechanical environment – the kinesis of the myocardium, in so doing we will recover the lost mechanical work *and* provide the mechanical cues necessary for growth and remodeling processes that are potentially restorative and rehabilitative in nature. With present CSDs, we may inhibit the symptoms of disease and perhaps slow the progression of disease, yet we are failing to provide true therapy, that is, we are failing to provide a legitimate attempt to cure the disease. Again, if we treat the mechanical environment, and seek to restore healthy mechanical cues, not only will we accomplish the goal of inhibiting disease progression, we may very well reverse the disease induced remodeling process and thereby reduce the size of the diseased ventricle.

It is interesting that given the long history of rehabilitative physical therapy with biologic tissues and organs, that efforts to provide such therapy for the diseased myocardium are conspicuously absent. Hippocrates (460-370 BC) proposed the application of what is now known as biomechanics, to treat musculoskeletal defects and injuries, thousands of years ago. Thus, Hippocrates advanced the field of orthopaedics before it existed formally. Nicolas Andry coined the term “orthopaedics” in 1741. From Greek, the word *ortho* means “to straighten”, *paedia* means “children”. Thus, early

orthopaedics focused on treating congenital defects and scoliosis. The point here is that for hundreds or even thousands of years we have known that by manipulating mechanical factors, by altering the mechanical environment, we can guide natural growth and remodeling processes as a therapy.

Presumably due to the long history of the field of orthopaedics, an important design consideration when developing a device based therapy or prosthetic, is the impact the device will have on the mechanical environment. It is well understood that it is not sufficient to merely treat the anomaly at hand, lest one create yet another problem. Engineers developing device based therapies for cardiovascular diseases must also adhere to this understanding. Vascular stents developed to treat diseased arteries by serving as a scaffold designed to prop open stenotic regions often cause restentosis, particularly near the ends of the stent – a region of substantial compliance mismatch. This compliance mismatch between stent and artery is not extremely difficult to overcome. It is curious that it was neglected in the first place, and particularly confounding that it remains neglected with the advent of drug-eluting stents. Rather than simply resolve a design flaw that imposes adverse mechanical conditions on the artery, we treat the consequences of the flaw with pharmaceuticals? It is acknowledged that some form of restenosis may occur regardless of compliance matching design considerations and that drug eluting stents may still be beneficial or necessary. The point here is to illustrate the perceived reluctance of those in the cardiovascular device industry to diligently and earnestly consider the mechanical implications of their

therapeutic solutions particularly given modern understanding of mechanobiology. In this case, the expense associated with device design that is thoughtful of the impact on the mechanical environment is not financial, rather intellectual.

The physical differences in appearance and function, between the device presented herein and previously existing devices, are often very subtle. On the other hand, the philosophy behind these subtle differences is not so subtle. Existing DCCDs invert the curvature of the heart, inducing aberrant strain patterns. The philosophy behind these devices is simple – squeeze as needed to generate sufficient blood flow. There is an inherent disregard for the natural, healthy, physiologic mechanical environment. While the active component of the device presented herein is similar to existing DCCDs, and the passive component is similar to existing CSDs; the device as a whole is in essence something altogether different. It is designed first to treat the mechanical environment, to enable the physician to manipulate the mechanics about the heart in such a way as to create the conditions most favorable for natural growth and remodeling processes that are restorative and rehabilitative in nature. In so doing, as a "side effect" we accomplish the goals of existing DCCDs and CSDs.

It is acknowledged that no evidence of reverse remodeling as a consequence of treatment with this device has been presented in this work. Pursuit of such evidence is absolutely essential to developing effective treatment plans and will be initiated in future studies. Nonetheless, we know that mechanical factors guide growth and remodeling processes

in the heart. Moreover, there is evidence in the literature that reverse remodeling in diseased hearts can be stimulated by device based therapies (see Section 3 above). These are often isolated instances and are likely due to specific patient conditions, i.e. for a given subset of patients the mechanical therapy *coincidentally* creates the appropriate conditions for reverse remodeling to occur. Alternatively, with some CSDs, e.g. Corcap, reverse modeling may occur but is limited; once equilibrium with the non-adjustable device is reached, reverse remodeling ceases. The goal here is to provide the physician with a versatile tool, incorporating design features and capabilities that enable the generation of a broad range of mechanical stimuli and support. Thus, treatment could be *deliberately* aimed at creating conditions conducive to reverse remodeling processes. The physician would essentially be able to artfully provide physical therapy for the heart to stimulate natural growth and remodeling processes that are potentially restorative and rehabilitative in nature.

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VITA

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In addition to his research pursuits, Michael plays lead guitar in the local hard rock band *Psychonauts*. He can be seen frequently, playing venues in and around Bryan/College Station, TX.

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