REAL TIME MODULATION OF END DIASTOLIC VOLUME AS A NOVEL THERAPY FOR DILATED CARDIOMYOPATHY AND CONGESTIVE HEART FAILURE

A Dissertation

by

SAURABH BISWAS

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 2011

Major Subject: Biomedical Engineering

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ABSTRACT

Real Time Modulation of End Diastolic Volume as a Novel Therapy for Dilated Cardiomyopathy and Congestive Heart Failure. (May 2011)

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Congestive heart failure (CHF) is a major public health issue in the developed and developing world. In the U.S., CHF affects more than 5.3 million people with 550,000 new cases diagnosed each year. Approximately 20% of hospitalizations are due to acute CHF, incurring a health-care system cost of $34.4 billion. Heart failure has two main forms: systolic dysfunction and diastolic dysfunction. Many patients with heart failure have both types of dysfunction. Though systolic heart failure is more commonly mentioned, there is growing recognition that CHF caused by a predominant abnormality in diastolic mechanics (filling and relaxation) causes significant morbidity and mortality. In patients with systolic heart failure, there are abnormalities in the pressure-volume relationship during systole that includes decreased ejection fraction (EF), stroke volume, and stroke work. In patients with isolated diastolic heart failure, the only abnormality in the pressure-volume relationship occurs during diastole, when there are increased diastolic pressures with normal diastolic volumes. Whereas the diastolic pressure-volume relationship may reflect a more compliant chamber, increased diastolic pressure

and abnormal relaxation reflect the presence of abnormal diastolic function. Therefore, patients with symptomatic heart failure have abnormalities in diastolic function, those with a normal EF have isolated diastolic heart failure, and those with a decreased EF have combined systolic and diastolic heart failure. Thus a critical gap in present device solutions to CHF is a single device that can address concurrently reduction of LV chamber dimensions (remodeling) and also improve and not impede LV filling by lowering the filling pressure (i.e. without impeding diastolic function).

The biphasic support and recoil device technology investigated in this dissertation would provide a means for guided intervention whereby normal growth and remodeling processes are directed toward a gradual reduction in size in systolic dysfunction and enhanced ventricular filling using diastolic recoil properties of the device. In this dissertation prototyping and testing of a novel minimally invasive cardiac device technology is presented. Our tests indicate that this technology has the necessary mechanical actions to enable the integration of therapy for systolic and diastolic dysfunction in two principal ways (1) adjustable passive cardiac support or progressive constraint to facilitate the gradual reduction in size of dilated, diseased hearts, thereby improving pumping efficiency; (2) diastolic recoil technology with the ability to transfer energy from systolic contraction to diastolic filling, which may potentially reduce ventricular filling pressures, without compromising ventricular systolic function.

DEDICATION

To my parents

&

To my teachers

ACKNOWLEDGEMENTS

At the outset I would like to express my deepest appreciation for my advisor, Dr. John C. Criscione, for giving me this opportunity to work with him and learn and contribute to the process of bringing a device from concept to design. A chance meeting during a presentation in 2004 opened up this possibility for me and I am indebted to him for giving me multiple opportunities to grow both as a scientist and an entrepreneur. I have shared with him the vision of doing research that can benefit patients directly and I believe he is among the very few people I have seen who share the passion of innovation and practical approach of solving problems. His great guidance, grasp of engineering and clinical concepts and support helped this work through its many challenges. No words can express my deepest appreciation for him. I'm also grateful to my dissertation committee members, Dr. William A. Hyman, Dr. Fred Clubb, Dr. Duncan Maitland and Dr. Matt Miller for their valuable suggestions, critique, input, support and understanding all through the course of this project. I am really fortunate to have had the guidance of such an experienced committee and have benefited tremendously from their insights.

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TABLE OF CONTENTS

CHAPTER Page

LIST OF FIGURES

FIGURE Page

FIGURE Page

FIGURE Page

FIGURE Page

LIST OF TABLES

CHAPTER I

INTRODUCTION: CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a debilitating condition being responsible for over 20% of all hospital admissions today among persons older than 65 years of age with an incidence approaching 10 per 1000 population. Though multiple drugs and devices are commercially available to clinicians and surgeons today to address CHF, considerable efforts are still underway to find a solution that is more than a maintenance therapy. Heart transplantation is the ideal solution for these patients with end stage heart failure but there are approximately 3000 hearts annually available with hundreds of thousands in need of transplant on waiting list and millions of patients progressing towards a condition where they would need a transplant. Thus other than present pharmaceutical approaches a more viable device solution is needed to address this epidemic. In last two to three decades left ventricular assist devices have provided a lot of hope to these patients but challenges have remained in terms of quality of life issues and complex post implantation infections and complications mostly due to blood contacting nature of the device.

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

Objectives

Cardiac support devices (CSD) are one of the new classes of devices that have evolved over last two decades with a theoretical foundation in Laplace law. CSD's are non-blood contacting and have exhibited safety in the clinical trials conducted over last decade but questions still remain of their efficacy because of some fundamental drawbacks in the design and clinical efficacy. Although CSD's have shown to be effective, significant problems remain and it is the goal of this dissertation to advance the technology of cardiac support. The objectives and the problems addressed are discussed in Table 1.

Table 1 Objectives and problems addressed in this dissertation

Objectives	Problems Addressed
1. Prototype and test in vivo and in-vitro cardiac support device which can be adjusted post implantation with progressive remodeling of the heart.	Adjustability post implantation: Non-adjustable nature of present cardiac support devices prevents any management of the device post implantation. With remodeling the device loses its girdling effect on the myocardium limiting device action to heart sizes at time of implant.
2. Prototype and test in-vitro an implantable device which would enhance the ventricular filling by utilizing recoil effect.	Impaired ventricular filling: Present devices because of its girdling effect on the ventricles reduce the ventricular filling by stiffening the ventricular wall, potentially leading to high atrial pressures.

Table 1 continued

Objectives	Problems Addressed
3. Prototype and test in-vitro combined biphasic support and recoil device to fully modulate diastolic mechanics.	As mentioned in objectives 1 and 2, combined device would address in a single integrated design the problems of both adjustability with present CSD's and also impaired ventricular filling in failing hearts.
4. Prototype a device which can significantly reduce pericardial adhesion post implantation and can be adjusted in size with anatomical changes of cardiac size for pediatric and adult patients.	Pericardial adhesion: Present cardiac support devices which are either made of polymer meshes or nitinol get attached to the myocardium through universal presence of adhesions between the heart and the mediastinal structures including the sternum, which increases the difficulty and potentially the risks of the procedure if there are any needs of repeat surgery. Also the constricting nature of the adhesions also prevents the natural cardiac motion, potentially leading to aberrant mechanics being induced during the recovery process. Also in pediatric patients with congenital heart defects where redo surgeries are needed. There are limited alternatives in terms of FDA approved solutions which mitigate adhesion formation where procedures through a median sternotomy become less complicated.

Background

Congestive heart failure (CHF) is a major public health issue in the developed and developing world. In the U.S., CHF affects more than 5.7 million people with 550,000 new cases diagnosed each year. Approximately 20% of hospitalizations are due to acute CHF, incurring a health-care system cost of $37.2 billion [1]. Heart failure has two main forms based on dysfunctions in either pumping or filling phase of cardiac cycle. One of the forms, *systolic dysfunction,* occurs when there is an abnormality in the ejection phase (i.e. ejection fraction reduced) the second form *diastolic dysfunction* occurs when there is abnormality in filling of the ventricle with a normal ejection fraction. Some patients with end stage heart failure have both types of dysfunction. In systolic dysfunction, the heart contracts less forcefully and cannot pump out as much of the blood that is returned to it as it normally does. As a result, more blood remains in the lower chambers of the heart (ventricles). In diastolic dysfunction, the heart is stiff and does not relax normally after contracting, which impairs its ability to fill with blood. The heart contracts normally, but is unable to pump a normal proportion of blood out of the ventricles because filling is sub-optimal. Often, both forms of heart failure (systolic and diastolic) occur together. Although systolic heart failure is more commonly mentioned, there is growing recognition that congestive heart failure (CHF) is caused by a predominant abnormality in diastolic function.

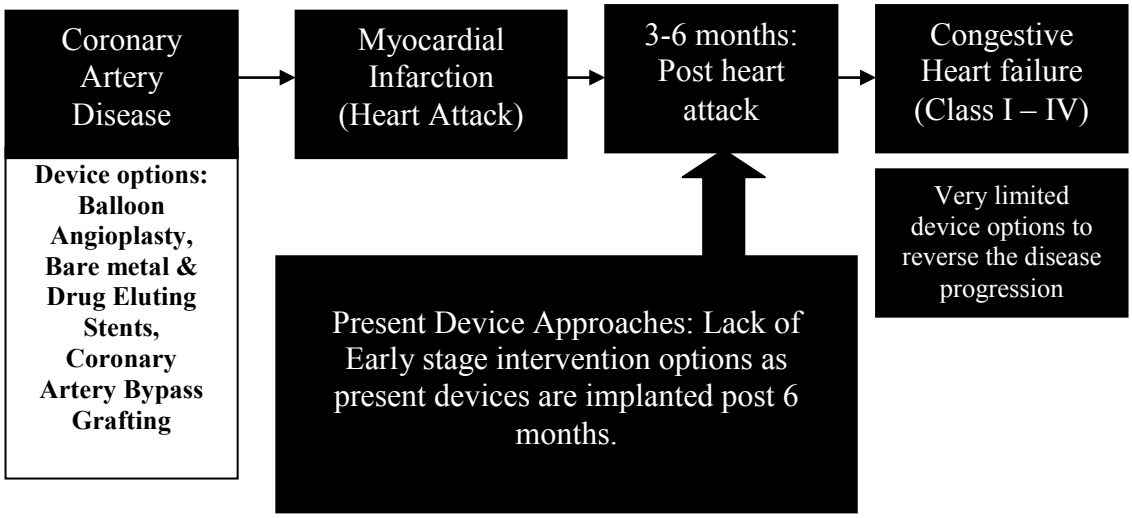

Figure 1. Coronary artery disease being the initial problem leads to an index event like acute myocardial infarction (Heart attack) which can be the starting point of congestive heart failure.

Heart failure is a progressive disorder which can be initiated by multiple cardiac index events like acute myocardial infarction, as shown in Figure 1, whereby the hemodynamic and symptomatic states of the patient worsen over time causing irreversible damage despite the absence of clinically apparent adverse events [2- 4]. Coronary artery disease causes approximately 70% of congestive heart failure. Acute myocardial infarction (AMI) due to obstruction of a coronary artery is the most common initiating event that can lead ultimately to heart failure. The symptomatic deterioration over a period of a time after the initial recovery period of AMI is accompanied by progressive left ventricular (LV) chamber remodeling or also referred to as cardiac remodeling [4-6]. LV remodeling is a progressive phenomenon characterized globally by changes in LV chamber size and shape and with implications at the cellular level, by ongoing loss of cardiomyocytes, myocyte hypertrophy and interstitial fibrosis [5]. The

important determinants of LV dysfunction and subsequent remodeling are myocyte loss, hypertrophy and accumulation of collagen in the interstitial compartment [5, 6]. The progressive remodeling leads to basically three broad class of ventricular dysfunction in most patient populations.

1. In patients with systolic heart failure two major changes are seen:

    - Altered ventricular contraction
    - Inability to empty

In patients systolic heart failure usually develops because the heart cannot contract normally. It may fill with blood, but it cannot pump out as much of the blood it contains because the muscle is weaker. As a result, the amount of blood pumped to the body and to the lungs is reduced, and the ventricle, usually enlarges. There are abnormalities in the pressure-volume relationship during systole, which includes decreased EF, stroke volume, and stroke work.

2. In patients with diastolic heart failure two major changes are seen:

    - Altered ventricular relaxation
    - Inability to fill

Diastolic heart failure can occur alone or in combination with systolic heart failure. In patients with isolated diastolic heart failure, the only abnormality in the pressure-volume relationship occurs during diastole, when there are increased diastolic pressures with normal diastolic volumes. When diastolic pressure is markedly elevated, patients are symptomatic at rest or with minimal exertion (NYHA class III to IV). With treatment,

diastolic volume and pressure can be reduced, and the patient becomes less symptomatic (NYHA class II), but the diastolic pressure-volume relationship remains abnormal.

3. Another form is combined systolic and diastolic heart failure. Patients may have only a modest decrease in ejection fraction (EF) and a modest increase in end-diastolic volume but a marked increase in end-diastolic pressure and a diastolic pressure-volume relationship that reflects decreased chamber compliance. Given that all patients with symptomatic heart failure potentially have elevated end-diastolic pressures, diastolic function is abnormal in all patients. Patients with a normal EF have isolated diastolic heart failure, and those with a decreased EF likely have combined systolic and diastolic heart failure.

Left ventricular remodeling: Mechanism for heart failure progression

The role of LV remodeling in heart failure is still under active debate as some investigators currently view LV remodeling simply as the end-organ response that occurs following years of exposure to the deleterious effects of long-term neurohormonal stimulation, but with clinical outcomes studies and understanding of the basic mechanism there is increasing evidence that LV remodeling may contribute independently to the progression of heart failure [7, 8]. Considering the complexity of the LV remodeling process, a number of changes occur during the process of LV remodeling and directly contribute to worsening heart failure. One of the most significant observations with respect to the abnormal geometry of remodeled ventricle was the consistent finding that the remodeled heart was not only larger, but was also

more spherical shape [9]. The events that lead to LV remodeling are numerous. 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 with LV remodeling 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 [10-13].

This LV remodeling becomes a cause of onset of a positive feedback loop, leading to acute dysfunctional cardiac pumping with worsening neurohormonal activation and inability of the remodeled LV to respond appropriately to these compensatory mechanisms. This in turn leads to a stage where the aggregate end-organ changes that occur within the cardiomyopathic ventricle may progress to the point that no amount of neurohormonal stimulation can maintain cardiovascular homeostasis, at which point heart failure may progress independent of the neurohormonal status. Given this 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 [14]. As the disease progresses there is a change in the shape of the ventricle from a prolate ellipse to a more spherically shaped ventricle. 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. 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.

Stress & strain: Key biomechanical factors in left ventricular remodeling

The heart is a biomechanical pump, and the important pillars of biomechanics: force (stress) and motion (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 should be further investigated in order to better define effective treatments for cardiovascular disease.

In the remodeling process, the left ventricle (LV) undergoes a transformation from prolate ellipsoid to a more spherical shape resulting in an increase in meridional wall stress of the LV, which in turn creates a number of de novo mechanical burdens for the failing heart. Progressive LV dilation and subsequent remodeling is one of the mechanisms that leads to LV wall stress and myocardial stretch [15, 16]. The imbalance of the normal stress pattern triggers increased myocardial oxygen consumption and myocardial stretch, activating stretch-response proteins that may play an important role in the development of maladaptive cardiomyocyte hypertrophy [17]. LV dilation and increased LV sphericity are also sensitive indicators of poor long-term outcome [18, 19].

Thus, cardiac wall stress, which can be defined as the force acting per unit of cross-sectional area of the ventricular wall, is directly related to pressure in the ventricles and ventricular radius, and inversely related to ventricular wall thickness [20].

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. 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. 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 with an increasing metabolic stress. Thus, ventricular remodeling is maladaptive, despite any potential incremental increase in ventricular wall thickness.

Biomechanical model of heart failure

In the last few decades several different clinical model systems, including a cardiorenal model, a hemodynamic model, and a neurohormonal model have been applied to understand the fundamental mechanisms and therapeutic approaches in treating the problem. Each of these models has strengths and weaknesses in terms of understanding the mechanisms responsible for heart failure and developing effective new therapies. 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" [21]. 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 [21] 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 [21, 22].

The advent of ACE 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 [23]. Although these three models explained some of the mechanistic aspects and disease symptoms in the heart failure patients, none of these models explain the relentless "disease progression" that occurs in this syndrome.

With increasing evidence of the relationship and importance of the interaction between myocardial systolic dysfunction and cardiac remodeling in the development and progression of heart failure, these observations suggest that heart failure can be viewed as a “biomechanical model” [8], in which heart failure develops and progresses as a result of the deleterious changes in cardiac function and cardiac remodeling that occur as the result of sustained neurohormonal activation. This model provides a new insight into the way the problem is approached but does not obviate the importance of the cardiorenal and hemodynamic models, and neurohormonal activation in the onset of heart failure. It extends the insights provided by this paradigm by focusing the treatment of heart failure on the downstream biological consequences of neurohormonal activation rather than on neurohormonal activation per se. Thus, 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. A key

aspect of the biomechanical model described by Mann et al 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 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 [24] as well as why many device-based therapies that concurrently affect LV pump performance and LV remodeling (e.g., cardiac resynchronization) are beneficial [8].

Conventional treatments for diastolic and systolic heart failure

For treating systolic heart failure there are several classes of solutions, e.g. pharmaceuticals, stem cells, electrical devices, mechanical devices, and surgical reconstruction. Each of these are designed for some limited target action (i.e., beta-blockade, ACE inhibition, electrical pacing, cardiac assist, etc); consequently, heart

failure remains a cause of tremendous morbidity and healthcare burden. Conventional approaches fail to address the possibility that mechanical stimuli are important parameters for guiding growth and remodeling, processes that may ultimately facilitate the recovery of mechanical organs.

The mechanical heart assist devices targeted to systolic heart failure are 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 (such as the DeBakey, Jarvik, Heart Mate), counter pulsation assist devices (aortic balloon pumps), and direct cardiac compression devices or DCCDs (Anstadt cup, Abio Booster). The passive, "support" devices (Cor-cap, Heartnet, Myosplint, etc.) directly interact with the heart to change shape or limit growth. Diastolic heart failure therapies presently include mostly pharmaceutical products and there are few, if any, devices available. There are presently no approved devices for treatment of the DHF symptoms. However, two preclinical stage recoil device concepts, LEVRAM and Imcardia (Corassist Inc) have a potential role in the treatment of DHF patients. Table 2 summarizes the present devices either approved by FDA or under development for treating congestive heart failure therapy.

Table 2 Present landscape of cardiac devices in congestive heart failure therapy

Disease State	**Present Device Solutions**	**Drawback of present FDA approved solutions**
Systolic heart failure	• LVADS • Biventricular pacemakers • CorCap & HeartNet (passive devices clinical trials)	Surgical complications with implantation of LVAD's as most require open heart surgery and post surgical patient management complexities Clinical efficacy of biventricular pacemakers questioned in patients with dilated cardiomyopathy and atrial fibrillation LVAD's are expensive as average cost is around $65000 and post surgical costs are higher Therapies approved for end stage patients: Very few options for early stage heart failure patients Present pharmaceutical options are also maintenance therapies
Diastolic heart Failure	• Presently no FDA approved devices • Imcardia & LEVRAM : preclinical stage devices	
Cardiac resuscitation & Post-Cardiotomy	• Counter-pulsation devices (IABP) • Single or biventricular support devices • Myovad: preclinical stage device	

Regenerative therapies incorporating stem cells 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 [25-28]. Stem cells are typically transplanted into the diseased myocardium where fiber alignment is highly disorganized and disrupted by fibrotic tissue. An advanced understanding of the stress and strain perturbations will be important for the future development of therapeutic and device

approaches involving surgical and catheter interventional treatments like passive ventricular constraint Corcap, Coapsys, Surgical Anterior Ventricular Restoration (SAVR), Dor, Fontan stitch, papillary muscle sling, Menicanti tri-level LV repair, coronary sinus cerclage, etc which are aimed at reversing deleterious LV remodeling. Although many devices are under development or FDA approved for treating patients with end stage heart failure there is a large unmet need for a device which can fully modulate the diastolic mechanics in a minimally invasive manner. Novel, minimally invasive devices and surgical strategies designed to reverse the LV remodeling by modulating the stress and strain abnormalities concurrently may be a new paradigm and a solution towards preventing the progression of global LV systolic and diastolic dysfunction. The research presented in the following chapters has been motivated predominantly by this concept.

In CHAPTER II, a central issue of ventricular remodeling i.e. progressively enlarging left ventricular size is addressed. Discussed is the development of a passive support device with a fundamental design innovation by introducing adjustability of passive chambers to modulate end diastolic volume in real time. Other clinically advantageous features like intrinsic pneumatic attachment negating the need to suture the device to heart, non-blood contacting and non- fibrotic bilayered design have been incorporated. This device would also be applicable to other structural heart diseases like idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and viral cardiomyopathy. The device has been prototyped and implanted in an acute ovine model where the

implantability, attachment and ability to modulate end diastolic pressure volume relationship was tested using both air and saline to adjust the device size.

In CHAPTER III, another aspect of heart failure which is abnormal ventricular filling is being addressed with the design of a diastolic recoil device based on the same platform of passive support device but with key design improvisations. The diastolic recoil device being prototyped is designed for clinical conditions like diastolic dysfunction, mitral valve regurgitation or diastolic heart failure. During diastolic phase of cardiac cycle the myocardial relaxation occurs leading to filling of ventricles with blood and this process is altered in patients with diastolic dysfunction. In addition to active and passive properties of the myocardium, geometrical characteristics of the chamber and external forces play an important role in the modulation of diastolic mechanics. This device is the first device designed to be implanted minimally invasively and enhance myocardial recoil during diastole leading to ventricular filling at lower pressure. The device design was prototyped and bench-top tested with use of a mock heart model.

In CHAPTER IV, the goal is to develop a device which can address both ventricular remodeling and filling problems in end stage heart failure patients in a minimally invasive approach. The proposed combined Biphasic support and recoil device is a significant innovation in heart failure device space, as it is a fully implantable device which can address the issue of cardiac support (passive constraint) and diastolic recoil in a single integrated design. This design incorporates both design features from

CHAPTERS III & IV and provide a single platform where multiple etiologies can be treated using a single device.

In CHAPTER V, we discuss a novel approach for prevention of pericardial adhesion post cardiothoracic surgery. One of the challenges in pediatric cardiothoracic surgeries which require multiple interventions is the change in anatomical dimensions of the heart with age as some surgeries need to be performed over a multiple year timeframe. The adjustable design of the device we have developed here is expected to provide the benefit of changing the device size with changing cardiac dimensions of the patient. Also the bilayered nature of the device provides the surgical plane to access the pericardium to the surgeon during the surgical intervention. We discuss the novel features of this device and its utility in this novel anti-pericardial device adhesion space

Thus utilizing our proposed device platform we intend to develop an integrated approach towards modulation of end diastolic volume in a minimally invasive manner. Present solutions are too invasive and do not improve the quality of life of the patients. We hypothesize that the combined passive girdling and diastolic recoil effect of the device

will prevent LV dilatation and sphericalization by positively impacting the stress patterns along with enhanced filling of the ventricles thereby lowering the left atrial pressure. Moreover, once normal cardiac kinematics is restored pharmacotherapy should be directed towards preventing the return of aberrant motions. We believe our results enable future investigations and will lead to more advanced and in-depth understanding of key biomechanical factors, mechanisms and interactive role of pathophysiological forces which lead to irreversible remodeling and myocardial damage and subsequent resistance to optimal drug therapy in millions of patients with end stage heart failure.

CHAPTER II

DEVELOPMENT OF A NOVEL CARDIAC SUPPORT DEVICE TO REDUCE VENTRICULAR DILATATION

Introduction

Heart failure typically begins after an "index event" leading to an initial decline in pumping capacity of the heart. Following this initial decline in pumping capacity, a variety of compensatory mechanisms are activated which with time trigger left ventricular (LV) remodeling and subsequent cardiac decompensation. As a consequence of resultant worsening LV remodeling and cardiac decompensation, patients undergo a transition from asymptomatic to symptomatic heart failure. To reverse this progressive disorder cardiac support devices have been of great clinical interest over the last two decades to intervene in the remodeling process and prevent the resulting ventricular dilatation.

Study Goals

With an understanding of the present state of the art in cardiac support devices and prominent role of geometric and mechanical factors in driving the remodeling associated with disease progression, an implantable device has been prototyped and tested which can be adjusted post implantation to reverse remodel the heart i.e. reduce heart size. Nitinol and polymer based support devices are under development and are presently in

clinical trials but these devices cannot be adjusted post implantation with the progressive remodeling of the heart. A novel device has been conceptualized to mitigate the present challenges of the support devices.

To advance the feasibility of the concept and the device design we have four important goals:

1. Prototyping of the device
2. Testing of the prototype in bench-top mock heart model
3. Testing of the prototype in vivo implanted through sternotomy
4. Testing of the prototype in vivo implanted through minimally invasive sub-xiphoid incision

The details of each goal are:

1. Prototyping of the device: Constructing a working prototype of a cardiac support device that is adjustable post implantation and implantable through a small one inch incision.

2. Testing of the prototype in bench-top mock heart model: Test the device in a bench-top experiment to assess the following:

- End diastolic pressure volume relationship (EDPVR) of Passive Constraint/Support with fluid (water) to adjust the passive chambers

3. Testing of a prototype in vivo in an ovine model through sternotomy: In this study the device was implanted through sternotomy and the passive chambers where filled with air. The goal was to assess the following:
    - Successful implantation of the adjustable cardiac support device
    - Intrinsic pneumatic attachment
    - End diastolic pressure volume relationship (EDPVR) of Passive Constraint/Support with air to adjust the passive chambers
4. Testing of a prototype in vivo in an ovine model through sub-xiphoid implantation in a minimally invasive manner: In this study the device was implanted in a minimally invasive manner and passive chambers were filled with saline. In the both studies goal was to assess the following:
    - Successful implantation of the adjustable cardiac support device
    - Intrinsic pneumatic attachment
    - End diastolic pressure volume relationship (EDPVR) of Passive Constraint/Support with saline to adjust the passive chambers

Background

The active and passive chamber properties play a significant role in the understanding of physiological and patho-physiological aspects of the cardiovascular system. The left ventricular systolic and diastolic pump properties are fundamental to advancing the understanding of cardiovascular pathophysiology and therapeutics, especially for heart failure.

P-V loop analysis and ventricular mechanics

In last two decades the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively) have emerged as a meaningful and useful way of characterizing intrinsic ventricular pump properties. Furthermore, the physiological significance of the ESPVR and EDPVR was reinforced by their deterministic link to myocardial energy demand. Because of the general applicability of the concepts to hearts of all species, pressure-volume analysis has become standard in studies of mice, humans, and animals of all sizes in between. Once a definition of end-systole (elastance max) and end-diastole is chosen, then for a given cardiac cycle, there is a single pressure-volume point that coincides with end diastole and a single pressure-volume point that coincides with end systole. If an intervention is performed that acutely changes the loading conditions on the heart but has no effect on myocardial contractility (e.g., transient inferior vena caval occlusion to reduce preload, administration of phenylephrine to increase afterload, etc.) a family of loops is obtained. The end-systolic and end-diastolic points of these loops delineate two distinct boundaries. The EDPVR, constructed by connecting the end-diastolic pressure-volume points of each loop, is nonlinear and defines the passive physical properties of the chamber with the muscles in their most relaxed state. The ESPVR, constructed by connecting the end-systolic pressure-volume points of each loop, defines a reasonably linear relationship that characterizes properties of the chamber with the muscles in a state of maximal activation at a given contractile state.

Assessment of systolic properties: Ventricular chamber properties depend on myocardial properties, muscle mass, and geometry. When mass and geometry are fixed, a shift of the ESPVR unambiguously signifies change in intrinsic myocardial contractility. Such observations would be typical, for example, of those observed during acute experiments in which inotropic agents (positive or negative) are administered. In the setting of chronic disease, however, geometry and muscle mass change. Important examples of this include the development of the eccentric hypertrophy in dilated cardiomyopathies and development of the concentric hypertrophy in idiopathic hypertrophic cardiomyopathy. In these cases, determination of the relative degree to which changes in the ESPVR reflect changes in chamber properties and changes in muscle properties is complex, with no single accepted standardized approach.

Assessment of diastolic properties: The EDPVR is intrinsically nonlinear, a characteristic attributed to the different types of structural fibers being stretched in different pressure-volume ranges. In the low pressure-volume range, where there is only a small increase in pressure for a given increment in volume, compliant elastin fibers and myocytes with sarcomeric titin molecules being stretched are believed to account for stiffness. As volume is increased further to a higher range, pressure rises more steeply as slack lengths of collagen fibers and titin are exceeded and stretch is more strongly resisted by these stiff elements. Therefore, chamber stiffness (the change of pressure for a given change of volume, dP/dV) increases as end-diastolic pressure (or volume) is increased. Shifts of the EDPVR may be reflective of changes in myocardial material

properties (e.g., fibrosis, ischemia, edema), physiological remodeling (e.g., as with normal growth), or pathological remodeling (e.g., as observed during development of hypertrophy and chamber enlargement in heart failure). In all cases, however, the EDPVR reflects the net effect of all facets of myocardial material properties, chamber structural properties, and extracellular matrix.

Theoretical foundation of support devices

The concept of cardiac support devices in general encompasses passive mechanical implants which can resist circumferential expansion of the left ventricle and subsequently global cardiac dimensions during diastole, without actively assisting contraction during systole. Laplace's equation provides a framework for defining means of mitigating ventricular remodeling. Using Laplace's equation, wall stress can be estimated from pressure, chamber size, and wall thickness For a cylinder-shaped ventricle:

$$T = P \times R/h$$

where T = myocardial wall force or wall stress along the cylinder axis, P = left ventricular end diastolic pressure, R = chamber radius and h = wall thickness

Ventricular wall stress can be reduced by decreasing transmural pressure, reducing cardiac chamber radius, promoting greater ventricular wall thickness, or by some

combination of the three. The fundamental role of a passive cardiac support device is intended to reduce wall stress by providing counter pressure to the ventricular wall.

$$\text{Diastolic Wall Stress} = \underbrace{\frac{\text{Radius} \times \text{Transmural Pressure}}{\text{Wall Thickness}}}_{\textit{(Myocyte Stretch)}}$$

$$\text{Transmural Pressure} = \text{LVEDP} - \text{Device pressure directed inwards}$$

Thus, a support device can have a significant impact on effective transmural pressure which can lead to a decrease in the wall stress and modulates the end diastolic volume.

Surgical therapies: Dynamic cardiomyoplasty & Batista procedure

Several surgical device based therapies have been tested in clinical trials and presently being implanted in FDA approved trials for mitigating symptoms of heart failure by physically remodeling the dilated heart. Stress reduction via Laplace's law is usually sited as the rationale for these therapies. The exact mechanisms of role of stress reduction and reverse remodeling is yet to be fully understood at molecular, cellular, tissue and organ level [28-32]. Consequently, the determination of a clear correlation between micro and macro level changes is beyond our current capabilities.

Since the mid 1980's dynamic cardiomyoplasty, has been in practice which involves surgically dissecting the patient's latissimus dorsi muscle, introducing it into the thoracic cavity, and then wrapping and attaching the muscle to the heart. An implantable electrical stimulator is connected to the muscle in order to stimulate and pace it in synchrony with the heart. This causes the muscle to contract and also transforms the

muscle, making it more fatigue-resistant. The original premise behind dynamic cardiomyoplasty was that these muscle contractions, by virtue of the geometry of the wrap, would squeeze the heart, and thus provide systolic assistance. The first reported clinical case of dynamic cardiomyoplasty using a latissimus dorsi wrap was published in 1985. Since then, over 1,000 patients have been treated with this experimental procedure. Numerous published studies have shown that the procedure produces significant improvement in clinical status, as graded by the New York Heart Association ("NYHA") classification scale, a slight but significant hemodynamic or systolic function improvement, and a reduction in the number of patient hospital visits after the procedure. However, an improvement in survival has yet to be consistently demonstrated. Furthermore, perhaps due to their frail condition, NYHA class IV patients have not fared well with the procedure. This has limited its use to NYHA class III patients. It appears that the skeletal muscle wrap, probably because of its deterioration over time, does not provide sustained squeezing of the heart over time. This lack of efficacy of the surgical procedure has led to considerable research into the underlying mechanisms of dynamic latissimus dorsi cardiomyoplasty.

Partial left ventriculectomy (PLV), also referred to as the Batista procedure, was introduced in 1994 by Brazilian cardiac surgeon Randas Batista to treat patients with dilated cardiomyopathy and was first performed in the United States in 1995. The procedure was developed to reduce the size and reshape the heart in order to improve mechanical function. Batista theorized that resecting a viable section of the lateral left

ventricular (LV) wall would reduce LV diameter and, consequently, LV wall stress in patients with dilated cardiomyopathy. The procedure consists of resecting the left ventricle between both papillary muscles from the apex to the mitral annulus. The procedure is usually done in conjunction with mitral valve annuloplasty or replacement, although it is sometimes performed alone. Despite initial enthusiasm, clinical studies showed that although estimated wall stress was reduced, a majority of patients did not experience improved hemodynamics or clinical status in the long term. One of the major limitations of this technique was the focus on its potentially beneficial effects on wall stress to the exclusion of considering its effects on overall pump function. Specifically, the effects of myocardial resection on diastolic ventricular properties were under-appreciated. When expressed in terms of end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively), theory predicted and clinical research later showed that despite the potentially beneficial effects on systolic properties of shifting the ESPVR leftward (increased chamber contractility), the Batista procedure was also associated with counteracting effects on diastole.

The concept of using a permanently implantable passive, non-contracting wrap around the heart to prevent its further deterioration is not new. Suggestions have been published in the literature. Kass et al.[33] questioned whether an "artificial elastic sock" could be used in lieu of skeletal muscle. They speculated that in dynamic cardiomyoplasty, the latissimus dorsi wrap provides some of its benefit by acting as an elastic constraint around the epicardial surface. They further suggest that the passive skeletal muscle wrap

stiffens gradually with stretch, unlike pericardium, which is highly compliant at low levels of stretch but becomes very stiff when expanded beyond resting dimensions. In the article, the importance of gradually increasing stiffness over the entire range of cardiac operating dimensions is emphasized. Despite the conceptual discussion, however, there is no mention of how a cardiac wrap that is both elastic over the entire range of cardiac dimensions and gradually stiffens with stretch can be designed or built.

Despite the prevailing sentiment that stimulated latissimus dorsi wraps should be more beneficial than non-stimulated wraps, the manner in which dynamic cardiomyoplasty has been executed clinically has limited its clinical success and clinical acceptance. The underlying mechanisms of dynamic cardiomyoplasty have been the focus of substantial investigation. Preservation of the latissimus dorsi as a power source has also been an issue. Because of muscle atrophy and fibrosis, the amount of squeezing power that is available has not been sustainable. Accordingly, there is still a need for a cardiac support device which does not foreshorten in the direction perpendicular to the primary direction of ventricular expansion, and that reduces wall stress by maintaining compressive contact over a significant portion of the cardiac cycle. Additionally, there is a need for a device that aids in preventing, in addition to treating, heart failure after acute myocardial infarction through attenuation of the remodeling process.

Thus fundamental drawbacks of present approaches are either clinical complexity of the procedures or lack of efficacy because of ineffective modulation of diastolic properties.

The present device developed in this dissertation is an effort to mitigate these issues in a novel passive support device which can fully modulate the diastolic mechanics with an adjustable component to enable progressive therapeutic benefits with decreased ventricular dimensions.

Present cardiac support devices & challenges

Current treatment options to minimize ventricular remodeling are suboptimal. For example, medications such as beta-blockers and angiotensin-converting enzyme (ACE)-inhibitors are often prescribed to attenuate cardiac remodeling and improve survival after myocardial infarction. However, despite a risk reduction of 15%-40%, most patients continue their progression to congestive heart failure, albeit at a slower rate. Furthermore, increasing dosages of these medications are generally associated with increased side-effects.

Present device treatment (undergoing clinical trials) options involve surgical placement of a passive restraint around the heart after in patients after an acute myocardial infarction or end stage congestive heart failure to alleviate wall stress and thereby prevent subsequent cardiac remodeling Examples of devices currently in development include the CorCap™ cardiac support device (Acorn Cardiovascular, St. Paul, Minn.), the Myosplint™ device (Myocor, Inc., Maple Grove, Minn.), and the Heartnet cardiac support device (Paracor Medical, Inc., Sunnyvale, Calif.).

Fundamental problem with the inelastic nature of fabric wraps, or knits, is that normal, healthy changes in the dimensions of the heart are not accommodated. In addition to chronic pathologic changes in ventricular diameter that can occur, such as those that accompany remodeling, normal physiological changes also occur. The devices like Corcap & HeartNet (presently awaiting FDA approval) do not have the capability to be adjusted post-implantation. These devices have a fixed size when implanted, though the devices are sized smaller than the end diastolic diameter but lack of adjustability chances of the device losing the wrap effect is highly probable. Thus with reverse remodeling the girdling effect of the device gets diminished over a period of time leading to reduction of the device.

One of the key aspects of devices being accepted into clinical practice is ease of surgical implantation and future ease of surgical intervention. All the devices presently being developed need to be sutured at the valve plane or needs to be attached to the myocardium in some way. This not only increases the time and complexity of

implantation but also increases the chances fibrosis over a period of time. Attachment of present devices to the myocardium is based on its ability to fibrose and secure itself to the tissue. Thus, any future surgical procedures performed to the heart can be difficult due to the development of fibrous tissue adhesions around the device and structures surrounding the heart.

The cardiac support devices under development have shown evidence in both preclinical and human studies that it can play an important role in both end stage heart failure and acute myocardial infarction by impacting the cardiac remodeling pathway. The cardiac support device prototyped in this dissertation is targeted towards treating end stage congestive heart failure. The device is also expected to prove effective in preventing onset of ventricular remodeling after acute myocardial infarction. This device has been designed to introduce fundamental innovations by introducing adjustability and other clinically advantageous features like intrinsic attachment negating the need to suture the device to heart, non-blood contacting and non- fibrotic bilayered design. This device would be also applicable to other structural heart diseases like idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and viral cardiomyopathy.

Prototyping of the Cardiac Support Device

The cardiac support device being prototyped here is an adjustable device designed to enable the gradual reduction of end diastolic volume as a means to rehabilitate the heart muscle of patients with end-stage heart failure. 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 support through epicardial compression. Cardiac support capabilities are designed to be progressively actuated over a period of months. A novel device has been built and multiple prototypes have been tested which has provided the proof of concept of the adjustable support feature of limiting the end diastolic dimension of the heart and shift the EDPVR demonstrating the efficacy of the design in an acute ovine model. To modulate the stress pattern and resultant diastolic mechanics, a necessary design constraint is that the diastolic and systolic configurations have normal cardiac curvatures. To meet these design constraints, a soft-shelled device consisting of inflatable, longitudinally oriented chambers that when deflated are collapsible has been prototyped (Figures 2 and 3). 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. The side of the chambers that are on the outer boundary form a shape that is similar to the end diastolic shape of the heart. The inner sides have folds and crenulations such that when inflated the chambers mostly expand inward.

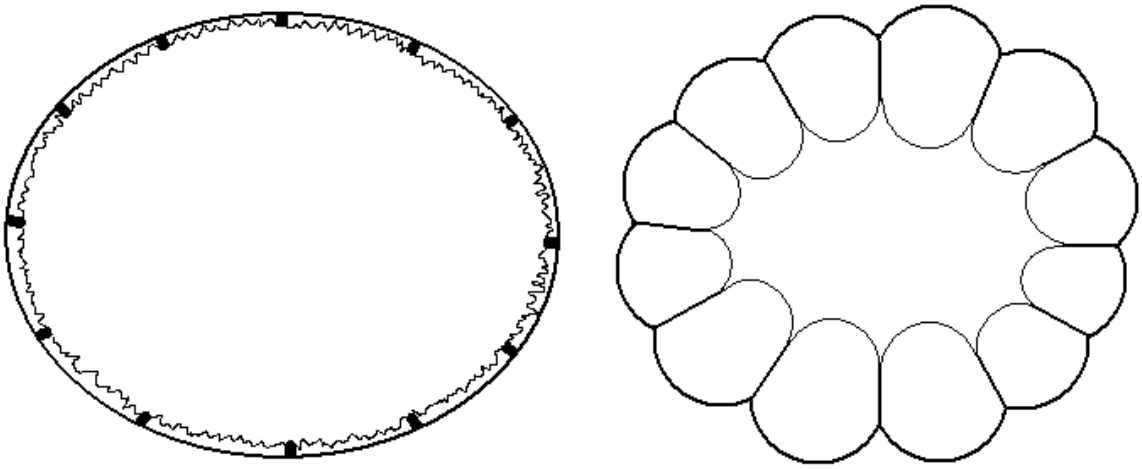

Figure 2. Schematic of cross-section of the device when deflated (left) and pressurized (right) without a heart inside.

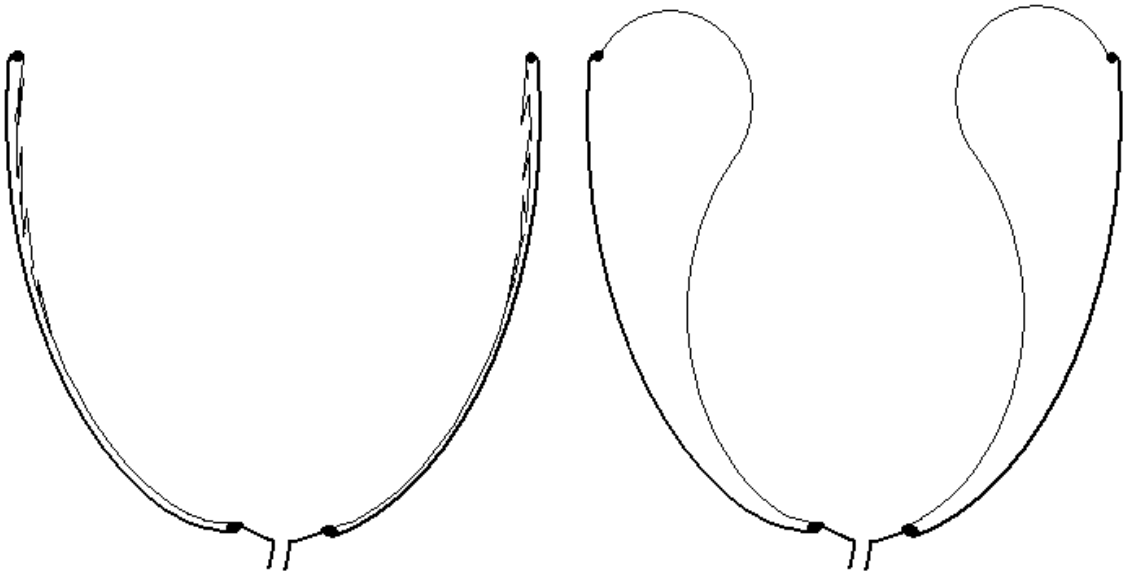

Figure 3. Schematic of long-section of the device when deflated (left) and pressurized (right) without a heart inside.

The fully pressurized shape without the heart inside is helpful for illustrating our design, yet the shape will be significantly different when the device surrounds a heart which contains blood under pressure (Figures 4 and 5). With a heart inside the pressure in the lumen of the device is higher than the pressure in the inflatable chambers. Since the chambers cannot fully expand, the inner film of the chambers is not taut. Rather than being supported by tension in the film, pressure on the lumen side of the longitudinal chambers is supported by contact forces on the epicardial surface. Without tension on the inner film, the attachment points are not drawn inward. Instead, the shape of the outer sides of the chambers becomes circular to support the pressure within the chambers (right side of Figure 4).

Because the inflatable chambers taper (as they go from base to apex) in a manner that resembles natural cardiac curvature the apex of the heart will have a physiological curvature. Moreover, because the device is semi-rigid when pressurized, the curved shape of the apical end will act to prevent the heart from being expelled from the device. Basically, for the heart to leave the device apical shape would have to pucker or a vacuum would need to form in the apical end of the device—both are unlikely. Consequently, the device, shown in Figure 6, is implanted with minimal fixation to the heart.

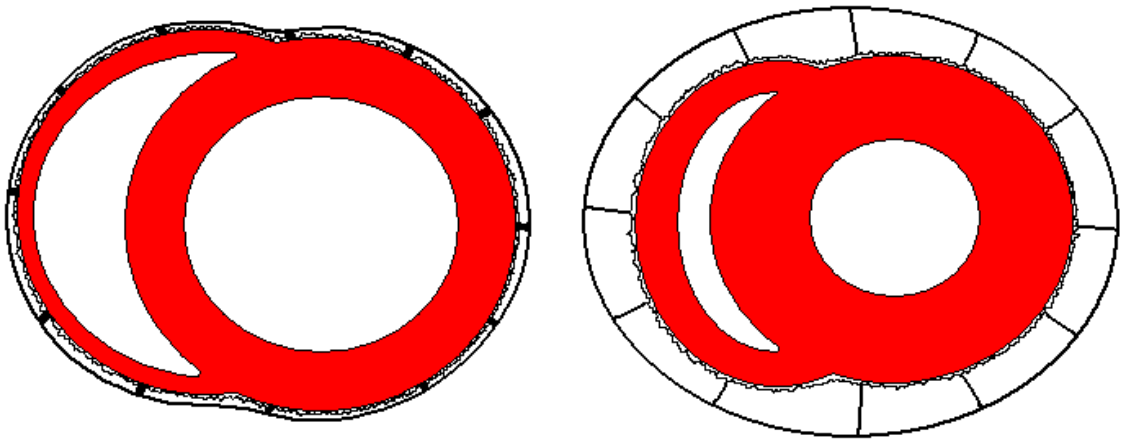

Figure 4. Schematic of cross-section of the device when deflated (left) and pressurized (right) with a heart inside.

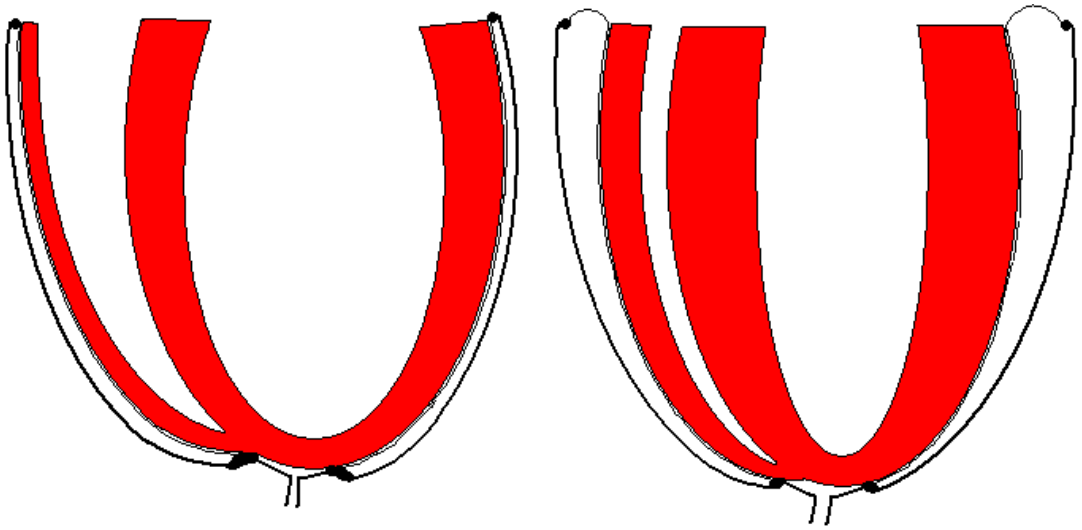

Figure 5. Schematic of long-section of the device when deflated (left) and pressurized (right) with a heart inside.

Additionally, a biocompatible lubricant, anti-clotting agent, anti-fibrosis, or antibiotic agent could be injected into the space between the heart and device. So that the device could be removed easily after weaning, the device should be covered with an anti-fibrotic coating or film that retards fibrous adhesions.

Figure 6. Schematic of alpha prototype after it is completed.

In summary, the major features of the design are:

1) When uniflated the device as shown in Figure 6 has a very low structural rigidity such that it can be inserted and implanted through a small, sub-xiphoid incision (Figure 7). Similarly, explantation will be minimally invasive and done through an enlargement/combination of driveline tracks.

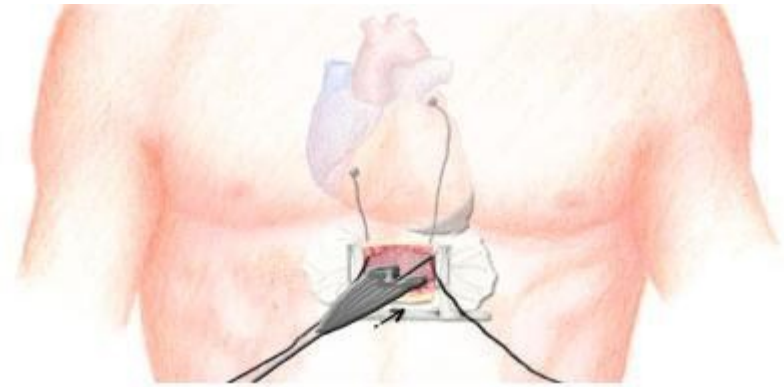

Figure 7. Implantation of proposed device.

2) In case of device failure, the soft shelled nature of the device is less likely to impede the function of the heart.
3) When inflated with a heart inside the device, our design takes on a systolic configuration with normal cardiac curvatures. The induction of this systolic shape intrinsically draws the heart into the device.
4) Because the heart is intrinsically drawn into the device, there is minimal sewing or similar attachment to the ventricles or valve plane. Hence, valve plane geometry and thus valve function will be unaltered and implantation will be quick and performed without cardiopulmonary bypass.
5) The amount of adjustability and hence support can be graded and thus a heart can gradually remodel of a period of time.

Key design parameters of the device

Table 3 below delineates the design constraints laid out for the cardiac support device.

Table 3 Key design parameters

Key Factors	Proposed Target	Requirement for Success	Present Practice	Associated Tech Barrier	Innovative Solution
Collapsibility	40 mm	40 mm	100 mm	Designing and prototyping the device components to both function and fold	Multiple inflatable chamber design permits collapse Status: Achieved
Morphing Capability	Tube to Fluted to Cup Shape	Tube to Fluted to Cup Shape	No Morphing	Designing and prototyping device support structure to change shape accordingly	Wire frame with multiple modes of storing energy to induce shape change. Status: Achieved
Intrinsic Attachment	No sewing needed	Minimal sewing	Suction cup or extensive sewing attachment	Pushing on the heart surface without dislodging the heart are opposing actions	Use pneumatic pressure applied to simultaneously stabilize the cup-like apical Curvature. Status: Achieved
Failsafe Mechanism	Floppy structure when deflated	Floppy structure when deflated	Non existent in previous devices	Encircling the heart with a device to act on the heart but also not act are opposing	Use of inflatable, soft Chambers makes the device floppy when deflated. Status: Achieved

Table 3 continued

Key Factors	Proposed Target	Requirement for Success	Present Practice	Associated Tech Barrier	Innovative Solution
Passive ED Adjustment	33% adjustment of inner diameter	10% adjustment of inner diameter	0% adjustment after implant	As the heart changes shape the device must change shape to apply tractions	Use of inflatable chambers to adjust shape pneumatically Status: Achieved
RV Inflow Adjustment	50 mL obstacle in RV inflow tract	Not known	Not evident in prior art	Left-Right flow is automatically adjusted by the systemic and pulmonary circulatory beds via unknown mechanisms	By inserting an inflatable obstacle over the inflow tract, RV inflow can be reduced in a graded manner. Status: Achieved
Diastolic Recovery	15-20% reduction	15-20% reduction	Spurious recovery	Development, growth, Remodeling processes in Heart unknown	Mechanical stimuli as proposed are most likely to be effective Status: Future chronic studies needed, acute study completed
Systolic Recovery	55% Ejection Fraction	55% Ejection Fraction	Spurious recovery	Development, growth, Remodeling processes in Heart unknown	Mechanical stimuli as proposed are most likely to be effective Status: Future chronic studies needed, acute study completed

Prototype Design

As mentioned in the study goals there were two devices fabricated which were used in two different studies. One of them involved sternotomy (open chest) and other study involved minimally invasive implantation through a inch long sub-xiphoid incision.

a. Study One: Prototype for the study consisting of implantation through sternotomy: The prototype device implanted in this acute ovine studies 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. 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 chambers were also attached to a nitinol scaffold which provided structural stability. In this study airs was used in filling the passive chambers and verify the adjustable nature of the device.

b. Study Two: Prototype for the study consisting of minimally invasive device implantation through a sub-xiphoid incision: The dimensions of the device were similar to previous device but the material used is nylon for this study. Figure 8 is a schematic of the nitinol frame of the device without the adjustable port.

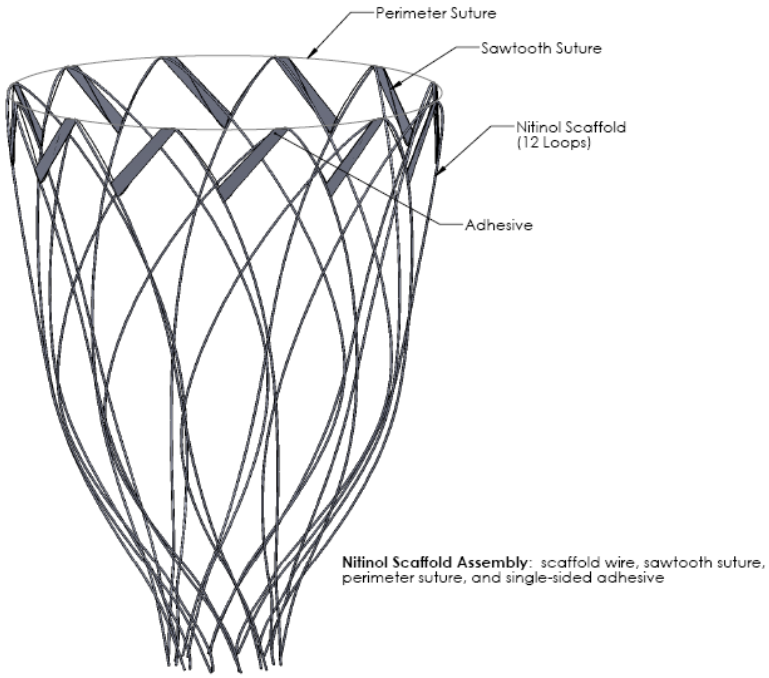

Figure 8. Prototype of the cardiac support device with nitinol elements which provides the structural rigidity to the device.

The Figures 9 & 10 depict the polymeric multi-chambered support device deployed about an excised ovine heart (Figure 9) and fluoroscopic image of a fully deployed device with the chambers filled with contrast-saline solution for imaging (Figure 10). This prototype forms the foundation of a novel device which was studied in vivo to test the various device parameters and also functionality as whether it can modulate the diastolic properties.

Figure 9. A prototype of the polymeric multi-chambered support device deployed about an excised ovine heart that is preserved and wrapped in thin latex for handling.

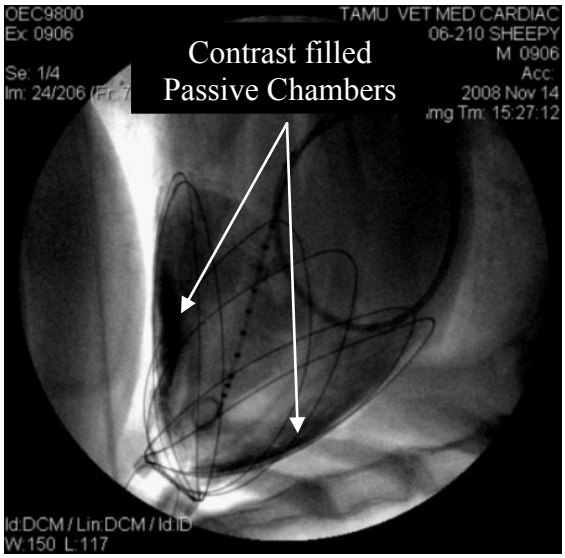

Figure 10. Fluoroscopic image of a fully deployed device. The passive chambers are filled with contrast-saline solution for imaging.

The overall device in this chapter being studied here is similar in design to that of the thesis project of Michael Moreno; the primary distinction between the Moreno thesis project and the project herein is that Moreno device was focused on combining an active assist device with an passive support whereas the project herein was devoted to studying a standalone adjustable support device. For the acute implant studies Dr. Criscione chose to combine the assist and support actions into a single device to maximize the use of financial and animal resources. The data runs related to device operation with support aspect of the device being functional only is being presented in this project here.

In vivo Studies: Animal Model and Experimental Set-Up

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 sternotomy, 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. 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.

Using the 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 15.18ml, and thus a total volume of 28.38ml esmolol administered.

Results: In vivo Proof-of-Concept of Adjustable Support Device

1. Successful implantation of the adjustable cardiac support device: After multiple design iterations and testing of prototypes on a bench-top model of the ovine heart, implantation was accomplished as shown in the fluoroscopic image in Figure 11.

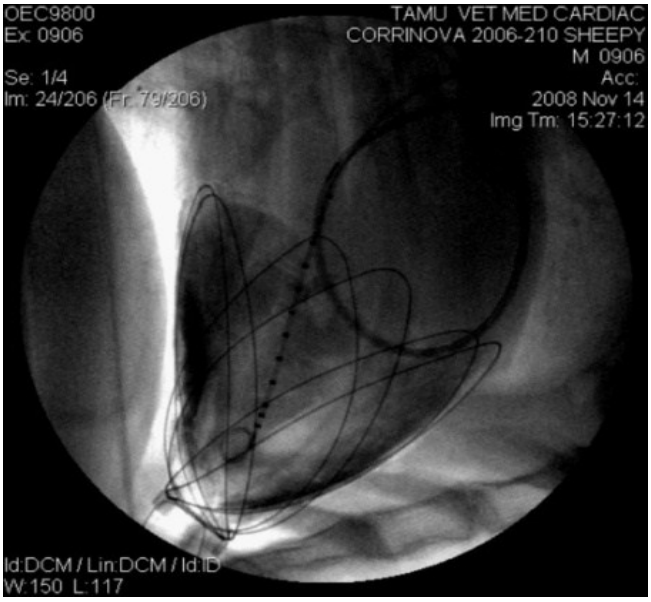

Figure 11. Device placed on the ovine heart and chambers filled with contrast agent.

2. Intrinsic pneumatic attachment: The device takes on a 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. Once air in the mediastinum is removed, the heart and device are pneumatically locked in a co-axial configuration. This feature was also verified by fluoroscopic imaging.

3. Study One: EDPVR Passive Constraint/Support with air to adjust the passive chambers with device implanted through median sternotomy: 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 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. One of the objectives of the study was to show how the device's passive constraint/support component could alter the EDPVR in a positive manner. The preload was altered by occluding the vena cava with a balloon. The vena cava occlusion was first done with a passive constraint of 0mmHg to develop a baseline EDPVR. The PV relationship was recorded for approximately twenty cardiac cycles after the occlusion as shown in Figure 12. After the heart recovered, the vena cava was occluded again but this time the cardiac support device applied a passive constraint pressure of 7.5mmHg. Again, the PV relationship was recorded for approximately twenty cardiac cycles. The end-diastolic points for each PV loop are plotted in Figure 13. The plots of the EDPVR for the 0mmHg versus the 7.5mmHg show that the EDPVR shifted upward with the 7.5mmHg passive constraint. This upward shift in the EDPVR indicates a decrease in the size of the left ventricle relative to pressure, i.e. the ventricle maintains the same filling pressure at a smaller volume. Therefore, the passive constraint is capable of manipulating the end-diastolic volume.

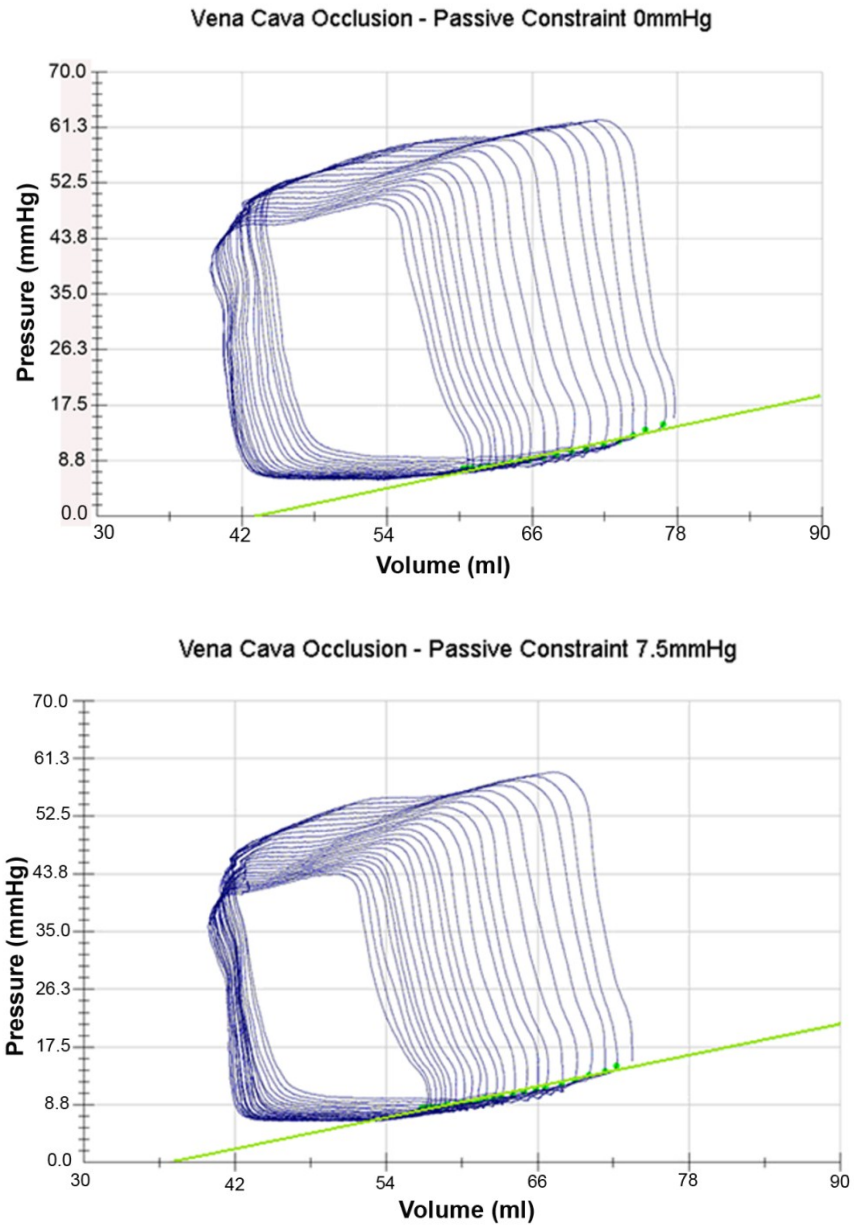

Figure 12. (Top) PV loops of left ventricle during vena cava occlusion with a passive constraint of 0mmHg. (Bottom) PV loops of left ventricle during vena cava occlusion with a passive constraint of 7.5mmHg.

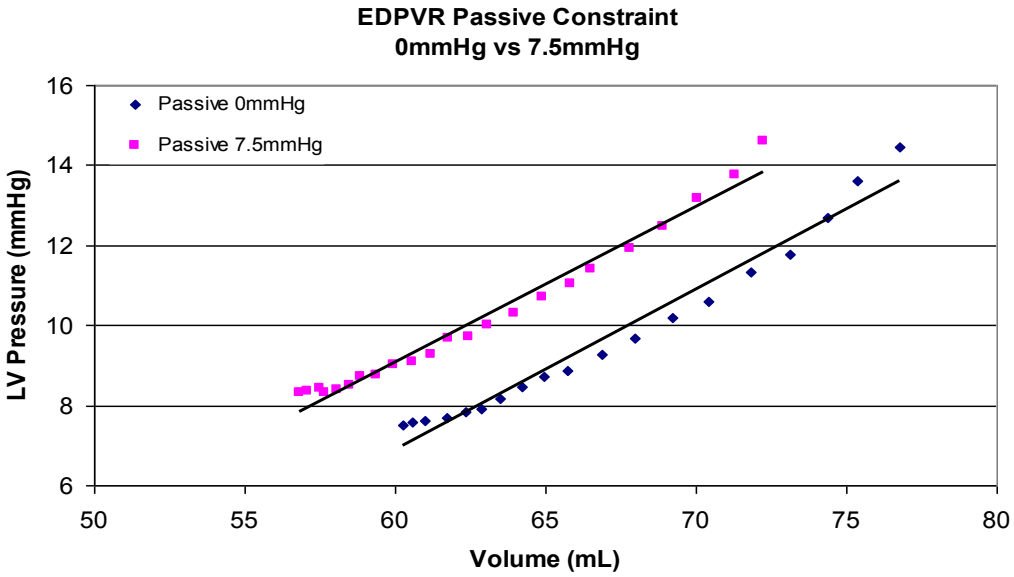

Figure 13. Plot of end-diastolic pressure-volume relationship for vena cava occlusion with a passive constraint of 0mmHg versus 7.5mmHg.

4. Study two: EDPVR Passive Constraint/Support with saline to adjust the passive chambers with device implanted in a minimally invasive manner through sub-xiphoid incision: The vena cava occlusion was first done with the passive support chambers filled with 0mL of saline to establish a baseline EDPVR as shown in Figure 14 (Note: In the previous study 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 Figure 15. 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.

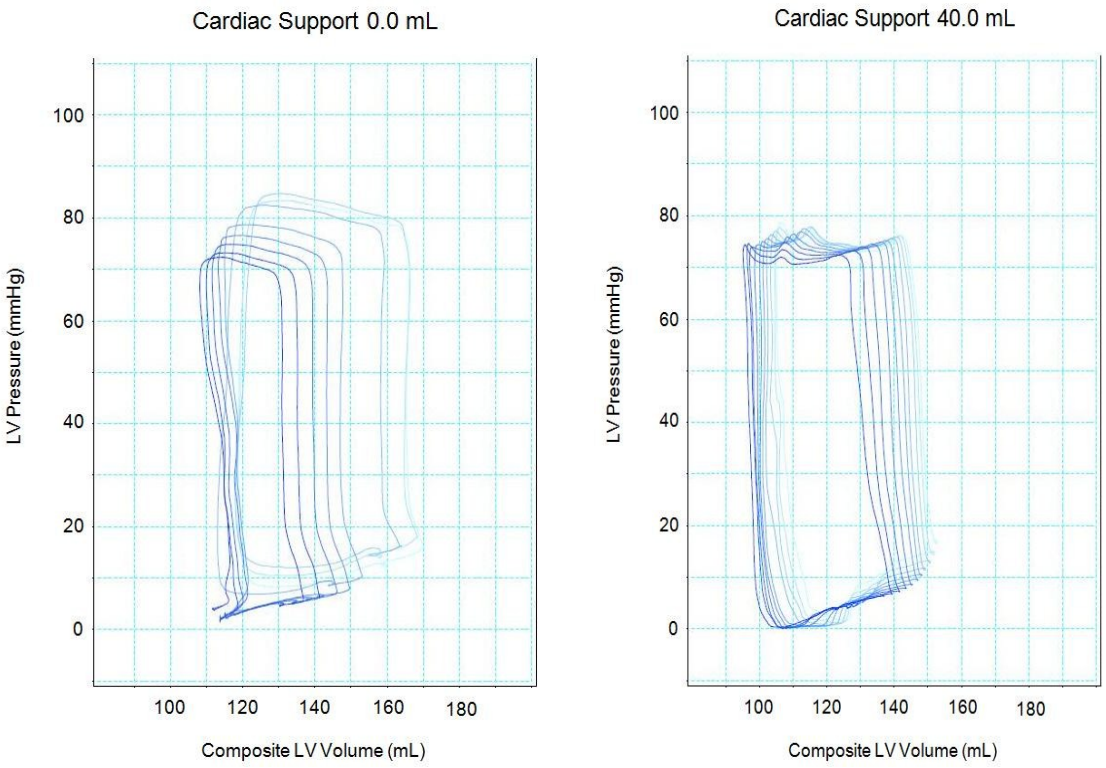

Figure 14. (Left) PV loops of the left ventricle during vena cava occlusion in the absence of passive support, i.e. cardiac support of 0.0 ml. (Right) PV loops of the left ventricle during vena cava occlusion with 40mL of passive support.

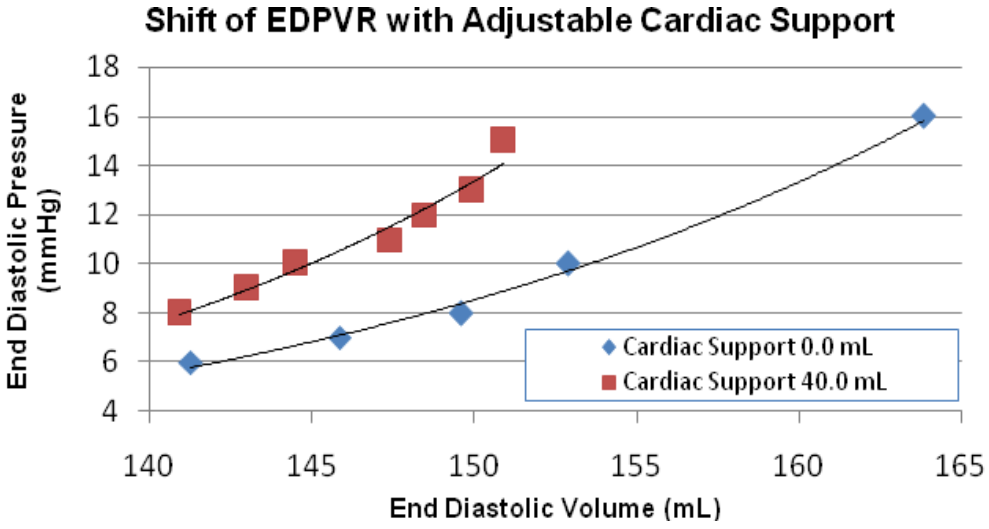

Figure 15. Plots of the EDPVR for both the 0mL of support and 40mL of support.

Bench-Top Proof- of- Concept of Adjustable Support Device

The bench-top study was conducted to obtain EDPVR's from a model heart and with the passive component of the proposed device in action to test the adjustable nature of the device and its impact on EDPVR; thereby allowing comparisons to be drawn between EDPVR's between acute ovine studies and bench-top studies. The plots of the EDPVR for the 0mL versus the 40mL was obtained with the goal being to study whether there is 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.

The project consisted of two phases. In the first, a model was created to mimic the EDPVR of a human heart. A model of the normal heart as shown in Figure 16, was chosen because the mechanics and response of the normal heart are better known and easier to model than the failing heart's complicating structural and mechanical alterations, and a model of the normal heart is sufficient to meet the goal of demonstrating the device's ability to effect modulation of end diastolic volume and impact on the pressure volume relationship. This model was used to set baseline values for later comparison to the results when the device was tested. Once a satisfactory model was built, the device (Figures 17 and 18) was tested using the experimental setup described in the remainder of the section. A model of the heart was constructed that simulated the EDVPR (end-diastolic pressure-volume relationship) of a normal human heart. The model was formed by creating a bladder approximately the size of both

normal human ventricles. The bladder was rigid upon full inflation, thus approximating the shape of the normal human heart.

The experimental setup is conceptually simple: pressure or volume was incremented, and therefore, known, while the corresponding change in the other variable (volume or pressure, respectively) was measured. The results were then plotted to create an EDPVR. At the outset of the project, volume was used as the independent variable, and incrementally increased while the corresponding change in pressure was measured using a manometer. This approach concentrated the readings in the low pressure region of the EDPVR, as incremental changes in volume led to major pressure changes as volume increased. Additionally, because a small volume change could create a major change in pressure at high volumes, it was difficult to create stable, easily repeatable relationships. To avoid these problems, pressure was made the independent variable. Pressure was incrementally changed by varying the difference in height between the model and a water reservoir. The volume change in the water reservoir corresponding to each pressure change was measured, and the results plotted to create an EDPVR. The experiment was designed to increment the model's volume, and measure the corresponding change in pressure. The results were then plotted to create an EDPVR. Figure 19 illustrates this setup.

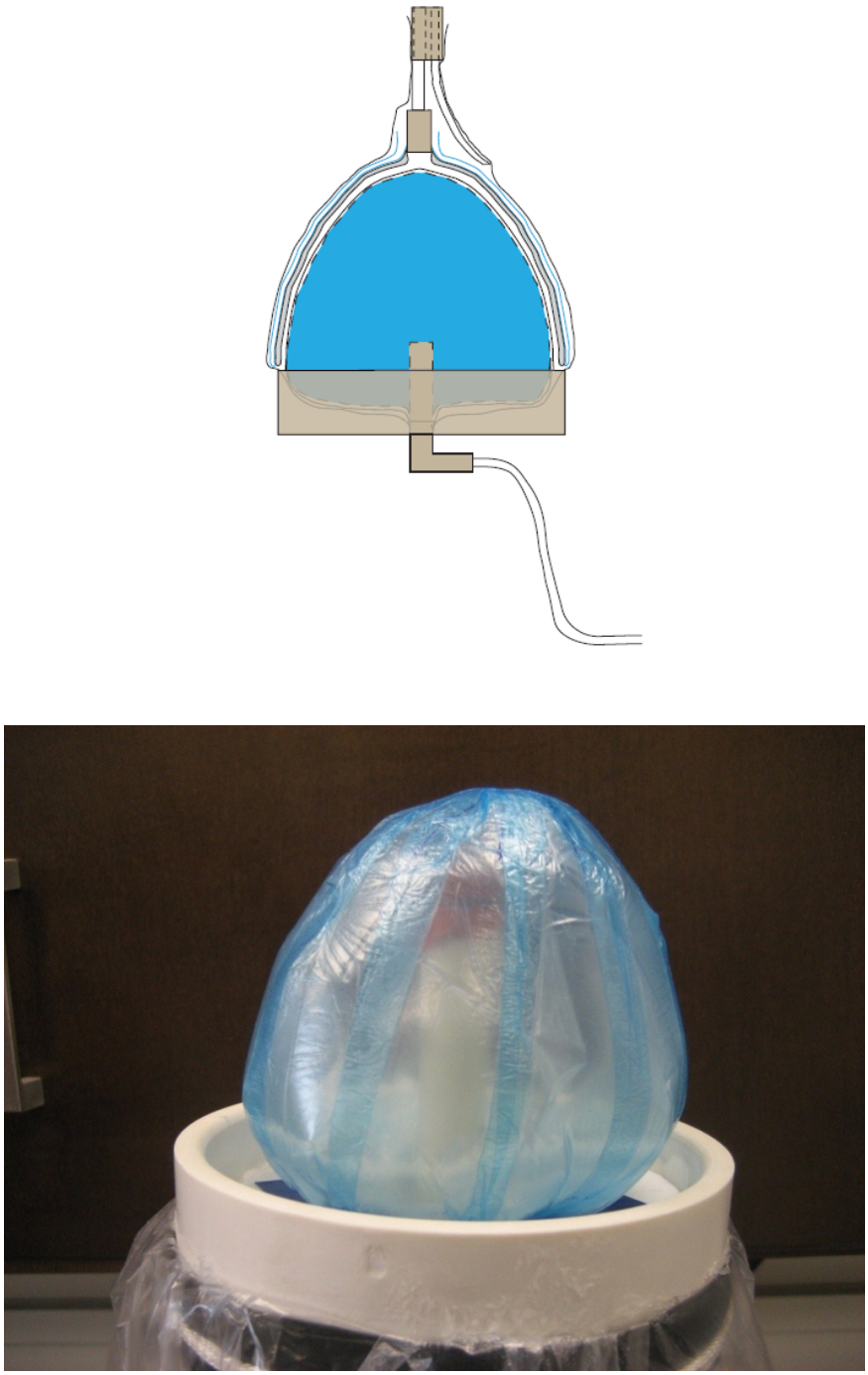

Figure 16. Heart model (top) Schematic design of the heart model in the experimental setup with uninflated support device placed on it; (bottom) Prototype of the model which is used to measure EDPVR of a normal heart.

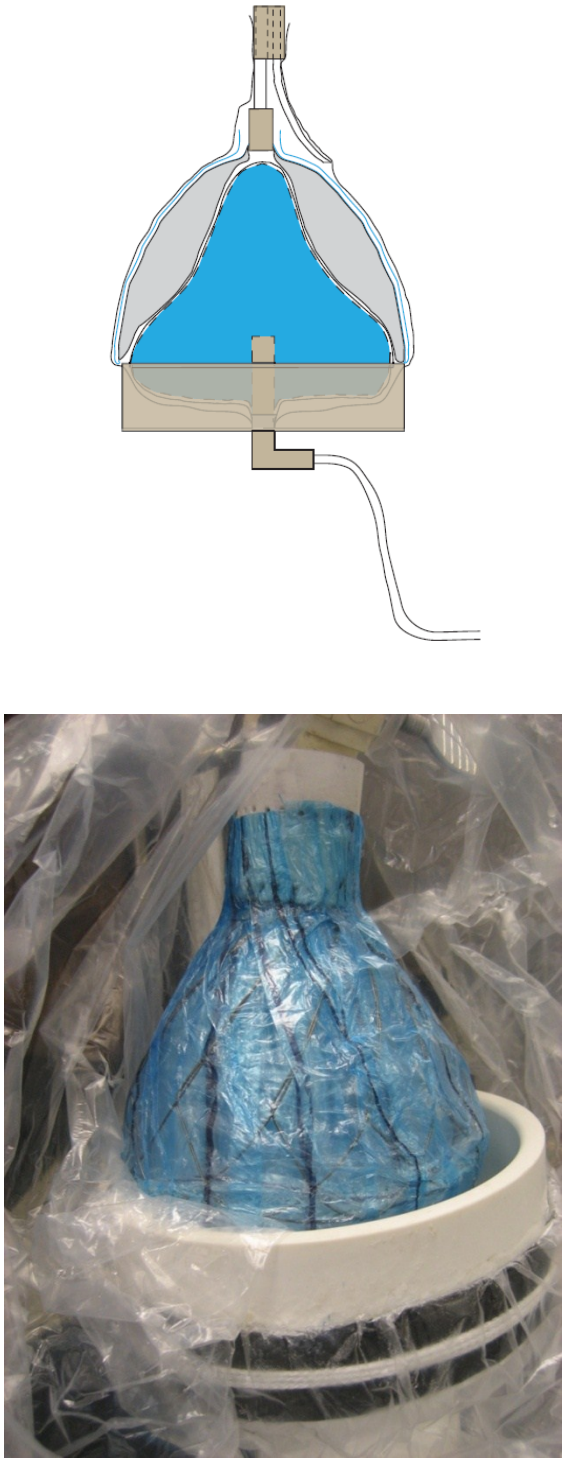

Figure 17. Cardiac support device (top) Schematic design of the inflated cardiac support device placed on the heart model in the experimental setup; (bottom) Prototype of the cardiac support device on the heart model which is used measure EDPVR.

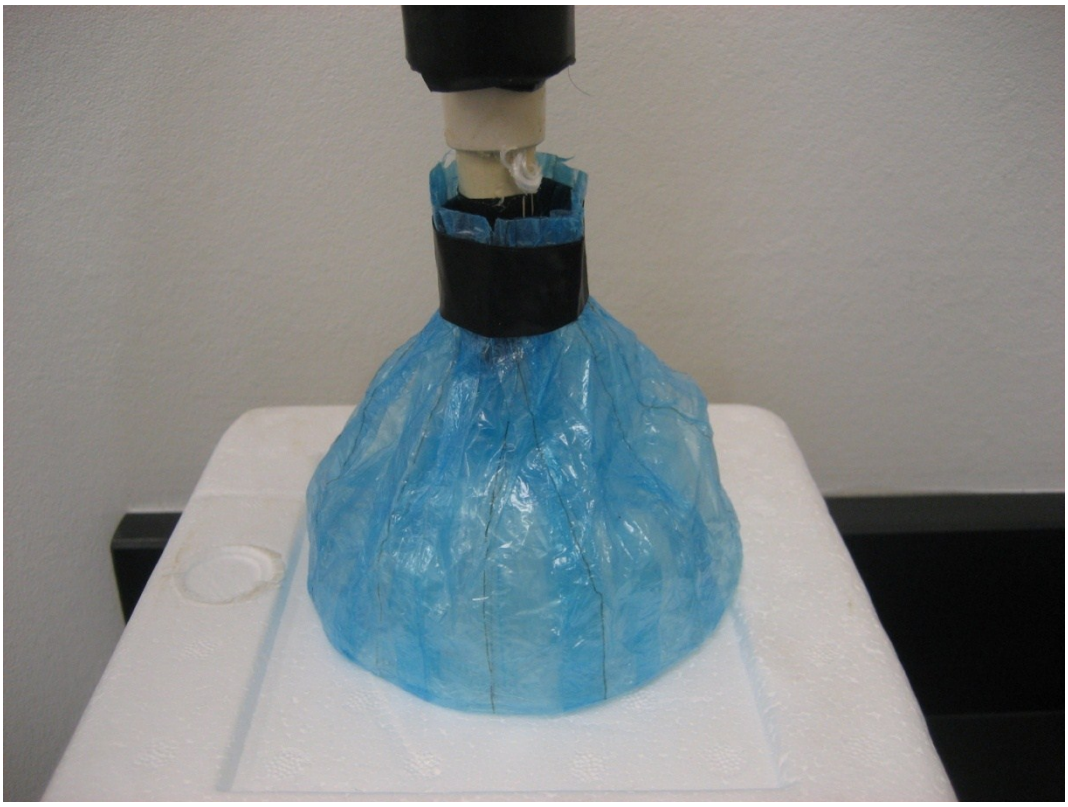

Figure 18. Prototype of the cardiac support device that was placed on the heart model in the experimental setup.

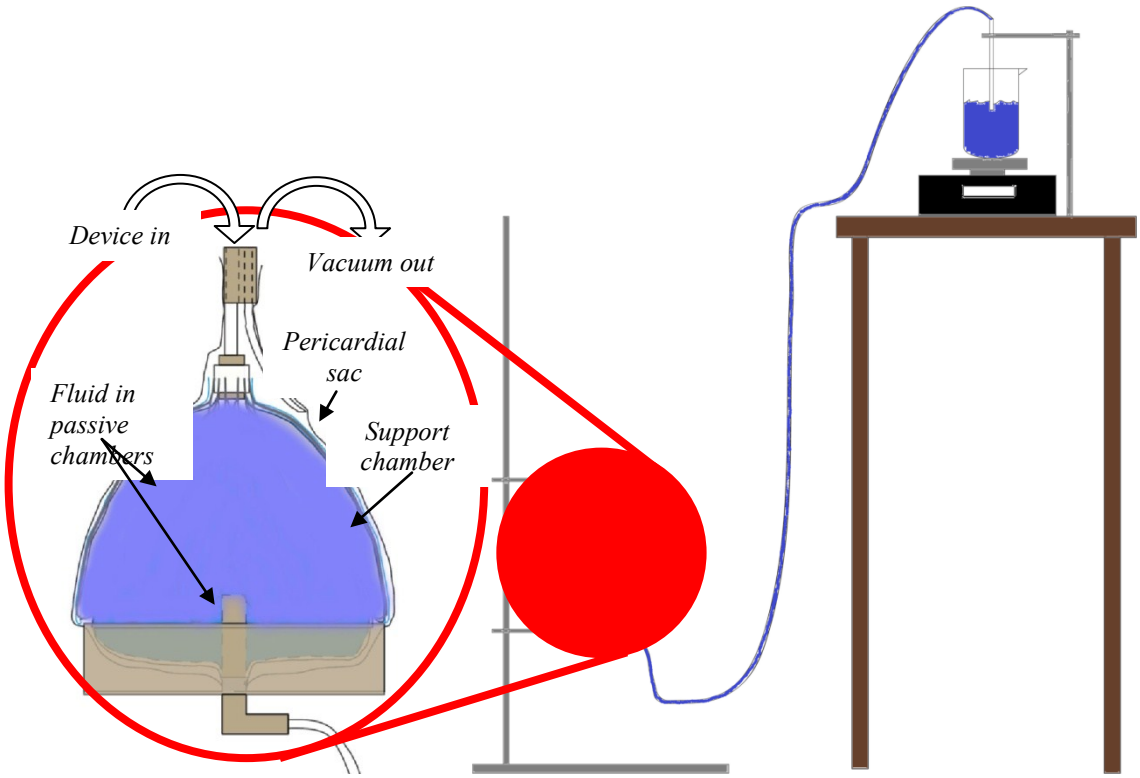

Figure 19. Close-up illustration of heart model, pericardial sac model, and cutaway device inflated passive support chamber.

Pressure readings were taken at 5 cmH_2O intervals. The heart has a normal left ventricular end-diastolic pressure of approximately 15 mmH, or 20 cmH_2O; thus, 5cm intervals were determined to be sufficient to allow an accurate EDPVR to be obtained. In order to obtain an accurate comparison and eliminate as much error as possible, new baseline values of the heart model alone were taken at the beginning of every trial. Once a baseline EDPVR was obtained, the passive support device was employed. The set of EDPVRs was obtained for the model heart and device along with the model at two volumes with gradual adjustment.

It is important to note that the device is not physically secured to the nitinol frame support structure; therefore, the diastolic support component relies on the presence of a vacuum to cause the ventricle walls to adhere to the device and follow it outward when it recoils as the heart enters diastole. In the body, the pericardial sac that surrounds the heart provides a vacuum. In this experimental setup, the pericardial sac was modeled by a vacuum drawn, as shown in Figure 20, in a sac placed around the heart model and device.

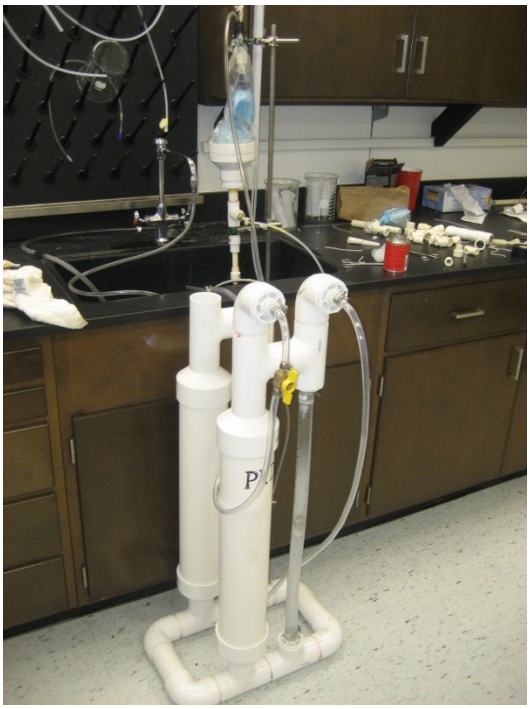

Figure 20. Device set-up to model a pseudo-pericardial sac.

Results: Bench-Top Study of Adjustable Support Device

End-diastolic pressure-volume relationship (EDPVR), which represents the passive filling mechanics of the left ventricle, was obtained in this bench-top study using a mock heart model. One of the objectives of the study was to show how the device's adjustable passive constraint/support component could alter the EDPVR in a positive manner and have comparable outcomes with the ovine studies. In the experiment three data runs were done, one with heart model only, second passive device with 0ml of water and third passive device with 40 ml of water. Figure 21, shows the baseline EDPVR of the heart model on the right. The device then placed on the model with passive support chambers unfilled (0mL of water) and a EDPVR was obtained. In the next data run the passive component was filled with 40 mL of water and EDPVR data taken. The EDPVR's are plotted in Figure 21. The plots of the EDPVR for the baseline heart model vs 0mL versus the 40mL show that the EDPVR shifted leftward with gradual decline in end diastolic volume. 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. Therefore, the passive constraint is capable of manipulating the end-diastolic volume.

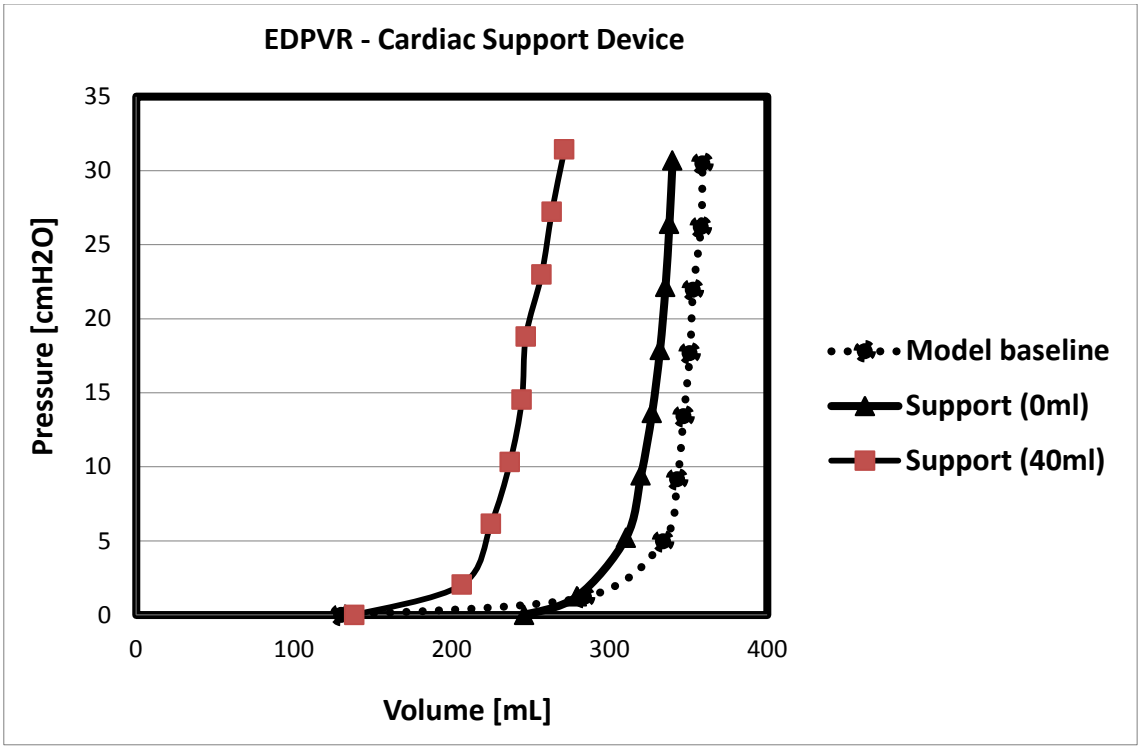

Figure 21: Bench-top verification of adjustable passive device with a fillable, pseudo-heart mimicking the baseline EDPVR. With the device placed on the pseudo-heart inside a sac with air evacuated (like the mediastinum) leftward shift of EDPVR and adjustability is evident.

Discussion

Over the last decade multiple studies have demonstrated the utility of cardiac support devices which function as passive ventricular restraint to mitigate the deleterious changes triggered by ventricular remodeling as a consequence of heart failure [15,34]. Presently awaiting FDA pre-market approval are the most studied ventricular restraint devices, such as the Corcap [35-48], Myosplint [49-52], Coapsys [53-57], and the Heartnet [58-62] do not have any means to adjust the therapy once implanted as the heart

is wrapped in prosthetic material to reduce ventricular dilatation over a period of time. The cardiothoracic surgeons implant the device 'snugly' on the epicardial surface thus providing no control over the modulation of the end diastolic volume, so once the device is placed at the initial procedure, the level of restraint is constant and unchanging, even as the heart undergoes reverse remodeling. The inability of current restraint devices to adjust restraint level and develop a therapeutic regimen to direct the heart towards a progressive reverse remodeling is a major drawback of the present devices.

The motivation of this device design was triggered by the premise that mechanical stimuli are critical factors for guiding the growth, remodeling, and maintenance of cardiac functions in a normal state. Hence a device therapy to intervene in a pathological state would need a fundamental design innovation which creates a normal physiological environment. Under normal conditions contractile proteins are in a constant state of flux being added 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. Thus 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. The non-adjustable passive CSDs are designed to resist chronic dilation of end-diastolic volume, as well as reduce ventricular wall stress and myocardial stretch. Thus over long terms these devices can induce reverse remodeling toward normal size and function. But one

of the major factors which limit the efficacy of the present CSDs is the lack of device adjustability with progressive reverse remodeling. With a change in ventricular dimensions caused by reverse remodeling there is a mismatch between relative geometry of the device as compared to the ventricular dimensions. Consequently, in order to achieve full reverse remodeling an adjustable device is desirable 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 adjustable cardiac support device prototyped and tested in this dissertation introduces an innovation in the class of passive support devices which for the first time introduces a minimally invasive support device which can fully modulate the diastolic mechanics. In the in vivo studies, we showed that adjustable restraint level shifts the end diastolic pressure volume relationship leftward indicating the device improves the passive diastolic properties revering the ventricular dilatation. We postulate that periodic adjustment of device through the subcutaneous port would be needed post-implantation to maximize therapeutic efficacy as the ventricle reverse remodels.

In our acute study we have adjusted the support level based on PV loop data using both air and saline to modulate the end diastolic volume. The goal of this study is to demonstrate the feasibility of a prototype cardiac support device which can modulate the end diastolic volume real time in an acute ovine model. In a clinical set-up we expect that the post-implantation adjustment of the device would be performed using real-time

echocardiographic data. Present devices undergoing FDA approval do not provide an option of post implantation adjustment. In our present study the device adjustment to modulate the end diastolic volume (EDV) in an ovine model was performed percutaneously after device implantation. We expect in a clinical set up all these activities would be performed outside of the operating room in a minimally invasive fashion utilizing physiologic parameters to guide therapy application.

The two in vivo studies we did were limited to evaluate the proof of concept of adjustability using two possible mediums. It is expected in a clinical set up a saline would be a more viable option to adjust the device. The main goal of performing this study is to demonstrate that an adjustable device can be implanted safely in a minimally invasive surgical procedure and the device can be adjusted postoperatively without any adverse physiological effect. With future ovine chronic heart failure model studies more questions regarding the protocol of the therapy would be answered like duration of device adjustment post implantation, quantitative assessment of long-term reverse remodeling and comparison of overall efficacy with present heart failure solutions.

Conclusion

In conclusion we have successfully prototyped and tested on a bench-top and in vivo a passive support device with adjustable passive chambers to modulate end diastolic volume in real time. Two different device designs have been tested with one being implanted through sternotomy and other one implanted in a minimally invasive manner

through a one inch sub-xiphoid incision. The device has been tested with both saline and air and implanted in an acute ovine model where the implantability, attachment and ability to modulate end diastolic pressure volume relationship was successfully tested to adjust the device size. Other clinically advantageous features like intrinsic pneumatic attachment negating the need to suture the device to heart, non-blood contacting and non- fibrotic bilayered design have also been incorporated in the design. Though this device is clinically targeted towards patients with systolic dysfunction caused by an infarct but it would also be applicable to other structural heart diseases like idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and viral cardiomyopathy. With the design features incorporated in the device a wide range of mechanical effects can be examined in chronic heart failure models so that a diseased hypertrophied heart can be gradually returned to normal size with restoration of function. The underlying goal of this device therapy would be to ultimately create the conditions under which natural growth and remodeling processes are guided in a physiologically appropriate manner to introduce the natural mechanical feedback loops.

CHAPTER III

DEVELOPMENT OF A NOVEL DIASTOLIC RECOIL DEVICE TO IMPROVE VENTRICULAR FILLING

Introduction

Heart failure which is manifested as left ventricle's inability to generate sufficient cardiac output, is commonly associated abnormalities in systolic function (emptying of left ventricular chamber), but its symptoms may also arise as a result of diastolic (filling of left ventricular chamber) dysfunction. Diastolic dysfunction might be present in both normal and abnormal systolic performance. In the event of diastolic dysfunction there are moderate to severe changes in ventricular diastolic properties with a deleterious effect on ventricular diastolic pressures and ventricular filling. An integral part of normal diastolic filling is the contribution of the left ventricular (LV) elastic recoil forces to the LV filling. Elastic recoil forces are generated within healthy myocardium during systolic shortening. The magnitudes of elastic recoil forces are inversely proportional to the volume of the LV, i.e., they increase as the LV volume decreases. Their contribution is important in early diastole because they allow rapid and enhanced early filling by assisting the expansion of the left ventricle. In a case of ventricular enlargement and/or the decrease of myocardial function due to hypertrophy the left ventricular elastic recoil forces may be diminished or nonexistent, therefore ceasing to assist early ventricular filling and leading to an increase of the ventricular filling pressure. In this chapter the

problem of ventricular filling is being addressed with prototyping of devices which can increase using diastolic filing by increasing the recoil effect.

Study Goals

With an understanding of the present state of the art in diastolic recoil devices and prominent role of torsional mechanics and understanding that early diastolic filling is directly related to the active process of LV relaxation leading to a ‘suction’ effect' , a novel device design has been conceptualized to mitigate the present challenges of the diastolic recoil devices. To advance the feasibility of the concept and the device design our goal is:

Prototyping of a recoil device to augment ventricular suction during diastole: Modification of the adjustable support device design to incorporate design features to integrate recoil effect in a single device. The goal of this device is to augment the torsional untwisting during diastole and increase the diastolic filling. Successful achievement of these milestones is central to proceed towards chronic experiments to assess heart remodeling—i.e., the next phase of studies.

Background

The term diastolic heart failure (DHF) generally refers to the clinical syndrome of heart failure associated with a preserved left ventricular EF, in the absence of major valvular disease [63]. Forty percent of incident CHF cases and 50–60% of prevalent CHF cases

occur in the setting of preserved systolic function [64]. Mortality rate among patients with DHF is considered lower than in systolic heart failure [65]. Some challenge this notion, showing that the natural history of patients with DHF may not be different from that of patients with systolic heart failure [64, 66]. The morbidity and rate of hospitalization are similar to those of patients with systolic heart failure [63, 66]. Due to its higher prevalence in the elderly population, the incidence of DHF is expected to rise with the increased aging of the western world population.

Of the 5.7 million people in the US and 25 million people worldwide who suffer from heart failure, between 30-55% of these patients suffer from diastolic heart failure (DHF) and are without effective treatment. The term diastolic dysfunction indicates abnormal diastolic distensibility, filling, or LV relaxation, regardless of whether the ejection fraction is preserved or abnormal or whether the patient is symptomatic or asymptomatic. The terms Diastolic heart failure (DHF) and Heart failure with normal ejection fraction (HFNEF) are used to describe patients with the signs and symptoms of heart failure, a preserved ejection fraction, and LV diastolic dysfunction [67]. Diastolic heart failure is most common in elderly patients and women with a history of essential hypertension, ventricular hypertrophy, diabetes, and cardiac ischemia [68]. As a result of the condition, mortality, morbidity, and healthcare costs are high [69]. Although DHF typically has a lower in-hospital mortality rate than systolic heart failure, hospitalization frequency for both conditions is comparable [70, 71]. Epidemiological studies have suggested that 30% to 50% of patients with active congestive heart failure (CHF) have

adequate LV systolic function [72-76]. Kitzman et al [76] found that 8% of patients older than 65 years have heart failure, 55% of whom have a preserved LV ejection fraction (LVEF). In addition, diastolic dysfunction has been shown to affect elderly women more than any other population subgroup [73, 74, 77]. Patients who have diastolic dysfunction are twice as likely to have diabetes mellitus [76]. Other commonly associated conditions include hypertension, renal dysfunction, myocardial ischemia, and ventricular hypertrophy [78]. Patients with DHF have a preserved ejection fraction despite increased LV diastolic pressure and pulmonary venous pressure. These patients have both increased passive stiffness and abnormal active relaxation of the left ventricle, which may work independently to cause abnormal diastolic physiology [79]. This effect has been suggested by showing that even after correction for slow relaxation, increased passive stiffness was found to be an important factor in LV diastolic dysfunction and DHF [79]. Under such conditions, the left ventricle typically cannot fill to the minimal volume without elevating diastolic pressures, eventually leading to pulmonary congestion, which in turn leads to DHF [80-82]. Ventricular relaxation, as an energy-dependent process, may be impaired by decreased availability of adenosine triphosphate (ATP) and changes in calcium metabolism [80, 83]. Removal of calcium from the cytosol may be delayed by a decrease in the activity of sarco/endoplasmic reticulum calcium adenosine triphotphase (SERCA) or an increase in the level of activity of phospholamban, which is a SERCA-inhibitory protein [80, 84, 85]. Pathologic ventricular hypertrophy, secondary to hypertension or aortic stenosis, with impaired relaxation of the ventricular muscle leads to a decrease in SERCA levels. Similar

changes are seen in the myocardium of patients with hypertrophic or dilated cardiomyopathy. One animal study [86] showed that the calcium pump rate in the sarcoplasmic reticulum is diminished in the hearts of senescent rats compared with younger rats. Levels of SERCA are also known to decrease with age. Older hearts have degenerative changes in the myocardium and reduced β-adrenergic tone [87].

Theoretical Foundation

In a case of ventricular enlargement and/or the decrease of myocardial function due to hypertrophy the left ventricular elastic recoil forces may be diminished or nonexistent, therefore ceasing to assist early ventricular filling and leading to an increase of the ventricular filling pressure. Implantation of the diastolic recoil device in the ischemic and enlarged ventricle may bring back the ability of the ventricle to store elastic energy during systole and return this energy in the form of elastic recoil forces during diastole. In a diastolic recoil device, this return of energy in the form of elastic recoil may contribute to the improvement of the diastolic function, i.e., decrease of the filling pressure and increase in the magnitude of the early filling in patients with ischemic and/or dilated cardiomyopathy. Intervention to alleviate the resultant symptoms of the physical changes described above may offer great benefit to patients with congestive heart failure or dilated cardiomyopathy. Administration of vasodilators, diuretics, sodium channel blockers, and inotropic agents have been used to reduce the number of acute events and slow the advance of disease, but cannot reverse the physical changes to the heart. Surgical intervention can reduce the volume of the ventricle such that cardiac

function is improved but carries high risk for the patient. Other less invasive modes of intervention offer improved function while reducing risk for the patient during and after the procedure.

Present Diastolic Recoil Devices

The treatment of patients with diastolic heart failure is mainly empirical. The treatment includes modification of the underlying risk factors for the disease (such as hypertension and diabetes) and administration of medications used for treating systolic heart failure. Presently, there are no medications or devices that can specifically improve left ventricular relaxation and diastolic function. There is a wide range of devices aimed to treat systolic heart failure, including left ventricular assist devices (LVAD) and biventricular pacing devices, all in clinical use. None of these devices can present a solution for the many DHF patients since they do not improve LV relaxation and filling. Diastolic heart failure therapies presently include mostly pharmaceutical products and there are few, if any, devices available. There are presently no approved devices for treatment of the DHF symptoms. However, clinical stage recoil device concept, Imcardia (Corassist Inc) has a potential role in the treatment of DHF patients.

Imcardia (Corassist): The ImCardia™ is an elastic self-expanding device that is attached to the external left ventricle surface of the heart through a simple off-pump procedure. It applies an outward expansion force on the ventricular wall to improve diastolic dynamic and filling performance. In vivo Safety evaluation on healthy model demonstrated that

the device is safe at 6 month follow up (including: systolic performance, general clinical evaluation and extreme conditions tests). In vivo Efficacy evaluation on diseased animal model with hypertrophic left ventricles revealed diastolic properties improvement. Ongoing results from Clinical safety study in which the ImCardia is implanted in patients admitted for Aortic valve replacement due to Aortic stenosis and suffering from Diastolic Dysfunction showed safety profile with first patients reaching 1 year follow-up.

Left Ventricular Twist Mechanics and Suction Effect in Diastolic Filling

The twisting motion of the left ventricle about its long axis results from the contraction of the obliquely oriented epicardial and endocardial fibers. Cardiothoracic surgeons intuitively check this twisting movement as a sign of healthy left ventricular (LV) function. Lower [88] studied LV torsion in the late seventeenth century. He described the twisting motion of the left ventricle as "the wringing of a linen cloth to squeeze out the water." Over the past 3 centuries, experimental and clinical explorations on LV twist have entailed the use of numerous techniques such as implanted radiopaque markers [89], biplane cineangiography [90], sonomicrometry [91-92], optical devices [93], gyroscopic sensors [94], MRI [95-97], and echocardiography [98-101]. Furthermore, the rapid pace of technologic advancements has resulted in the development of innovative techniques in which LV twist is readily computed from gray-scale cardiac ultrasound images obtained at the bedside. Torsion helps bring a uniform distribution of LV fiber stress and fiber shortening across the wall [102]. It has been demonstrated in a

mathematic model that normal torsion causes sarcomere shortening of 0.20 μm in the epicardium and 0.48 μm in the endocardium [103]. Elimination of the torsion, however, decreases epicardial shortening (0.10 μm) and increases endocardial shortening (0.55 μm). Thus, disappearance of torsion would increase endocardial stress and strain and increase oxygen demand, thereby reducing the efficiency of LV systolic function. In the subendocardium, torsion causes fiber rearrangement such that subendocardial fibers are sheared toward the left ventricle cavity for LV wall thickening while the left ventricle base is pulled toward the apex, shortening the longitudinal axis of the left ventricle. Torsion also provides a key association between systole and diastole. Twisting and shearing of the subendocardial fibers deforms the matrix and results in storage of potential energy during systole, then abruptly releases with sudden untwisting during isovolumic relaxation, generating intraventricular pressure gradients for LV diastolic filling [91].

Prototyping of a Novel Diastolic Recoil Device

The device being prototyped, shown in Figure 22, has following design requirements so that it can fulfill the following functions:

- Device is capable of exerting elastic forces on the external ventricular wall in a tangential direction, in addition to the externally-directed radial forces. These tangential forces are of importance for the following two reasons:

    1. Allows even distribution of applied forces across the left ventricular wall surface;

2. Assist the diastolic movement during untwisting of the left ventricle in a manner more similar to its normal physiological torsional mechanics.

- Anatomically and physiologically compatible
- Biocompatible and configured for compact and long-term implantation.
- Readily adapted to the precise topographic conformation of the heart
- Delivered in a minimally invasive manner.

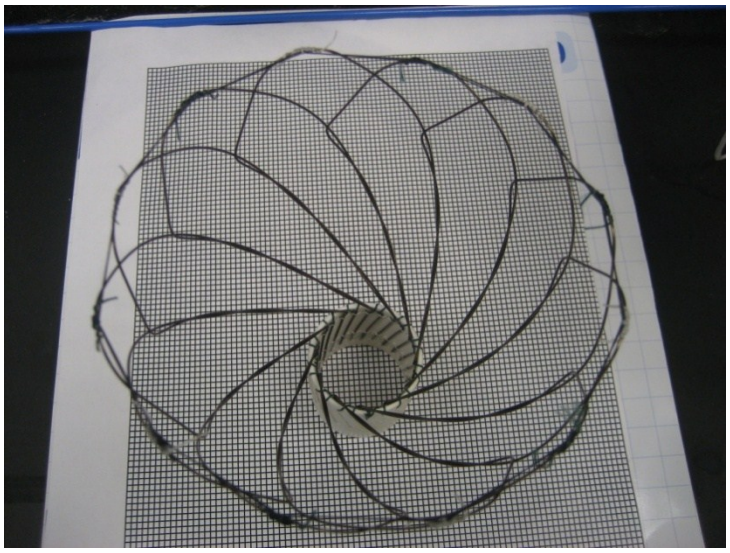

Figure 22. Diastolic recoil device prototype with nitinol elements.

The diastolic recoil device being prototyped here is designed for clinical conditions like diastolic dysfunction, mitral valve regurgitation or heart failure. During diastolic phase of cardiac cycle the myocardial relaxation occurs leading to ejection of blood to systemic

circulation. The active and passive properties of the myocardium, geometrical characteristics of the chamber and external forces play an important role in the modulation of diastolic mechanics. A reduction in ventricular compliance (i.e., increase in stiffness of ventricular heart wall) may result in less diastolic expansion of the ventricle, less ventricular filling (i.e. decreased end-diastolic volume EDV) and a greater diastolic pressure, resulting in a change in the ventricular diastolic pressure-volume characteristics. In a case of ventricular enlargement and/or the decrease of myocardial function, the left ventricular elastic recoil forces may be diminished, therefore leading to increase of the ventricular filling pressure. The device designed here in is the first device which in a minimally invasive manner can impact all the metrics of diastolic mechanics. The novel diastolic recoil device developed here is an innovation over the cardiac support device explained in CHAPTER II and there is a fundamental difference in design between the two devices. Though on initial review it might seem to a simple change in coil pattern but the difference between the two designs provides this diastolic recoil device the ability to store energy during the cardiac cycle. This stored energy is responsible for higher ventricular filling in ventricle with pathological passive properties. The device described here is made of nitinol elements which elastically distorts during systole and recoils during diastole to augment the ventricle's natural recoil action. Implantation of the present design would lead to enhanced diastolic recoil resulting in storing compressive forces in the elastic NiTi frame of the device. The origin of compressive forces is a bending deformation of the resilient frame. The decrease of the unconstrained frame diameter to the end systolic dimensions leads to flexing

deformation of the elements triggering a rebounding force attempting to return the frame to the unconstrained diameter. These outward recoil forces are transmitted to the myocardium thus applying pressure against the wall of the ventricle. The diastolic recoil device is elastic and its configuration changes from a small diameter at end-systole to a larger diameter at end-diastole. The compression of the diastolic recoil device from end-diastolic to end-systolic configuration causes additional compressive forces to be stored in the elastic frame of the device and is designed to be substantially equivalent at end systole to the elastic restoring forces that originate in the myocardium in a healthy heart. Thus the amounts of outward recoil forces that are transmitted to the walls of the ventricle during diastolic filling are enhanced and augment outward motion of the ventricular walls. Resultantly, stress is decreased in the myocardium, which is beneficial for more efficient mechanical function. As stress is a major cause of dilation, implantation of a device and its contribution of recoil forces back to the heart wall may limit remodeling in the ventricle. The Figures 23 and 24 show the design innovation incorporated in the cardiac support device to utilize the same design platform into a new recoil device which can store energy during systole and release during diastole. This innovation leads to improved ventricular filling along with limiting diastolic volume.

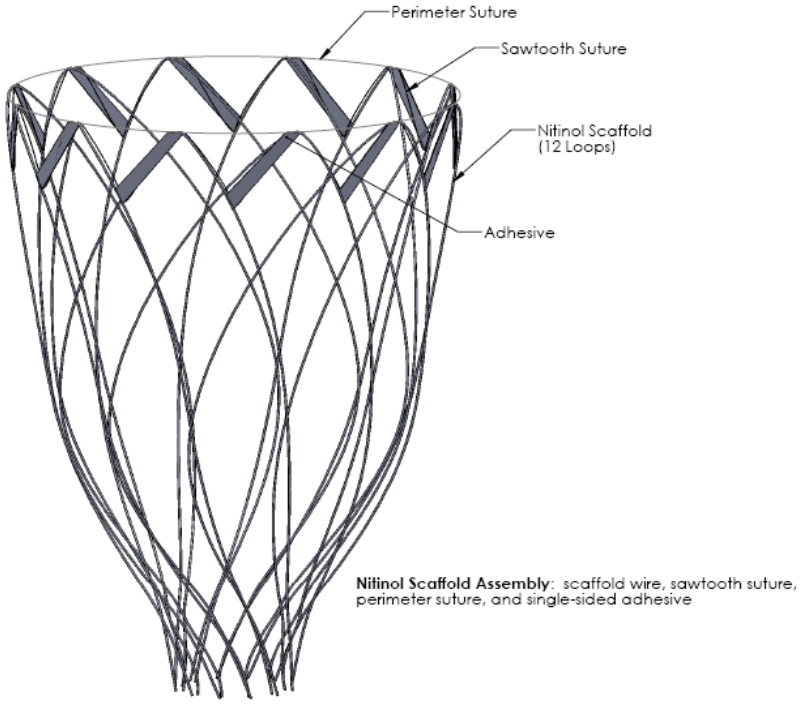

Figure 23. Cardiac support device: Open nitinol element design provides the device structural rigidity and also makes it collapsible enabling minimally invasive implantation.

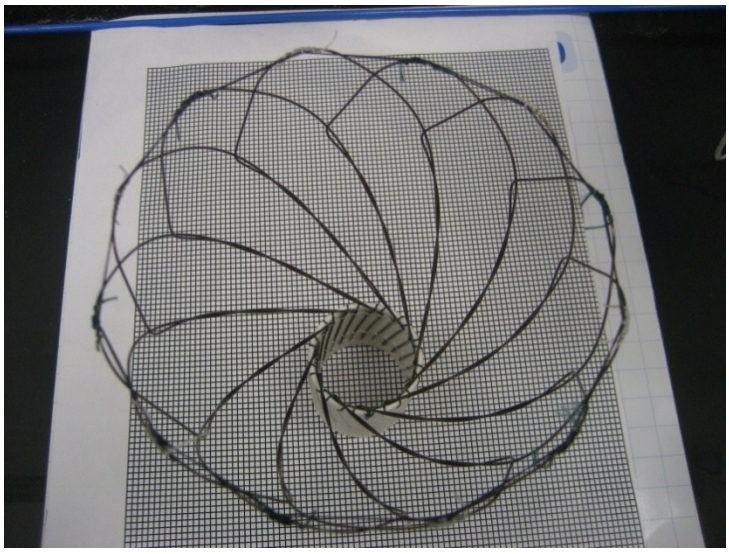

Figure 24. Diastolic recoil device: Refinement of cardiac support device by overlapping of the nitinol elements providing storage of potential energy at the time of systolic contraction.

This storing and release of energy by the frame occurs in synchrony with the action of the heart. This transfer of energy may decrease the ventricular pressure in diastole, increase the atrio-ventricular pressure gradient, increase filling, and thus improve ejection fraction. Dyskinetic or aneurystic ventricular walls result in dyssynchronous behavior during the cardiac cycle, leading to inefficient pumping function. The present device can play an important role also in removing those dyssynchronous contributions to heart rhythms, restoring overall synchrony in the cardiac cycle, and thus improve ejection fraction. The active recoil elements of the device are made of nitinol. It has the advantageous capability of being able to remain elastic over a great range of strain, up to 4%, which is greater than other metals.

Discussion

The heart spends more than half its time in diastole (relaxing and then filling to prepare for the next ejection). Although abnormalities of diastolic function are well recognized and common to virtually all forms of heart failure, just how they affect basal and reserve function and their relative role in clinical heart failure remain unclear. There are a number of reasons for this. First, diastole assessment ideally requires invasive measurements that are nontrivial to obtain, whereas noninvasive surrogates often reported in clinical studies reflect integrative properties that lack specificity. Second, relatively few animal models recapitulate human diastolic disease, particularly chamber stiffening, which is often normal in murine models despite extensive matrix, myofibrillar, or signaling abnormalities. Third, there are few if any targeted treatments

that can specifically test the impact of altering diastolic function on heart failure pathophysiology and outcome. Last, diastolic function has been less amenable to reductionist approaches given the potent roles that chamber geometry, loading (both intrinsic and extrinsic to myocytes), extracellular matrix, and myocardial perfusion all bring to bear.

This rapid early diastolic untwist in normal people may be an important component of the phenomenon known as diastolic suction where blood is actively 'sucked' into the LV from the LA [104]. It is this suction effect that is diminished in the earliest stages of diastolic dysfunction and hence this may be reflected in decreased apical untwist before changes in the standard diastolic parameters. This may explain the moderate correlation between the traditional diastolic criteria and the untwist parameters since the former reflects pressure and flow differences between the atria and ventricle while the latter is more likely the precursor and reflects intrinsic LV myocardial mechanics [104]. It remains widely presumed that diastolic abnormalities are important to heart failure pathophysiology, and this is driving new research to elucidate the biochemical and structural mechanisms that underlie it, clarify its role to clinical heart failure, and develop targeted treatments for it. Important insights are being gleaned from genetically engineered models that facilitate molecular hypothesis testing in the intact chamber.

Conclusion

In this chapter we have documented the design and prototyping of a diastolic recoil device that can enhance filling of a ventricle caused by the recoil effect during untwisting of the ventricle during the early diastolic filling. In CHAPTER IV we have tested this recoil assist device in combination with the support device and presented the data to develop a bench-top proof of concept for the biphasic mode of action.

Traditional concepts of heart failure have largely focused on the hemodynamic consequences of LV systolic dysfunction. Using a time-dependent model of heart failure, it has been proposed that diastolic and systolic heart failure are phenotypic expressions of the same disease process that evolves gradually as a continuum of clinical events. Thus device designs which address the torsional mechanics may provide superior therapeutic advantages as they would provide an better understanding of the pathophysiological insights into the mechanism of heart failure; however, this remains inadequately addressed in today's clinical options for addressing diastolic heart failure .

In early stages of cardiac dysfunction, ventricular relaxation either regionally or globally becomes abnormally slow and impaired with a progressive loss of the ventricle to modulate the timing of onset of relaxation. The epicardial function may remain relatively unaffected, and circumferential strain and twist either remains normal or shows exaggerated compensation for preserving the LV systolic performance. Compensatory features such as myocardial hypertrophy attempt to reduce subendocardial stress; however, such changes are usually maladaptive and detrimental. Furthermore, loss of

cardiac muscle resilience also causes progressive delay in LV untwisting. Loss of early diastolic longitudinal relaxation and delayed untwisting attenuates LV diastolic performance, producing elevation of LV filling pressures. In conclusion we have successfully prototyped a diastolic recoil device with adjustable passive chambers to modulate end diastolic volume in real time and address the torsional mechanics of the heart which has a direct impact on the myocardial energetics.

CHAPTER IV

DEVELOPMENT OF A COMBINED BIPHASIC SUPPORT & RECOIL DEVICE TO FULLY MODULATE DIASTOLIC MECHANICS

Background

End stage congestive heart failure (CHF) patients represent complex etiologies which makes it a daunting challenge to design a single device that not only prevents progressive remodeling but then initiates reverse remodeling. There are three factors that together come into play during progression of congestive heart failure ---1) failing hearts with low cardiac output, 2) failing hearts growing larger, and 3) high filling pressures due to loss of recoil preventing complete filling during the diastolic phase of cardiac cycle. Presently there are separate device solutions with left ventricular assist devices (LVAD), cardiac support devices (CSD) and diastolic recoil devices (DRD) which approach these problems individually. A significant unmet need in CHF device development is an implantable device which can address both factors of support and recoil in a single device design.

The proposed combined Biphasic support and recoil device is a significant innovation in heart failure device space, as it is a fully implantable and minimally invasive device under development which can address the issue of cardiac support (passive constraint) and diastolic recoil in a single integrated design. The patient population it can serve includes patients with either systolic or diastolic heart failure, but also those with

combined systolic and diastolic failure. The combination of the cardiac support device and the diastolic recoil device (each of which has been prototyped and explained in the CHAPTERS II & III) represents an innovation that when deployed into the pericardial space surrounding the heart can fully modulate the diastolic mechanics of a failing heart. Our bench-top studies have shown that adjustable passive support and diastolic recoil technology achieves modulation of end diastolic volume and ventricular filling at low end diastolic pressure. Thus we expect this combined device would play a significant role in ventricular size reduction and also enhanced ventricular filling in both systolic and diastolic heart failure patients. Advancements in novel cardiac device technology are needed and toward this end, we have developed a proof of concept of this combined device with multiple prototypes tested.

Two potential problems with current support technology (i.e., static meshes that surround the heart like Acorn's CorCap) are: 1) the device cannot be adjusted post implantation and 2) support devices may increase chamber stiffness and worsen the filling dynamics. Our goal with this device is to evaluate the efficacy of adjustable support technology and combined recoil/support technology. Clinical experience has been greatest with the Acorn device, which has been shown to reduce end-diastolic volume, shear strain, and infarct area in preclinical studies. But there is concern about the effect of passive constraint on diastolic LV chamber stiffness and pump function.

Study Goals

Test the hypothesis that combining diastolic recoil enhancement with adjustable cardiac support is possible and that such a combination results in a biphasic type support device as determined by bench-top studies: In a failing, remodeled heart, passive stiffness and slow relaxation time (i.e. diastolic recoil) is often a primary problem, thus an increase in diastolic recoil could improve cardiac function. With a combined recoil and support device, the EDPVR could be shifted downward for lower volumes and leftward for limiting the overall heart size.

Device Design: Biphasic Support & Recoil Device

The device technology prototyped in this dissertation is designed to fully modulate diastolic mechanics and address both systolic and diastolic dysfunction by use of 1) adjustable support to limit and/or reverse chamber dilation that contributes to poor systolic function and 2) recoil assist to help the heart fill more rapidly during diastole. The device has an intrinsic pneumatic attachment to the exterior surface of the heart that enables heart motions such as twisting and ejection along with dynamic support. The concept of a biphasic support is a fundamental innovation in the field of heart failure devices.

The device technology is innovative in four important aspects:

1. Control of target end-diastolic volume: Our Dynamic Support Device with the recoil elements embedded in the frame is the first device that is biphasic about an

adjustable “phase transition point” (a target end-diastolic volume, TEDV). As shown in Figure 25, for cardiac volumes below TEDV, the device enhances filling (i.e., “filling enhancement” phase), and for cardiac volumes above TEDV the device impedes filling (i.e., “filling impediment” phase). The adjustability of TEDV via infusion of saline in a subQ port will enable ongoing support to promote reverse remodeling—i.e., as the diseased heart begins to respond to the support by becoming smaller, the TEDV can be adjusted to provide the same amount of support as the initial treatment intervention. The “filling enhancement” of the biphasic component acts to enhance diastolic recoil. Our device has an elastic memory component that is utilized when cardiac pressures are lower than TEDV by creating a uniform negative pressure that promotes ventricle filling. Diastolic recoil enhancement is potentially critical for effective treatment because diastolic heart failure secondary to fibrosis is likely to be present in end-stage systolic heart failure. Figure 25 demonstrates the biphasic support component of our device. When ventricular volumes are below TEDV the device acts to enhance filling and increase ventricular volume, but when ventricular volumes exceed TEDV, the device acts to constrain filling and cardiac volume.

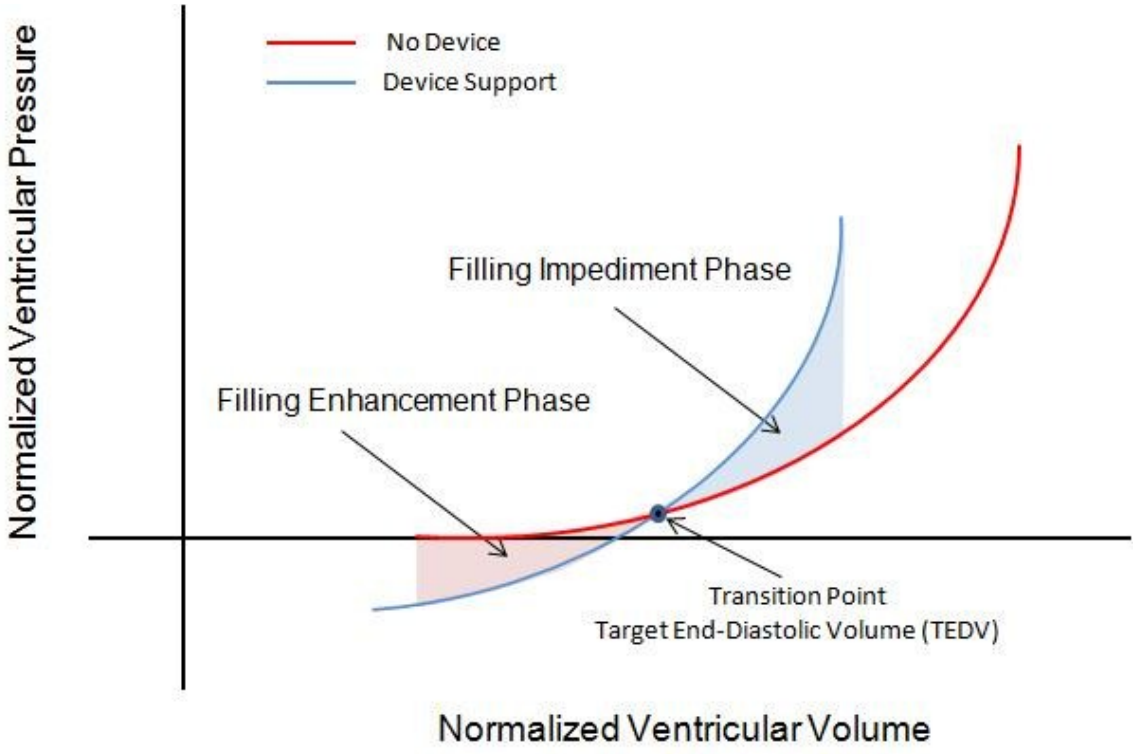

Figure 25. An illustrative plot that demonstrates the biphasic character of the device wherein the effect of the device is to impede filling above the transition point (or target end-diastolic volume) and enhance filling below the transition point (or target end-diastolic volume).

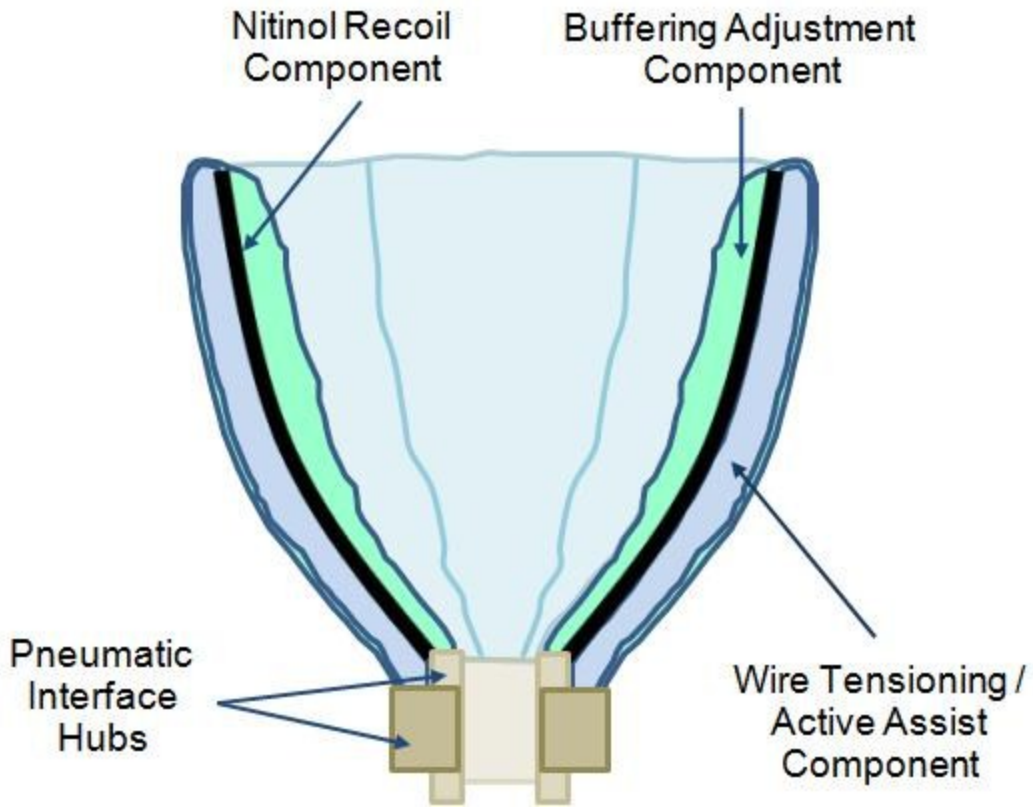

Figure 26. Cross-section of biphasic support and recoil device that depicts the support and recoil components.

2. Combination of recoil and adjustable passive support: Though devices exist with specific indications for support, the proposed Biphasic and Dynamic Support Device will be the first device which has a dual component of recoil assist and adjustable passive support. Adjustable passive support is essential in reducing the size of an enlarged heart. Passive support is helpful long term, but likely causes acute increases in venous pressure. With the recoil component, this complication can be mitigated. The recoil component apart from providing a structural rigidity

also acts as a loaded spring which stores energy during the systolic contraction and releases the stored potential energy hence increasing the ventricular filling at low end diastolic pressure. Figure 26 represents the cross section of the device with the dynamic support and recoil component.

3. 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 patient's response to the treatment strategy. Heart transplant 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 extend beyond the applications herein. This technology is an excellent candidate for combination therapies which combine mechanical, electrical, pharmaceutical, and/or stem cell therapies.
4. Anti-pericardial adhesive barrier: Our Biphasic and Dynamic Support Device consists of multiple layers of a biocompatible film with fluid filled bladders between the film layers, these prevent trans-thoracic adhesions between the epicardial surface of the heart and the chest wall and permit the film layer touching the heart to move independently from the film touching the chest wall. The inner layer of the device is allowed to form adhesions to the epicardial surface of the heart while the outer layer of the device is allowed to form

adhesions to the chest cavity. The fluid filled bladder between the two layers acts as a barrier preventing adhesions between the epicardial surface of the heart and the chest wall. Not only will this device allow for easier access to the heart in case subsequent surgeries are required but it allows the heart to move freely inside the chest cavity during normal cardiac contraction.

Bench-Top Proof- of-Concept of Combined Support and Recoil Device

As can be inferred from the study goals, the entire focus of the bench-top study was to obtain EDPVR's from a model heart alone and with various components of the proposed device in action; thereby allowing comparisons to be drawn between EDPVR's in order to evaluate the potential effectiveness of each component.

The project consisted of two phases. In the first, a heart model was created to mimic the EDPVR of a human heart. A model of the normal heart was chosen because the mechanics and response of the normal heart are better known and easier to model than the failing heart's complicating structural and mechanical alterations, and a model of the normal heart is sufficient to meet the goal of demonstrating the device's ability to effect a bi-phasic modulation of the heart cycle. This model was used to set baseline values for later comparison to the results when the device was tested. Once a satisfactory model was built, the device was tested using the experimental setup described in the remainder of the chapter. A flexible alloy frame that compresses during systole and acts to transfer energy to the beginning of diastole is placed around the heart, creating a negative

pressure in the ventricles that assists recoil and augments ventricular filling. This frame is completely enclosed in a sealed chamber surrounding the heart, filling the dual role of preventing fusion to the heart wall and allowing adjustable systolic support. A model of the heart was constructed that simulated the EDVPR (end-diastolic pressure-volume relationship) of a normal human heart. The model, shown in Figures 27 and 28, was formed by creating a bladder approximately the size of both normal human ventricles. The bladder was rigid upon full inflation, thus approximating the shape of the normal human heart. Figures 29 and 30 show the device prototypes which were placed on the heart model.

The experimental setup is conceptually simple: pressure or volume was incremented, and therefore, known, while the corresponding change in the other variable (volume or pressure, respectively) was measured. The results were then plotted to create an EDPVR. At the outset of the project, volume was used as the independent variable, and incrementally increased while the corresponding change in pressure was measured using a manometer. This approach concentrated the readings in the low pressure region of the EDPVR, as incremental changes in volume led to major pressure changes as volume increased. Additionally, because a small volume change could create a major change in pressure at high volumes, it was difficult to create stable, easily repeatable relationships.

To avoid these problems, pressure was made the independent variable. Pressure was incrementally changed by varying the difference in height between the model and a

water reservoir. The volume change in the water reservoir corresponding to each pressure change was measured, and the results plotted to create an EDPVR. Figures 31 and 32 illustrate this setup. The experiment was designed to increment the model's volume, and measure the corresponding change in pressure. The results were then plotted to create an EDPVR. Pressure was incrementally changed by varying the difference in height between the model and a water reservoir. The volume change in the water reservoir corresponding to each pressure change was measured, and the results plotted to create an EDPVR.

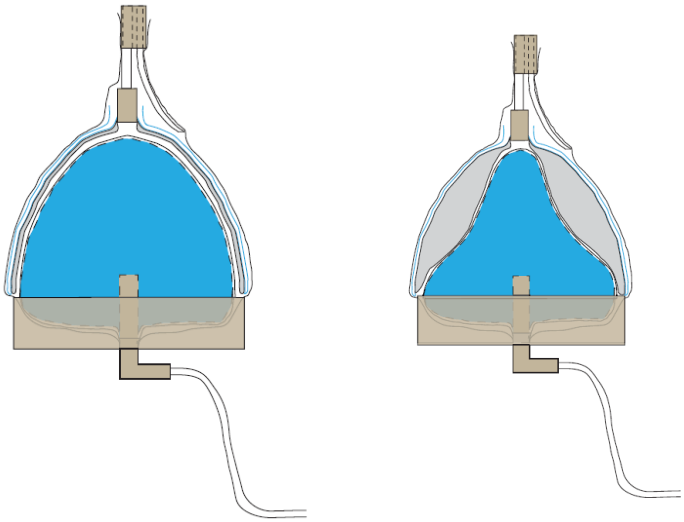

Figure 27. Schematic design of the heart model (left) experimental setup with uninflated support device placed on it; (Right) inflated support device placed on the model.

Figure 28. Cardiac support device (top) Prototype of the model which is used to measure EDPVR of a normal heart (bottom) Prototype of the cardiac support device on the heart model.

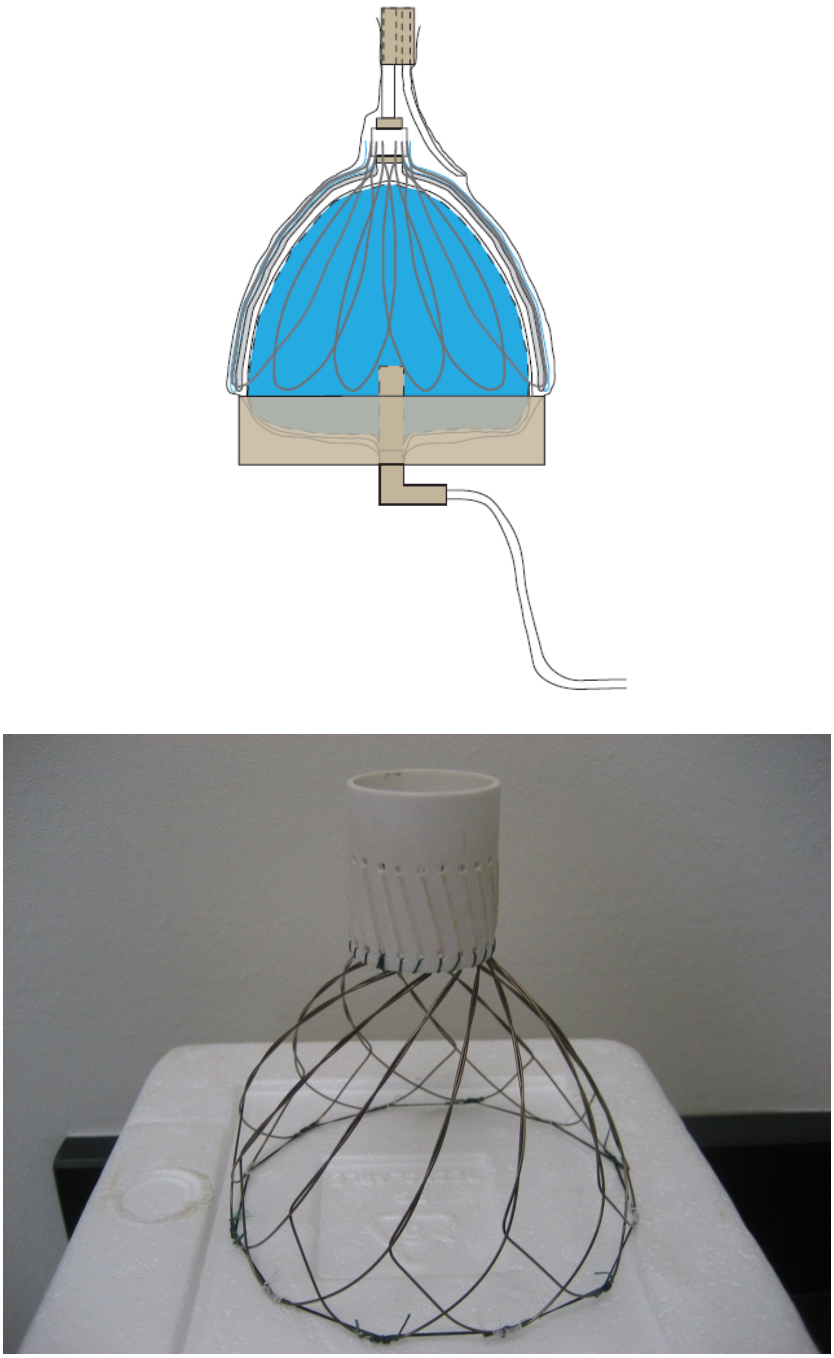

Figure 29. Diastolic recoil device (top) Schematic design of the uninflated diastolic recoil device placed on the heart model in the experimental setup; (bottom) Prototype of the diastolic recoil device.

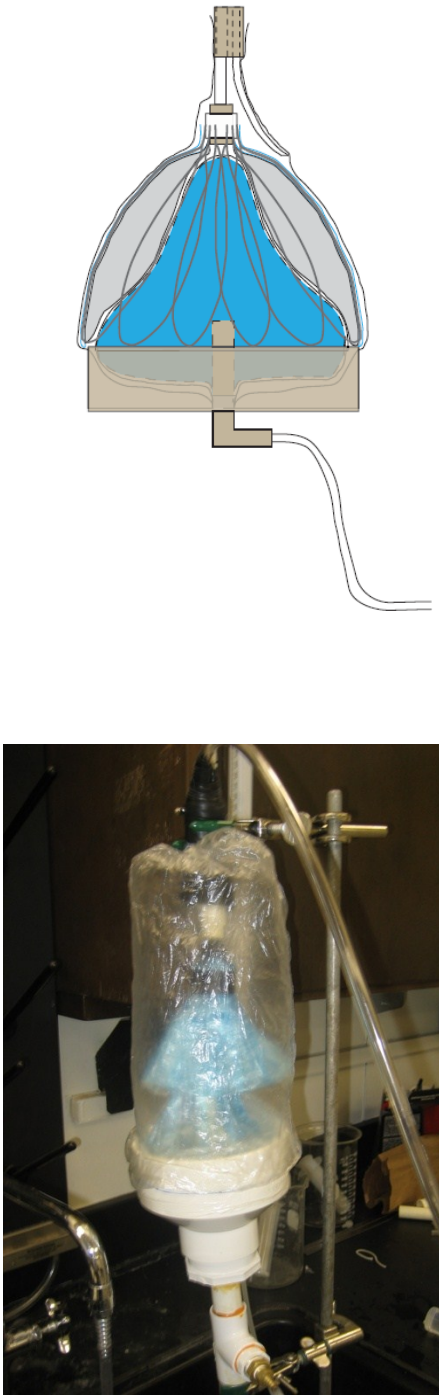

Figure 30. Diastolic recoil device (top) Schematic design of the inflated diastolic recoil device placed on the heart model in the experimental setup; (bottom) Prototype of the diastolic recoil device inside the pseudo pericardial sac.

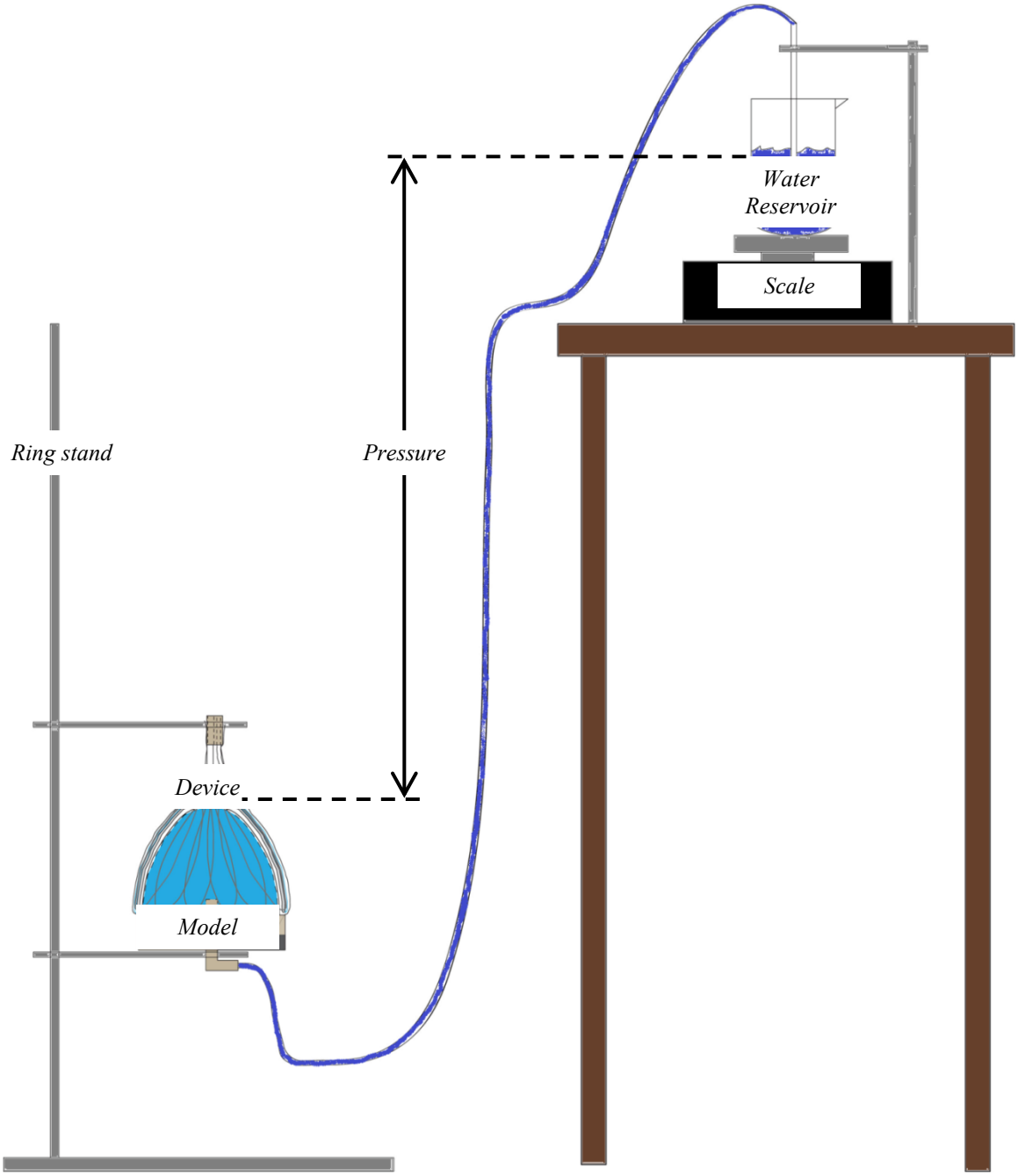

Fig 31. Experimental setup of bench-top study for measuring EDPVR of the biphasic device.

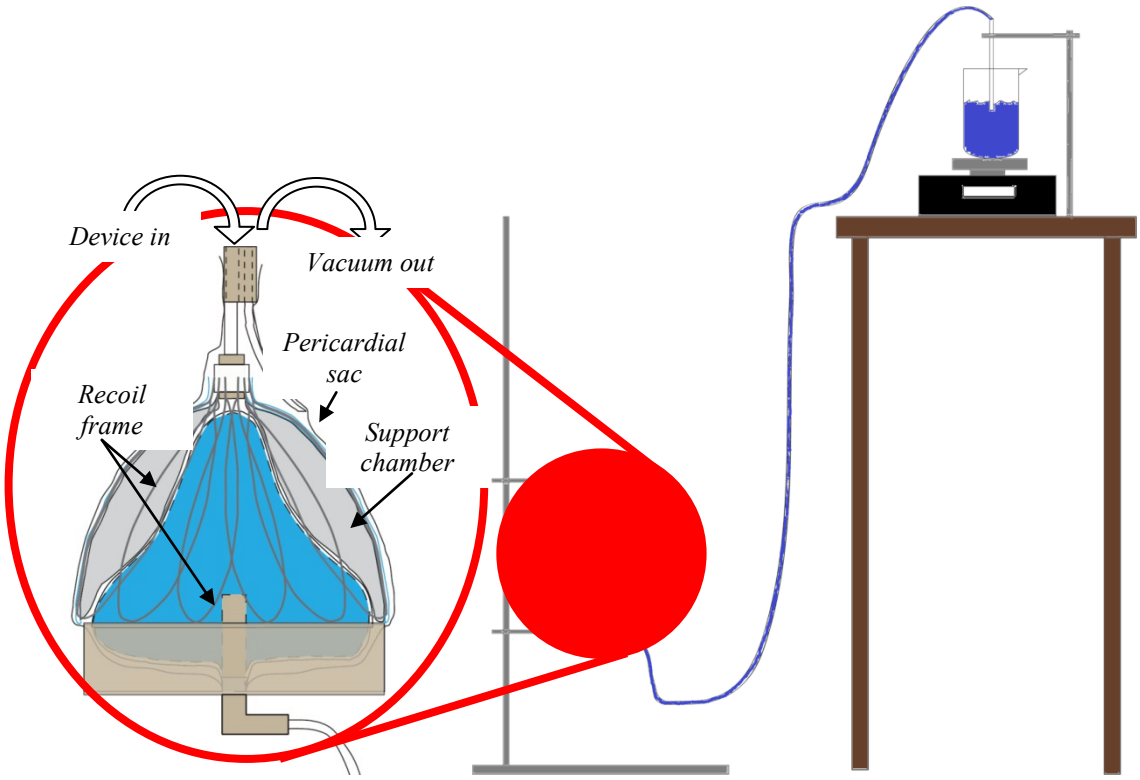

Figure 32. Close-up illustration of heart model, pericardial sac model, and cutaway device with diastolic recoil frame and inflated passive support chamber.

Pressure readings were taken at 5 cmH_2O intervals. The heart has a normal left ventricular end-diastolic pressure of approximately 15 mmHg , or 20 cmH_2O; thus, 5cm intervals were determined to be sufficient to allow an accurate EDPVR to be obtained. In order to obtain an accurate comparison and eliminate as much error as possible, new baseline values of the heart model alone were taken at the beginning of every trial. In this experimental setup, the pericardial sac was modeled by a vacuum drawn, as shown in Figure 33, in a sac placed around the heart model and device.

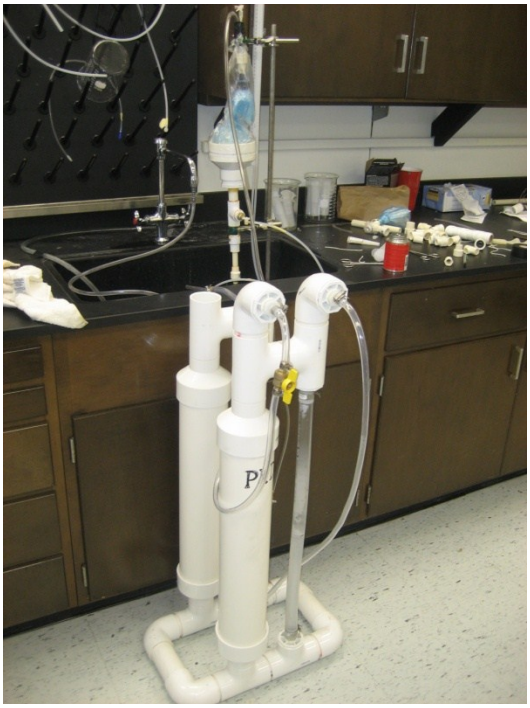

Figure 33. Device set-up to model a pseudo-pericardial sac.

Once a baseline EDPVR was obtained, the passive support device was employed without the recoil component. Finally, the recoil component was inserted in the passive support device (Figure 34). The sets of EDPVRs gained can then be compared and the effects of each component – passive support and recoil support – determined. It is important to note that the device is not physically secured to the recoil component; therefore, the diastolic support component relies on the presence of a vacuum to cause the ventricle walls to adhere to the device and follow it outward when it recoils as the heart enters diastole. In the body, the pericardial sac that surrounds the heart provides a vacuum i.e. a space without free fluid.

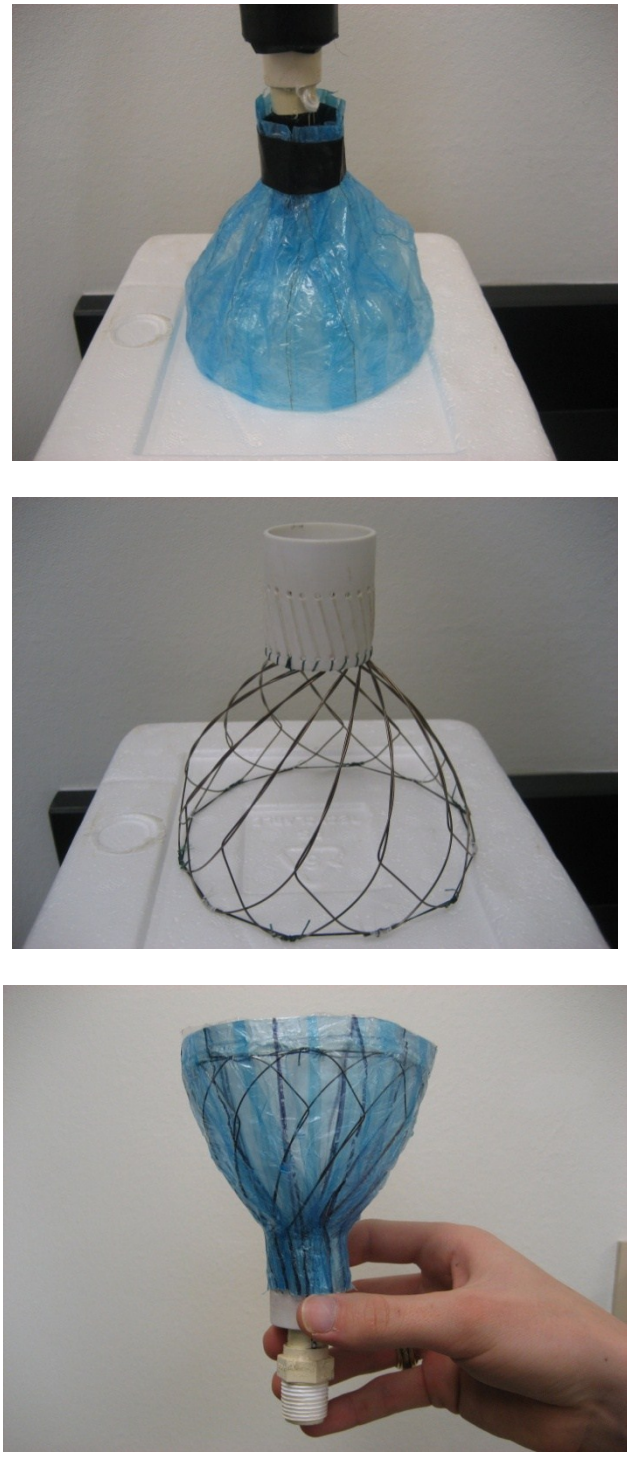

Figure 34. Prototype device showing the different components of the biphasic device. Passive support component (top) recoil assist component (middle) and combined biphasic device (bottom).

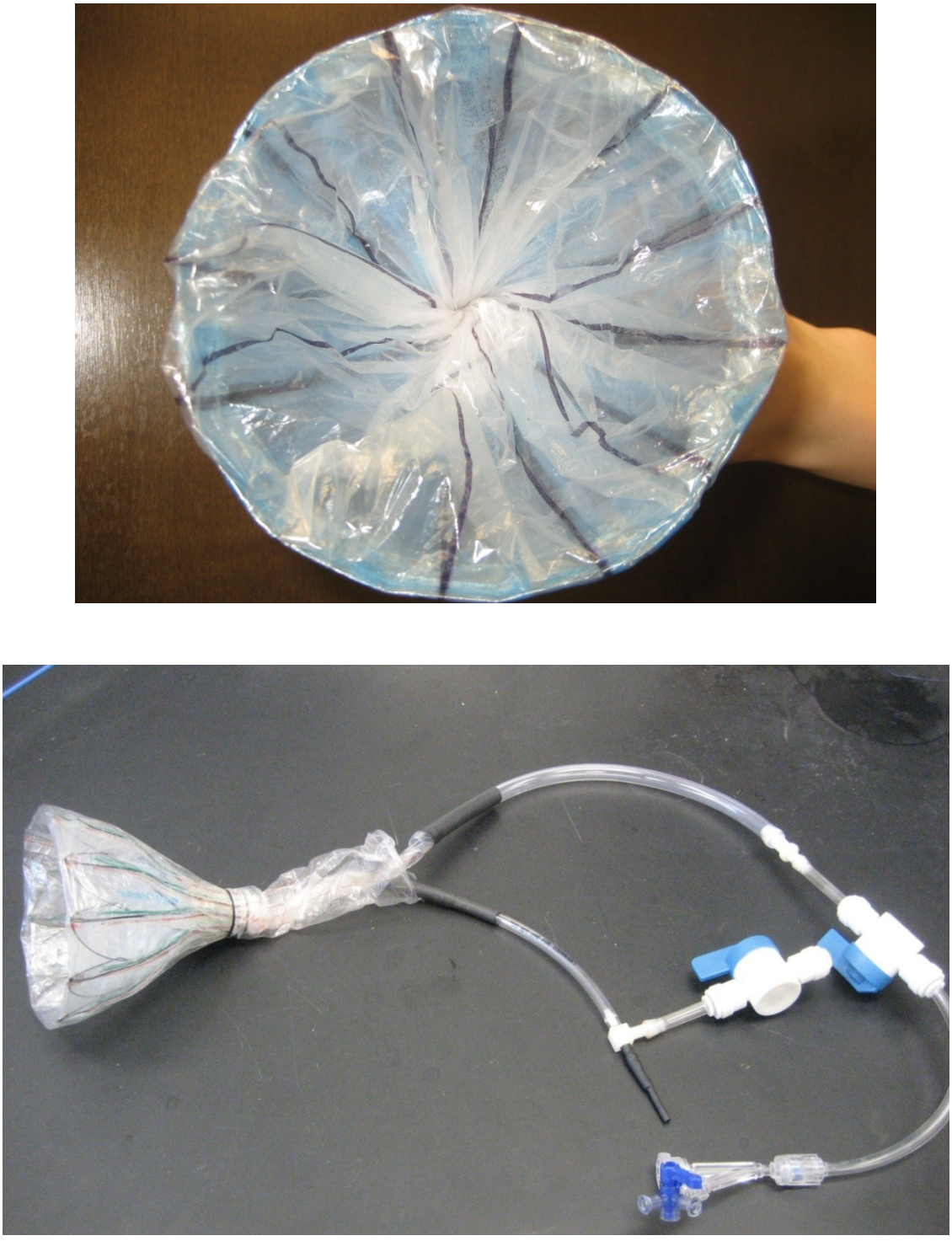

Figure 35. Prototype device composed of the adjustable support and recoil component. (top) Internal surface of the device showing the passive chambers and nitinol frame inside, (bottom) complete device with tubings connected to chambers for adjustability.

Results

To test the ability of a combined recoil/support device (Figure 35) to enhance filling at low volumes and limit filling at high volumes, we performed a bench-top study using a mock heart with a PV relationship that is compliant at low volumes and stiff at higher volumes. The device used in the bench-top study was similar to that of the in vivo studies, however, we made the nitinol scaffold removable. End-diastolic pressure-volume relationship (EDPVR), which represents the passive filling mechanics of the left ventricle, was obtained in this bench-top study using a mock heart model with recoil assist and support device. One of the objectives of the study was to show how the device's adjustable passive constraint/support component could alter the EDPVR in a positive manner and have comparable outcomes with the ovine studies and also exhibit recoil effect in addition to adjustable passive support. In the experiment three data runs were done, one with heart model only, second passive device with 0ml of water and third passive device with 40 ml of water. Figure 36, shows the baseline EDPVR of the heart model on the right. The device was then placed on the model with passive support chambers unfilled (0mL of water) and an EDPVR was obtained. In the next data run the passive component was filled with 40 mL of water and EDPVR data taken. The EDPVR points are plotted in Figure 36. The plots of the EDPVR for the baseline heart model vs 0mL versus the 40mL show that the EDPVR shifted leftward with gradual decline in end diastolic volume. This leftward 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. The downward shift of the EDPVR indicates the enhanced

filling being made possible by recoil assist component of the combination device. Therefore, bench-top studies have shown that two components i.e. the passive constraint (capable of manipulating the end-diastolic volume) and the recoil assist (augment ventricular filling at lower pressures) can make modulation of diastolic mechanics a viable goal using a single device.

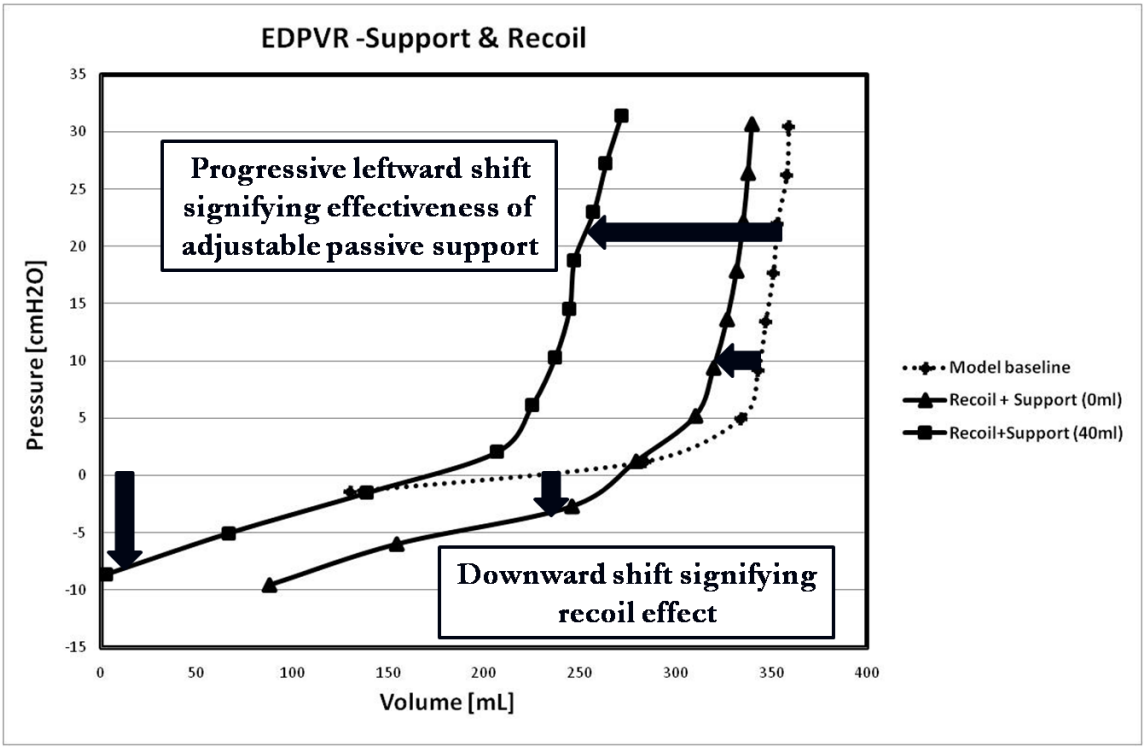

Figure 36. Bench-top verification of biphasic support device with a fillable, pseudo-heart mimicking the baseline EDPVR. With the device placed on the pseudo-heart inside a sac with air evacuated (like the mediastinum) and with the wires maximally tensioned to get the most recoil effect, biphasic modulation is evident.

Discussion

The results clearly demonstrate the ability of the proposed device to biphasically modulate the EDPVR of a model normal heart. The diastolic recoil frame, the particular interest of this study, created substantial negative pressures at low volumes. This pressure drop would lower the filling resistance in ventricles with high stiffness, increasing filling volume, decreasing filling time, and ameliorating diastolic dysfunction and the associated biochemical responses to it. Also, the constraint of the passive systolic support device on maximum filling volumes was also demonstrated in these trials, shifting the EDPVR leftward. This size reduction would prevent overfilling and reduce the abnormal stresses on the heart, limiting adverse biochemical cascades and inhibiting or even reversing degenerative remodeling and the associated systolic dysfunction.

Upon implantation of the device in a live model, several factors will be of special interest. The vacuum sac used in the model maintained a vacuum and had no fluid between the device, model and sac. In vivo, the vacuum in the pericardial sac is maintained mechanically post-operatively until the entrance hole in the pericardial sac heals. The pericardial sac is lubricated, which may substantially change the shear stresses acting on the device and holding it in place. In addition to differences in the pericardial sac, substantial fibrosis is expected to occur. The two layer design of the device is designed to compensate for this by allowing the pericardium to fibrose to the

outside of the device and the myocardium to fibrose to the inside, maintaining the heart's freedom of movement.

Another factor of interest will be the difference in wall thickness between the left and right ventricles. The model used in this study modeled the two ventricles as a whole, with no distinguishment between the left and right ventricles. It is possible that the lower resistance of the right ventricle will absorb a proportionately larger amount of the device's constraint and recoil, inhibiting right ventricular function and dampening the effects on the left ventricle, although a previous unpublished study in sheep of the support prototype's efficacy did not indicate that this was a significant problem (contained in Moreno Thesis currently in publication hold to allow filing of patents).

The two basic components – passive support and diastolic recoil of the biphasic device are based on the theoretical foundations of Laplace law (wall stress reduction --- support component) and torsional mechanics where potential energy stored during the systole is released as a recoiling force when myocardial fibers untwist during diastole. The ultimate goal of the device being to initiate the reverse remodeling processes and create a normal pattern of systolic and diastolic mechanics leading to a smaller less dilated heart. The goal of this device has been to incorporate the design elements which can manifest these physical principles and improve upon the devices which are presently in different stages of evaluation on the path to final market approval. Table 4 provides a comparative analysis of the proposed device and other devices under development,

Table 4 Comparison of biphasic support and recoil device with present state of the art support and recoil devices

COMPARATIVE ANALYSIS	**Proposed Device**	**Acorn**	**Corassist**	**Paracor**
Device Name:	*Biphasic device*	CorCap™	Imcardia	Paracor Heartnet™
Type of Product:	Bridge to Recovery	Destination Therapy	Bridge to Recovery	Destination Therapy
Mode of Assist:	Passive Support & Diastolic recoil	Passive Support	Diastolic recoil	Passive Support
Device Adjustability	Yes	No	No	No
Promoter of Physiological Motion	Yes	No	No	No
Attachment to Heart	Sutureless, pneumatically attached	Requires suturing	Requires suturing	Requires suturing
Risk of Fibrosis	Negligible	Very High	High	Very High
Minimally Invasive:	Yes	Yes	Yes	Yes
Contact with Blood:	No	No	No	No
FDA Approved:	No, still in development	Human Clinical Trials	Human Pilot Trial (Safety)	Human Clinical Trials
Currently on the Market (USA):	No	No	No	No

Table 4 continued

COMPARATIVE ANALYSIS	**Proposed Device**	**Acorn**	**Corassist**	**Paracor**
Currently on the Market (Europe):	No	Yes, received CE marking	No	No
Length of Time Product Remains in Patient:	Minimal: a few weeks to a month	Permanent	Permanent	Permanent
Device Removable:	Yes	No (Redo surgeries are challenging due to adhesion)	No (Redo surgeries are challenging)	No (Redo surgeries are challenging due to adhesion)

With use of Biphasic and Dynamic Support Device, it is expected to able to continually shrink the heart over a period of several months (with 3-4% reduction every 3 weeks), it is possible that a diseased heart can be returned to normal size—regardless of the etiology. Contractile protein roll-over is ongoing, at a rate of one-half the muscle mass per week, and with progressive reduction in end-diastolic volume (EDV), the contractile proteins (i.e., end-diastolic sarcomere lengths) may be reset to smaller volumes. Reduction of heart size is highly significant because heart size and function are inversely related (via the Law of Laplace). We hypothesize, thus, that our Biphasic Dynamic Support and Recoil Device 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. Our treatment hypothesis to be tested

is that an enlarged, dilated heart can gradually be reduced in size without affecting the ventricular filling and reducing chamber stiffness.

Conclusion

The results of the bench-top trials provide *in vitro* support of the feasibility of pneumatic locking as a means for a diastolic recoil device to engaging the heart. This approach avoids the hemo-compatibility issues, among others, encountered by alternate methods, and naturally lends itself to a combination with systolic support components for a biphasic support/assist device that modulates the entire heart cycle. Future studies would be particularly focused on the limitations pointed out in the discussion where pneumatic locking for diastolic recoil devices in vivo would be of interest.

In conclusion we have prototyped and tested the biphasic support and recoil device and it successfully fulfills the goals that were set. We have shifted the EDPVR leftward and downward showing both support and recoil components effectively contributing to the device performance. Thus a proof of concept has been achieved which would need to be tested in pivotal preclinical studies. With over six decades of device research for an less invasive effective implantable device, today still there are very few FDA approved

options for Class III & IV heart failure patients who have mechanical dysfunction of the heart. With optimal drug regimen, resynchronization therapies and the present biphasic device implanted in a minimally invasive manner and which can contribute to both systolic and diastolic performance, we believe would be another option for the patients who have a remodeled heart caused by an index event like myocardial infarction. The path for Class III devices are long and expensive from bench-top to clinical adaption, but with promising bench-top, preclinical acute data and prototype designs we are confident further work would be successfully conceived and performed in future to move it towards successful clinical adaption.

CHAPTER V

ADJUSTABLE CARDIAC DEVICE TO PREVENT PERICARDIAL ADHESIONS AND IMPROVE CARDIAC MOTION IN MULTISTAGE CARDIAC SURGERIES

Introduction

Fibrosis, the formation of excessive amounts of fibrotic or scar tissue is a major problem in medicine as scar tissue blocks arteries, immobilizes joints and damages internal organs, with serious consequences on the body's ability to perform important roles. Every year, about 1.3 million people are hospitalized due to the damaging effects of fibrosis with few therapeutic solutions to mitigate the problem. Adhesions are fibrous structures that connect tissues or organ surfaces that are not normally joined. They can cause significant complications such as bowel obstruction following abdominal surgery, infertility following gynecologic surgery, serious complications during secondary cardiovascular surgical procedures, restricted limb motion following orthopedic surgery, and pain following any surgery. Moreover, adhesions that form as a result of surgery can increase the complexity, duration and risk of subsequent surgery. In the United States surgeons perform an estimated 500,000 abdominal operations annually to remove adhesions. In the absence of an efficacious means of intervention, the formation of adhesions becomes a virtually unavoidable byproduct of the trauma caused to internal tissue surfaces during the surgical procedure.

Study Goals

Explore and expand the application of the prototyped cardiac support and recoil device as an anti-pericardial adhesion device in pediatric and adult patients undergoing multistage cardiac surgery requiring sternotomy. The device features like size adjustability and anti-adhesion nature of the fluid filled chambers would allow for growing cardiac anatomy in pediatric patients and also allow for finding the surgical plane during repeat sternotomies. In addition to these features the basic device features like anatomical compatibility and ventricular support would improve the overall cardiac performance of the patients.

Background

One of the most important pathologies for which fibrosis is a problematic factor is cardiac surgery. The number of patients undergoing cardiac surgery has been steadily increasing, and as a consequence, the number of cardiac reoperations has also increased [105-111]. It has been estimated that one out of every five patients undergoing coronary artery bypass surgery will require a reoperation [107, 108]. Re-operative cardiac surgical procedures are associated with a significantly greater complication rate than that of the initial procedure [110, 111]. For example, the post-operative complication rate following a reoperative coronary artery bypass procedure nearly doubles. As a consequence, cardiac reoperations are associated with increased morbidity and mortality [106-111]. An important contributory factor for the increased complications with cardiac reoperations is the adhesions which form secondarily from the initial entry into the

pericardium [105-111]. These fibrous adhesions begin to form immediately following the surgical procedure and consist of collagen and other extra cellular proteins [112, 113]. It has been demonstrated in a number of cell systems that enhanced collagen synthesis can occur due to increased production of angiotensin II (Ang II) and subsequent activation of the Ang AT1 receptors [114-116]. The post-operative period following cardiac surgery is associated with heightened neurohormonal stimulation, which in turn could potentially contribute to pericardial adhesion formation [117].

Adhesion formation after open-heart surgical procedures is a significant complication at the point of performing a secondary procedure. It is estimated that secondary procedures (re-do's) account for 15-20% of the approximately 425,000 open-heart surgeries performed annually in the United States. Extensive adhesions form between the surface of the heart (epicardium) and the inner surface of the sternum after virtually every open-heart surgical procedure. These adhesions make opening the sternum and accessing the heart a time consuming and dangerous process in the secondary procedure.

Recently a large number of patients with congenital heart defects have required repeat sternotomy because reoperations and staged surgical procedures are increasing. Repeat sternotomy and dissections carry a risk of further reoperation because mediastinal adhesion formation may result in iatrogenic injury of the heart, arteries, or veins. In addition, mediastinal adhesions make it difficult for surgeons to identify anatomical features, prolong the operating time for dissections, and increase blood transfusion

requirements. Closure of the pericardium is one of the strategies to prevent these drawbacks. However, pericardial closure is usually impossible because it may cause cardiac tamponade or late constriction after surgery. Moreover, in a 2nd or 3rd repeat sternotomy, there remains no pericardium available for chest closure. So far, various materials, such as silicone rubber, polyurethane, fascia lata, expanded polytetrafluoroethylene (ePTFE), heterologous porcine, equine, or bovine pericardium, Dacron, and dura mater have been employed as pericardial substitutes to secure safer resternotomy. The widely used ePTFE sheet is reported to be safe and effective in preventing cardiac injury at resternotomy. However, such nonabsorbable material might cause dense adhesions and severe inflammatory reactions including fibrotic change, calcification, and mediastinitis after implantation. An ideal pericardial substitute to prevent these drawbacks in reoperations is required, especially in the field of pediatric cardiac surgery where multistage operations are often needed.

Present Anti- Pericardial Adhesion Devices

There are multiple anti pericardial adhesion products in market which are FDA approved and also off label use of these materials. Some of the products in clinical use today are Interceed® (Johnson & Johnson), Seprafilm® (Genzyme), CoSeal® (Angiotech Pharmaceuticals, Inc.), and Adept® (ML Labs Ltd.), both licensed in certain markets to Baxter International, CardioWrap® (Mast Surgical),and licensed, in certain markets, to CryoLife and Preclude® (WL Gore). Several other companies including, Anika Therapeutics, Inc., Alliance Pharmaceuticals, Corp., Covidien, Integra Life Sciences,

Inc. and Fziomed, Inc. are pursuing the development of products for the prevention of adhesions. The anti-adhesion market is characterized by a limited number of products currently on the market with limited (as a percent of total surgical procedures using such products) penetration with key differentiators being clinical efficacy, biocompatibility, ease of use and price.

Adjustable Device Solution to Prevent Pericardial Adhesion

The adjustable support device prototyped here can function as a contoured pericardial adhesion barrier device that reduces pericardial adhesions between the epicardial surface of the heart and the chest wall after a sternotomy or cardiac procedure. The pericardial adhesion barrier device does not need to be sutured or directly attached to the heart. Rather, the pericardial adhesion barrier device intrinsically attaches to the heart via pneumatic locking. There is no free air in the chest to go between the device and heart—so if the heart becomes smaller (due to ejection of blood), the device must be pulled inward. Likewise, when the device pushes outward, it applies a suction-like traction to the heart. If free air were present in the chest (it is normally not) the suction-like traction would draw air to come between the device and heart. However, with no free air, the suction traction is applied directly to the heart surface. After air in the mediastinum is removed, the heart and device are pneumatically locked in a co-axial configuration.

The pericardial adhesion barrier device, as shown in Figure 37, consists of at least two layers of a biocompatible film and a fluid filled bladder between the two layers which

prevents and/or reduces postoperative pericardial adhesions between the epicardial surface of the heart and the chest wall. The bladders within the pericardial adhesion barrier can be used to correct end diastolic and end systolic configurations of a damaged or diseased heart. The bladders of the pericardial adhesion barrier device may also be used to assist a damaged or diseased heart in cardiac output and motion without significantly perturbing the physiological shape of the heart. Many patients that undergo cardiac surgery must have multiple reoperative procedures, including repeat sternotomies. The device reduces postoperative adhesions making subsequent surgeries easier to perform. The device is implanted after a sternotomy around at least a portion of the heart to accommodate the lack of a complete pericardium due to cardiac surgery. The inner layer of the pericardial adhesion barrier device is allowed to form adhesions to the epicardial surface of the heart while the outer layer of the device is allowed to form adhesions to the chest cavity. The fluid filled bladder between the two layers acts as a barrier preventing adhesions between the epicardial surface of the heart and the chest wall. Not only will this device allow for easier access to the heart for subsequent surgeries but it will also allow the heart to move freely inside the chest cavity during normal cardiac function. The pericardial adhesion barrier device can also be used to adjustably control the end diastolic shape of the heart, actively control the end systolic shape of the heart, and assist in normal cardiac function via diastolic recoil capabilities and direct cardiac compression for various cardiac pathologies.

Figure 37. Two layers of a biocompatible film and a fluid filled bladder without the recoil elements, between the two layers; the device prevents and/or reduces postoperative pericardial adhesions between the epicardial surface of the heart and the chest wall.

The pericardial adhesion barrier device described in Figure 38 uses the intrinsic pneumatic attachment and its elastic properties to enhance the diastolic recoil of the heart. At the end of systole and the beginning of diastole the pericardial adhesion barrier device acts like a loaded spring, applying negative pressure to the exterior epicardial surface of the heart, helping the ventricles of the heart to fill.

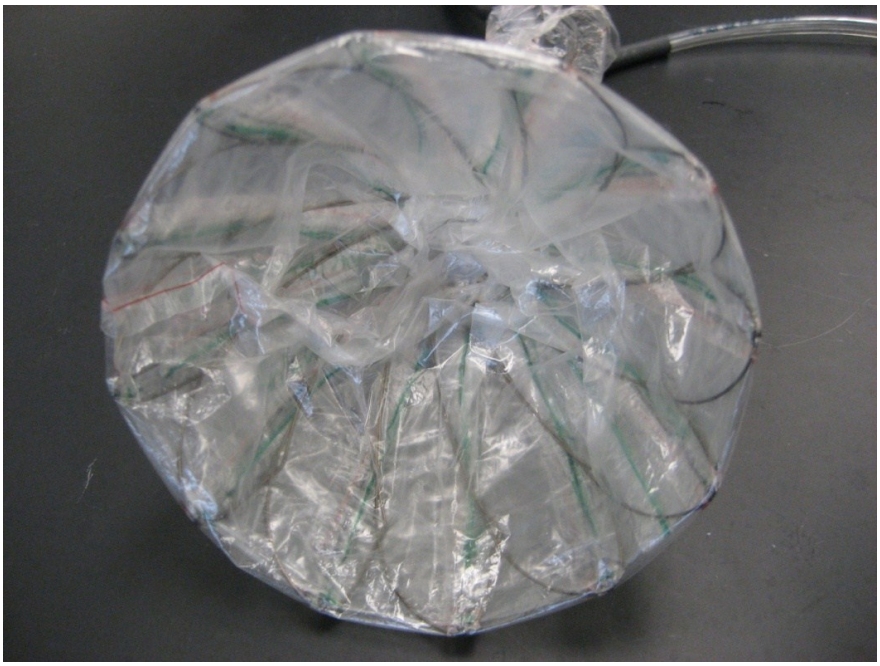

Figure 38. Two layers of a biocompatible film and a fluid filled bladder with the recoil elements between the two layers; the device prevents and/or reduces postoperative pericardial adhesions between the epicardial surface of the heart and the chest wall. This device not only creates a recoil effect with better filing and also has the tubing connected to subcutaneous port which is used to modulate the device size with the changes in cardiac dimensions primarily in pediatric patients.

The device includes a selectively inflatable end-systolic heart shaped bladder with one or more contoured supports configured to surround at least a portion of the heart to provide curvatures similar to the proper shape of the heart when pressurized and one or more fluid connections in communication with the selectively inflatable end-systolic heart shape bladder for pressurization and depressurization. The contoured supports form inflatable compartments having an expanded curvature optimized to fit generally the proper end-systolic shape of the heart. The selectively inflatable end-systolic heart shaped bladder comprises an inner membrane that is at least partially folded when depressurized and at least partially unfolds when pressurized.

Important Features of the Device

The device prototyped here when supported by a good surgical technique is expected to decrease significantly post-surgical adhesions. The benefits are following:

1. Making redo surgery safer:
    a. making the surgical procedure easier and also less painful,
    b. lowering the time of procedure (and anesthesia),
    c. limiting other clinical risks
2. Biphasic device adds minimal time to the overall procedure as it conforms to the cardiac anatomy and does not require suturing as its anchors to heart through pneumatic attachment.
3. Full view of the surgical site as the device is made of transparent film that does not impede the surgeon's full view of the surgical site during or after application, allowing visualization of key anatomical landmarks for safe and optimal placement.
4. Biocompatible as the polymer materials used in biphasic device have been used in numerous other medical implants and are well recognized as safe and biocompatible.
5. Easy access to surgical plane hence reduced risks associated with sternal re-entry and dissection of post-operative cardiac adhesions which expose the patient to critical risks and significantly higher complication rates, hence reduced risk of severe hemorrhage with significant morbidity and mortality

Conclusion

In conclusion we have explored a new application of the cardiac device prototyped here which can be applicable as an anti-pericardial adhesion device. The device would significantly benefit both pediatric and adult patients undergoing cardiothoracic surgeries with clinical indications needing multiple sternal entries. Presently all anti adhesion options are materials which are available as films which needs to be surgically fitted after the vascular or cardiac surgery is completed. This anti adhesion device solution would be first in class that also functions as a device, which apart from preventing pericardial adhesion post surgically can modulate diastolic mechanics with an adjustable feature to optimize the device size allowing for changes in cardiac anatomy. Pediatric patients can benefit immensely from this as their cardiac anatomy undergoes rapid growth. Thus a novel device solution has been proposed with next steps being preclinical evaluation in large animal models.

CHAPTER VI

CONCLUSION & FUTURE WORK

Conclusion

The present critical gap in the development of non blood contacting cardiac support devices for both systolic and diastolic dysfunctions is a device solution that can concurrently modulate diastolic mechanics to improve ventricular filling while providing a passive constraint to prevent ventricular dilatation. An approach that can address the dual aspects of improved filling and effective passive support to induce reverse remodeling would be a major improvement over present solutions.

Passive constraint devices seeking FDA approval like Paracor Heartnet and the Acorn CorCap fabric "jacket", and experimental ones the fluid-filled balloon described by Ghanta and colleagues are presently developing non blood contacting approaches to prevent ventricular dilatation. Experience has been greatest with the Acorn device, which has been shown to reduce end-diastolic volume and, shear strain, and infarct area in preclinical studies. On the other hand, there has been concern about the effect of passive constraint on diastolic LV chamber stiffness and pump function. *In this dissertation we have discussed* a novel device approach that features a biphasic, dynamically adjustable cardiac support device with recoil elements in a single integrated design. This device is designed to address both systolic and diastolic dysfunction by

being uniquely able to provide a tunable constraint compared to deleterious acute impact of a passive girdle.

In this project we have tested the hypothesis that *adjustable cardiac support* in conjunction with a recoil feature can be combined to modulate the diastolic mechanics leading to improved early diastolic filling while limiting the overall heart size. It is expected that this would have a significant impact on the both therapeutic approaches involving passive constraint devices for patients with systolic heart failure and also in diastolic heart failure where passive elastic properties are impacted. As heart size returns to normal we hypothesize that cardiac function will improve, at a minimum because of Law of Laplace effects (i.e., as heart diameter decreases the myocardium gains mechanical advantage and performs better) and possibly because of recovery of the myocardium. We further hypothesize that cardiac function can be improved acutely during the progressive support regimen with the use of recoil; and moreover, that the combination of support and recoil can potentially lead to much greater improvement because two separate characteristics of CHF are addressed, systolic and diastolic dysfunction respectively. We have performed studies with our prototypes to test the following objectives:

A. Test the hypothesis that adjustable cardiac support can be employed to left shift the End-diastolic pressure Volume Relationship. The end-diastolic pressure–volume relationship (EDPVR) is one of the most important means of characterizing the passive ventricular properties of an individual heart. In

particular, the EDPVR indicates the physiologic determinant of preload by indicating the amount of diastolic filling that will occur for a specified filling pressure.

B. Test the hypothesis that combining diastolic recoil with adjustable cardiac support would limit heart size without constraining the early diastolic filling. In a failing heart passive stiffness and slow relaxation time i.e. diastolic recoil is a primary problem in remodeled hearts, and thus an increase in recoil could improve cardiac function without impeding the filling during diastole. The EDPVR measurement would be used to quantify this specific aim.

The biphasic dynamic support and recoil prototype device discussed in this dissertation is being developed to address a vast unmet need of a minimally invasive implantable device solution to reverse LV remodeling (ventricular size) and concurrently reduce the ventricular filling pressure in patients with end stage heart failure. We have prototyped and tested a novel device technology which fully modulates diastolic mechanics in two principle ways (1) adjustable passive cardiac support or progressive constraint to facilitate the gradual reduction in size of dilated, diseased hearts, thereby improving pumping efficiency; (2) diastolic recoil technology with the ability to transfer energy from systolic contraction to diastolic filling, which may potentially reduce ventricular filling pressures, without compromising ventricular systolic function.

As for any new technology there are risks which are being addressed from early stages to clinical introduction as the design iterations are being implemented at each stage of development from bench-top to completion of human trial. The technical risks of this technology are both treatment specific and device specific. Overcoming these barriers is key to curing heart failure. The risk is considered high at this early stage with limited preclinical data about how this intervention will affect the biological remodeling and repair processes in the heart. These barriers are surmountable as rudimentary implantation methods and device adjustment methods are already working, and human clinical studies will require somewhat modified approaches from those used with animals as we undergo multiple iterations and feedback analysis. Once we complete the proposed design work, make transition to GMP processes and obtain efficacy data, funding will be sought to develop solutions to barriers for moving to clinical adaption. The risks and feasibility are divided into two subparts below: device specific risk and treatment specific risk.

Device specific risk: Being classified as a possible class III implantable device, the proposed device definitely has high design risks as there are with developing an implantable device which would be placed inside the pericardial sac and having the device be deployed in a minimally invasive manner. The passive cardiac support devices are in development over 15 years and there has been no significant safety issue of these devices as they have been in clinical trials for over 10 years. But as of today these devices have yet to penetrate the market place as an approved device. Corcap from

Acorn Cardiovascular and Heartnet from Paracor Medical are the devices closest to market and would open up a completely new therapeutic option for patients with end stage heart failure. The indications of these devices might be expanded in future as an intervention post acute myocardial infarction to stabilize the myocardium.

With implantable devices, biocompatibility and sterilization are obvious risks which are primarily addressed with appropriate choice of materials and sterilization method. The most technically difficult aspect of safety then, is in mitigating device failure over a period of time. Living tissues are constantly repairing broken fibers and other microstructural defects whereas implantable devices accumulate damage. Given the loading of the cardiac device at a constant pressure, the device construction has to meet very high standards of quality and mechanical testing. Devices that appear simple from engineering standpoint on the bench-top can be grand technological innovations when designed for implantation. Moreover, the risk associated with the procedure to achieve implantation can be so great, that implanting the device is simply not an option for some portion of the patient population. Therefore, leading edge minimally invasive deployment techniques are preferred. This requires substantial innovation in the design of the device and its deployment technique, as the device must transform from one that is collapsed or compacted for minimally invasive delivery to one that is reconstituted and functions completely as intended after deployment. With the exception of aortic balloon pumps, heart assist and support devices are not implantable in a minimally invasive manner. In summary, device interaction with the heart is intrinsically high risk

because of *known* unknowns and many *unknown* unknowns. There is always a substantial technological risk and failure mitigation comes from many cycles of prototyping, testing, evaluating failures, and redesigning.

Treatment specific risk: Technology that fully modulates diastolic mechanics in a minimally invasive way is not available today as a device option; hence the benefits and complications of the proposed intervention are mostly unknown. Though the proposed technology is well founded on sound scientific principles and evidence from studies of mechanobiology in the literature, it is entirely possible that there will be new findings on the device design side. Wall stress, electrical depolarization, calcium handling, oxygen utilization, reversion to fetal myosin isoforms, and many other phenomena have been implicated in end stage CHF and other structural cardiomyopathies. These may be secondary to kinematical etiologies, yet it is possible that some and perhaps all may be primary contributors that are more important than the end diastolic and end systolic configurations that this device will modulate. Well-designed, scientific long term animal studies are needed to assess the proposed treatment effectiveness. Multiple design cycles of prototyping, testing, evaluating failures, and redesigning have been conducted, and the latest prototypes demonstrate the necessary capabilities. In addition, we have developed and tested strategies for mitigating possible failures of the device. In a passive mode of operation we believe there will be a minimal chance of any restriction of normal cardiac function triggered by any operational functioning of the device.

The biphasic device is expected to inhibit the remodeling processes or progressive enlargement associated with advancing disease. Given that contractile proteins in the heart are in a constant state of flux with absorption and formation occurring simultaneously—at rates equal to approximately half of the heart muscle mass per week, it is hypothesized that with an *adjustable* cardiac support device it may be possible to not only inhibit enlargement but to stimulate reverse-remodeling processes with incrementally smaller diameters. Preclinical and clinical evidence from multiple studies done with Corcap (Acorn Cardiovascular) and Heartnet (Paracor Medical) device shows that it might be possible that the same device could prove efficacious in early intervention post acute myocardial infarction to stabilize the myocardium and limit infarct expansion. The device developed is also applicable in reducing pericardial adhesion in multi-stage cardiothoracic surgeries in pediatric and adult patients.

In conclusion, the proposed adjustable support device with assist and recoil capabilities would provide an integrated approach to treating CHF whereby the therapeutic target is improving global cardiac function. As the essential first step toward that end, we need to investigate the benefits of adjustable passive support with and without diastolic recoil. It is hypothesized that adjustable passive support combined with diastolic recoil will provide the best device based therapeutic option in the treatment of end stage heart failure and that reverse remodeling processes may be stimulated by such an intervention thereby providing the foundation for a therapeutic regimen targeting cardiac rehabilitation and a viable alternative to transplant therapy. The device does not contact

the blood, can be delivered via minimally invasive procedures, and is held in place by an intrinsic pneumatic attachment (i.e. does not require suturing to the heart). Specifically, we are developing a technology that will (1) provide adjustable passive cardiac support and constraint by controlling the target end-diastolic volume which is designed to facilitate the gradual reduction in size of hypertrophied diseased hearts and enhance diastolic recoil, thereby improving pumping efficiency; (2) provide recoil assist designed to reduce chamber stiffness and increase ventricular filling (3) be deployable via minimally invasive procedures; and (4) create a fluid filled barrier between the heart and chest wall to prevent trans-thoracic adhesions and improve cardiac motion. Thus combining passive support and recoil capabilities may lead to greater improvement because two separate indications of CHF are addressed, systolic and diastolic failure respectively. Our preliminary studies demonstrate that our device is safe and operates as intended. We now need to examine the effectiveness of such a comprehensive device based therapy in the treatment of CHF.

Future Work

The present work has been conducted to bring a novel device idea to proof of concept and there exists a long road ahead to take it from preclinical to clinical stages following the path of FDA approval. From historical analysis of FDA's regulatory guidance on similar class of devices for treating end stage heart failure, this device would be categorized as a Class III device and going by the complexity and resources needed to take this device forward it would require multiple sources of funding from both

academic and commercial routes. In the sections below we discuss the proposed efficacy studies and the path to commercialization, as the real benefit of this project would be realized when this device can be successfully implanted in a patient in a clinical setting with positive clinical outcome.

Preclinical evaluation: Efficacy study

The efficacy study is designed to evaluate the effectiveness of the novel cardiac support device with recoil elements to fully modulate the diastolic mechanics and reverse the ventricular remodeling leading to better understanding of mechanisms of heart failure progression and recovery. The goal of the study, as shown in the preclinical study design in Figure 39, would be to develop a clear understanding of the contribution of recoil and adjustability to passive support devices. Towards that goal, five groups each comprising of five sheeps with the same model of heart failure (LAD occlusion) would be studied. All the groups will be monitored for 8 weeks after induction of Myocardial Infarction (MI) for postoperative recovery and then randomized into five different groups.

The five groups would be followed for 16 weeks until a terminal study (earlier if complications arise). The groups have differing device interventions as follows:

1. SHAM (MI + No device, n=5): This group would have the device being implanted and removed .Group will be monitored for the same period as treated groups (16 weeks post MI) and undergo the same terminal procedure with pathology evaluation.

2. FXDCSD (MI + Fixed support device, n=5): At 8 weeks post MI, this group will be implanted with a device that surrounds the heart; however, the device will not be adjusted. The device would be like a fixed or non-adjustable CSD, such CorCap or HeartNet. Hence, this group is referred to as the fixed CSD group.

3. ADJCSD (MI + Adjustable support device, n=5): At 8 weeks post MI, this group will be implanted with an adjustable CSD that can be progressively tightened with infusion of saline in a subQ injection port. With 12 adjustments (one per wk), the size of the heart will be progressively constrained.

4. REC+FXDCSD (MI + Fixed support device with Recoil elements, n=5): At 8 weeks post MI, this group will be implanted with a CSD adjusted similar to ADJCSD, however, the device will also have recoil elements embedded in it to obtain 10 cmH20 suction at end-systolic volume.

5. REC+ADJCSD (MI + Adjustable support device with Recoil elements, n=5): At 8 weeks post MI, this group will be implanted with a CSD adjusted similar to ADJCSD, however, the device will also have recoil elements embedded in it to obtain 10 cmH20 suction at end-systolic volume.

Data Collection time points:

1. BASELINE (BASE): 0 weeks, Data collected prior to induction of CHF
2. PRETREATMENT (PRE): 8th Week: Data collected prior to randomization and device implantation
3. POSTREATMENT (POST): 16th Week: Data collected at terminal evaluation

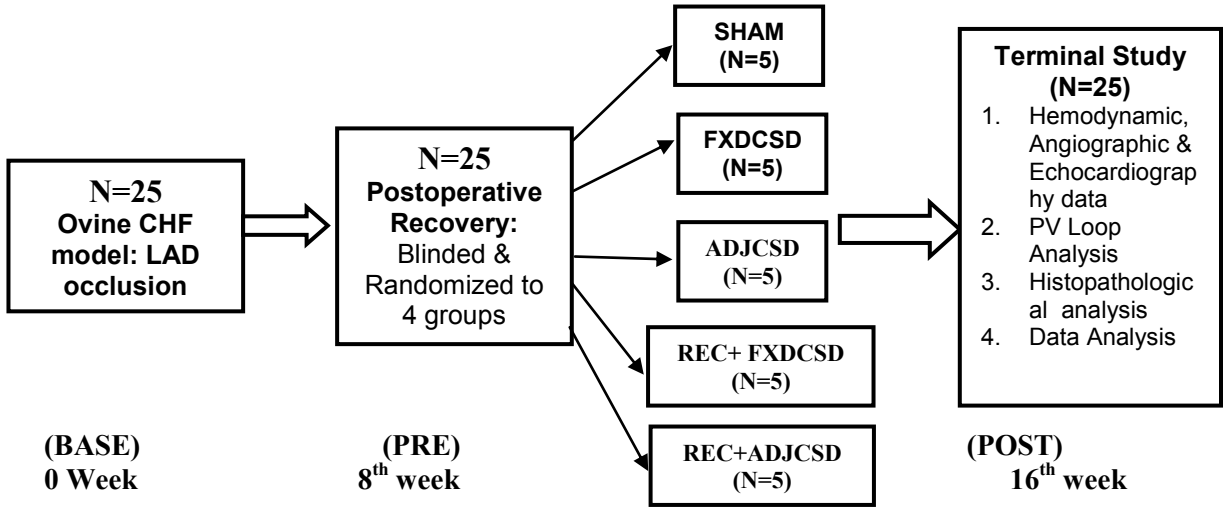

Figure 39. Summary of chronic preclinical study design.

In this project we will test three hypotheses:

1. A*djustable cardiac support* is more effective than fixed (i.e., non-adjustable) cardiac support,

2. Combination of *recoil assist* with fixed cardiac support is more effective than only fixed cardiac support, and

3. Benefits of *adjustable cardiac support* and *recoil assist* are additive because they target separate mechanisms.

The technology developed here is not ready for clinical use; yet, the scientific question here is critical to the development of the next generation of support technology—i.e., can recoil assist and/or adjustability increase the efficacy of cardiac support. Toward this end, this novel device technology is ideal because with the same device profile, with the same surface area of interaction with the heart, and with the same implantation procedure we can deliver the four different devices needed.

From preclinical to clinical path

The research conducted over last five years leading to the device discussed in this dissertation, has been developed keeping in mind the FDA's concept of "critical path initiative". The FDA critical path involves design and manufacturing according to GMP regulations, preclinical animal studies following GLP regulations and clinical trials utilizing GCP regulations. (GMP stands for "Good Manufacturing Practice", GLP stands for "Good Laboratory Practice", and GCP stands for "Good Clinical Practice".) It is understood that advancement along the critical path is a serial progression with design constraints and choice of materials mapping to manufacturing processes and to animal testing requirements with animal study outcomes mapping to clinical trial design and disclosure of potential risks. Ideally, device development progresses from manufacturing to animal studies and then to clinical trial. An investigation device exemption (IDE) for clinical trials requires manufacturing characterization and animal study data. Our

approach is as per FDA recommendations with implementation of a quality system for design and manufacturing, followed by a pre-IDE meeting with FDA to outline requirements for preclinical animal studies and clinical trial design. This approach is detailed below with plans to reach six milestones.

Regulatory Milestones:

1. Develop design controls and quality systems regulation for the development of Biphasic Support & Recoil Device. The next step in the commercialization of the biphasic cardiac device is to develop and implement quality systems regulation (QSR) with design controls—a necessary component of GMP. The QSR will be designed, implemented, and evaluated based on the criteria discussed in the *Design Control Guidance for Medical Device Manufacturers*, which are guidelines set forth by the FDA. This technical objective will be completed when satisfactory QSR and design controls are in place for evaluating the design development of cardiac support devices and minimally invasive deployment fixtures. In short, to move forward on a path toward clinical introduction of this technology it is imperative that QSR be implemented. Briefly, design guidelines are focused on the following: design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file.

The development process shown in figure 40 below is an example of a waterfall model based on FDA guidance. In the development process, requirements or design inputs are determined from user needs and a design process is used to meet those requirements. When the design input has been reviewed and the design input requirements are approved, an iterative process of translating those requirements into a device design begins. The design process phase involves the conversion of design input requirements into system specifications, which become design output. The design output is then evaluated through the verification process and the result becomes the design input for the next step in the design process, and so on.

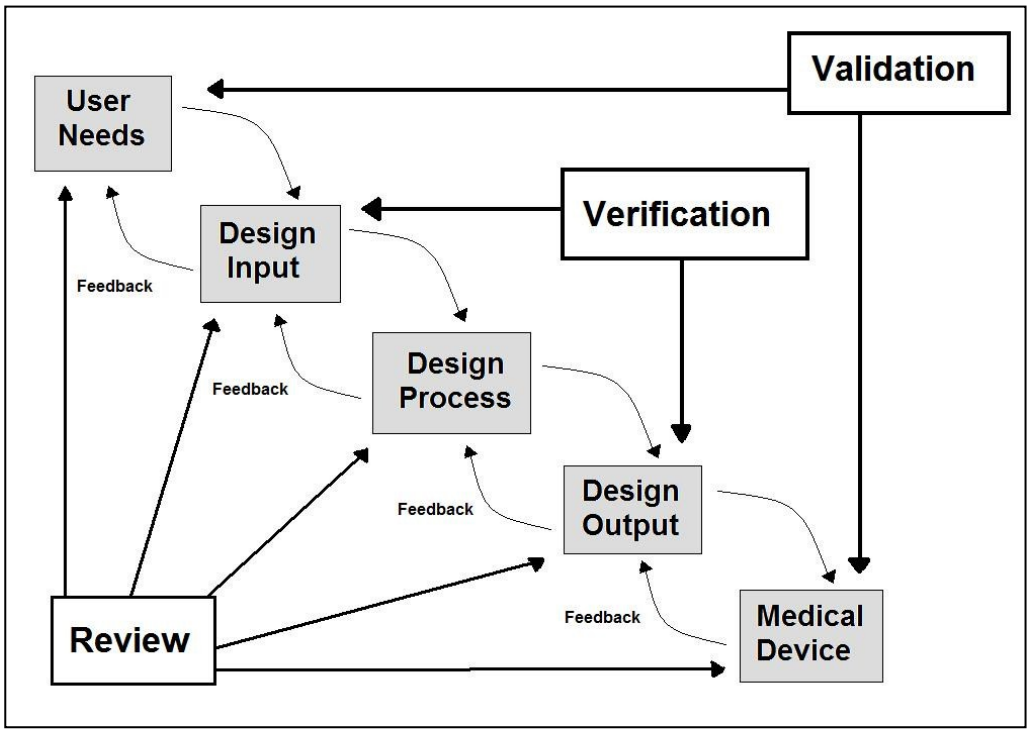

Figure 40: Design development process shown is an example of a waterfall model.

Once all of the design inputs have been processed and design outputs have been verified then the outputs are transferred to production. Feedback paths are required between each phase of the process and previous phase to ensure that there is cohesion between phases. Design reviews are conducted at strategic points in the design process. An example of a design review includes assuring design input requirements are adequate before they are converted to design specifications. Basically, design reviews are used to verify that an activity or phase has been completed effectively before moving on to the next activity or phase. The final step in the waterfall model is validation, which encompass verification and extends the assessment to address whether the device produced meets the requirements and expectations of its intended use.

2. Employ the design controls and quality systems regulation developed to produce functional prototypes, "freeze" the design, and complete a pilot production run. Presently, all devices are made by hand using off-the-shelf materials and supplies. The hand-made devices have enabled completion of proof-of-concept and safety studies. The design of the device and delivery systems must now be optimized for manufacturing without loss of performance. Once an appropriate design has been developed using the design controls and quality systems regulation, pre-pilot and pilot production run will be executed. All devices and delivery systems produced in this run will be validated using appropriate bench-top tests as identified in the design process.
3. Conduct pre-IDE meeting with FDA: Given the need to assure high quality in the design, manufacture, and usage of class III medical devices, meetings with FDA

would be conducted to achieve a common goal of safety and efficacy. Once the design features and material characteristics are defined, preclinical animal studies plan and clinical trial design would be discussed in pre-IDE meeting with FDA.

4. Perform preclinical animal studies as per pre-IDE meeting with FDA: Once the device is manufactured using the legacy materials with a known toxicity profile animal safety studies are expected to be focused on adjustability of cardiac support (16 weeks), safety of biphasic support (16 weeks), and cardioprotective capabilities (buffering of heart in fluid filled space with lack of fibrous adhesions of heart to chest wall).
5. Design clinical trial as per pre-IDE meeting with FDA: Clinical trials for cardiac support devices (bridge-to-transplant and destination therapy) as well as for support devices (Cor-cap) have been designed, approved by FDA, and published. In such trials, the device would need to show usefulness of the support and recoil technology for inducing and sustaining heart recovery
6. Obtain Investigation Device Exemption (IDE) from FDA to begin clinical trials: One of the major milestones in the design and development stage before reaching human trials is submission of IDE application to FDA and approval of IDE to begin clinical trials.
7. Complete clinical trials and initiate statistical analysis.

Table 5 provides a path to final product design, GMP manufacturing and market roll-out.

Table 5 Proposed commercialization path of the device from concept to market

Phase	Expected Milestones
Phase I	1. Fabrication of prototype device for animal studies 2. Successful implantation of recoil and adjustable cardiac support device , in an ovine CHF model, in a minimally invasive manner via a minimally invasive, one-inch long sub-xiphoid incision 3. Acute reduction of end-diastolic diameter of the end-diastolic diameter by 3-5% without compromising cardiac output in an ovine CHF model. 4. Pre IDE meeting with FDA to develop a strategy for a publishable preclinical study and possible designs of pilot and pivotal clinical trials.
Phase II	1. Design and fabrication of prototype for pivotal preclinical studies 2. Assess the treatment effectiveness of an adjustable cardiac support device with for an ovine CHF model as compared to conventional (e.g., CorCap) and to best medical management 3. Implementation of Quality System Regulations (QSR) 4. Manufacturing Systems Auditing - ISO 9000 & CE 5. Assess the treatment effectiveness of a recoil and adjustable cardiac support device for an ovine CHF model as compared to adjustable CSD and conventional CSD, and to best medical management.
Phase III A	1. Design of prototype device for pilot human clinical trials. 2. Selection of GMP-qualified manufacturer, & fabrication of prototypes for Clinical Trials. 3. Investigational Device Exemption (IDE) Application to FDA for conducting Clinical Trials. 4. Identify site for and obtain IRB Approvals for clinical trials. (Likely source is Texas Heart Institute). 5. Identify Contract Research Organizations (CRO) for initiating global clinical trials.

Table 5 continued

Phase	Expected Milestones
Phase III B	1. Initiation of a Randomized Multisite Clinical Trial in US, and globally. 2. Continuous Design Feedback from user group and working with the regulatory agencies.
Phase IV	1. Achievement of Premarket Approval (PMA) Application from FDA & also European, Asian, Canadian Regulatory Agencies 2. Negotiation with regulatory agencies regarding any requirements or changes in the Clinical Trial & Quality Systems Design Reviews 3. Negotiation with Medicare on Reimbursement issues 4. Implementation of Customer support, sales/marketing, and service functions 5. Acquisition, sales or selective licensing of technology to strategic corporate partners

While effective pharmacologic therapies have improved outcomes for mild-moderate heart failure, the potential impact of newer therapies and minimally invasive mechanical circulatory support for advanced heart failure has not yet been realized. Though implantable devices have been shown to be safe and effective, further work is needed to realize the full potential of mechanical support and recoil in the treatment and

maintenance of CHF as well as the possibility of stimulating ventricular recovery and cardiac rehabilitation. Results of adjustable support devices are encouraging and support our hypothesis that such devices can be employed to reverse remodel the heart. However, the combination of support and recoil will enable a complete modulation of the mechanical environment of the heart to guide remodeling processes. Given the mechanical nature of cardiac function, the role of mechanics in cardiac development and the role of mechanics in the progression of heart failure, it is reasonable to expect that therapies that enable the manipulation of mechanical factors about the heart may provide essential modes of therapeutic intervention that could be vitally beneficial to patients with congestive heart failure.

REFERENCES

[1] American Heart Association (AHA). 2010, "Heart disease and stroke statistics: 2010 update," American Heart Association, Dallas, TX

[2] Ertl, G., and Kochsiek, K., 1993, "Development, early treatment, and prevention of heart failure," Circulation, **87**(5): pp IV1-IV3.

[3] McKee, M., 1997, "Indicators of clinical performance: problematic, but poor standards of care must be tackled," BMJ **315**(7101): pp 142

[4] Konstam, V., Hijjazi, K.H., Surman, O., Fierstein, J., Konstam, M., Turbett, A., Dec, G.W., Keck, S., Mudge, G., Flavel, C., McCormack, M.A., and Hurley, L. 1997, "A longitudinal study of health related quality of life in heart transplantation recipients," Journal of Applied Rehabilitation and Counseling, **28**(1): pp 51-56.

[5] Sabbah, H.N., Shimoyama, H., Kono, T., Gupta, R.C., Sharov, V.G., Scicli, G., Levine, T.B., and Goldstein, S., 1994, "Effects of long-term monotherapy with Enalapril, Metoprolol, and Digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction," Circulation, **89**(6): pp 2852–2859.

[6] Goldstein, S., Ali, A.S., and Sabbah, H.N., 1998, "Ventricular remodeling: mechanisms and prevention," Cardiol Clin, **16**(4): pp 623–632.

[7] Cohn, J.N., 1995, "Structural basis for heart failure: ventricular remodeling and its pharmacological inhibition," Circulation, **91**(10): pp 2504–2507.

[8] Mann, D.L., Bristow, M.R., 2005, "Mechanisms and models in heart failure: the biomechanical model and beyond," Circulation, **111**(21): pp 2837-2849.

[9] Linzbach, A.J., 1960, "Heart failure from the point of view of quantitative anatomy," Am J Cardiol, **5**(3): pp 370–382.

[10] Ross, J.J., 1983, "Mechanisms of cardiac contraction. What roles for preload, afterload and inotropic state in heart failure?" Eur Heart J, **4** (Suppl A): pp 19-28.

[11] Ross, J,J., 1985, "Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy," J Am Coll Cardiol, **5**:(4): pp 811–826.

[12] Hirota, Y., Saito, T., Kita, Y., Shimizu, G., Kino, M., and Kawamura, K., 1986, "The natural history of dilated cardiomyopathy and pathophysiology of congestive heart failure," J Cardiogr Suppl, **9**: pp 67–76.

[13] Pouleur, H., Rousseau, M.F., van Eyll, C., Melin, J., Youngblood, M., and Yusuf, S., 1993, "Cardiac mechanics during development of heart failure. SOLVD Investigators". Circulation **87** (Suppl 5): pp IV14–IV20.

[14] Pfeffer, M.A., Lamas, G.A., Vaughan, D.E., Parisi, A.F., and Braunwald, E., 1988, "Effect of Captopril on progressive ventricular dilatation after anterior myocardial infarction," N Engl J Med, **319**(2): pp 80–86.

[15] Cohn, J., Ferrari, R., and Sharpe, N., 2000, "Cardiac remodeling—concepts and clinical implications," J Am Coll Cardiol, **35**(3): pp 569–582.

[16] Sadoshima, J., Jahn, L., Takahashi, T., Kulik, T.J., and Izumo, S., 1992, "Molecular characterization of the stretch-induced adaptation of cultured cardiac cells. An in vitro model of load-induced cardiac hypertrophy," J Biol Chem, **267**(15): pp 10551–10560.

[17] White, H.D., Norris, R.M., Brown, M.A., Brandt, P.W.T., Whitlock, R.M.L., and Wild, C.J., 1987, "Left ventricular end-systolic volume as the major predictor of survival after recovery from myocardial infarction," Circulation, **76**(1): pp 44–51.

[18] Douglas, P.S., Morrow, R., Ioli, A., and Reicheck, N., 1989, "Left ventricular shape; afterload and survival in idiopathic dilated cardiomyopathy," J Am Coll Cardiol, **13**(2): pp 311–315.

[19] Margulies, K.B., 2003, "Blocking stretch-induced myocardial remodeling," Circ Res, **93**(11): pp 1020–1022.

[20] Dreifuss, P., 1998, "Therapy of terminal dilated cardiomyopathy with growth hormone," Z Kardiol, **87**(6): pp 425–435.

[21] Packer M., 1992, "The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure," J Am Coll Cardiol, **20**(1): pp 248-254

[22] Massie, B.M., 1998, "Clinical trials in heart failure: Can we expect the results to be replicated in clinical practice?" J Card Fail, **4**(3): pp 243-247.

[23] Bristow, M.R., 1984, "The adrenergic nervous system in heart failure," N Engl J Med, **311**(13): 850-851.

[24] Nohria, A., Lewis, E., and Stevenson, L.W., 2002, "Medical management of advanced heart failure," JAMA **287**(5): pp 628-640.

[25] Zimmet, H., and Krum, H., 2008, "Using adult stem cells to treat heart failure – fact or fiction?" Heart Lung Circ, **17**(Suppl 4): pp S48-S54.

[26] Braun, T., Martire, A., 2007, "Cardiac stem cells: paradigm shift or broken promise? A view from developmental biology," Trends Biotechnol, **25**(10): pp 441-447.

[27] Guan, K., and Hasenfus, G., 2007, "Do stem cells in the heart truly differentiate into cardiomyocytes?" J Mol Cell Cardiol, **43**(4): pp 377-387.

[28] Rubart, M., and Field, L.J., 2006, "Cardiac regeneration: repopulating the heart," Annu Rev Physiol, **68**: pp 29-49.

[29] Francis, G.S., 2001, "Pathophysiology of chronic heart failure," Am J Med, **110**(7 Suppl 1): pp 37S–46S.

[30] Sabbah, H.N., Kono, T., Stein, P.D., Mancini, G.B., and Goldstein, S., 1992, "Left ventricular shape changes during the course of evolving heart failure. Am J Physiol, **263** (1pt 2): pp H266–H270.

[31] Frigerio, M., and Roubina, E., 2005, "Drugs for left ventricular remodeling in heart failure," Am J Cardiol, **96**(12A): pp 10L–18L.

[32] Reddy, H.K., Tjahja, I.E., Campbell, S.E., Janicki, J.S., Hayden, M.R., and Tyagi S.C., 2004, "Expression of matrix metalloproteinase activity in idiopathic dilated cardiomyopathy: a marker of cardiac dilatation," Mol Cell Biochem, **264**(1-2): pp183–191.

[33] Kass, D.A., Baughman, K.L., Pak, P.H., Cho, P.W., Levin, H.R., Gardner, T.J., Halperin, H.R., Tsitlik, J.E., and Acker, M.A., 1995, "Reverse remodeling from cardiomyoplasty in human heart failure. External constraint versus active assist," Circulation, **91**(9): pp 2314–18.

[34] Cohn, J.N., 1995, "Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition," Circulation, **91**(10): pp 2504–2507.

[35] Acker, M.A., Bolling, S., Shemin, R., Kirklin, J., Oh, J.K., Mann, D.L., Jessup, M., Sabbah, H.N., Starling, R.C., Kubo, S., 2006, "Mitral valve surgery in heart failure: insights from the Acorn clinical trial," J Thorac Cardiovasc Surg, **132**(3): pp 568–577.

[36] Donal, E., Leclercq, C., Linde, C., Daubert, J.C., 2006, "Effects of cardiac resynchronization therapy on disease progression in chronic heart failure," Eur Heart J, **27**(9): pp1018–1025.

[37] Murphy, R.T., Sigurdsson, G., Mulamalla, S., Agler, D., Popovic, Z.B., Starling, R.C., Wilkoff, B.L., Thomas, J.D., Grimm, R.A., 2006, "Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy," Am J Cardiol, **97**(11): pp 1615–1621.

[38] Walsh, R.G., 2005, "Design and features of the Acorn CorCap cardiac support device: the concept of passive mechanical diastolic support," Heart Fail Rev, **10**(2): pp101–07.

[39] Sabbah, H.N., 2003, "The cardiac support device and the Myosplint: treating heart failure by targeting left ventricular size and shape," Ann Thorac Surg, **75**(6 Suppl): pp S13–S19.

[40] Chaudhry, P.A., Mishima, T., Sharov, V.G., Hawkins, J., Alferness, C., Paone, G., and Sabbah, H.N., 2000, "Passive epicardial containment prevents ventricular remodeling in heart failure," Ann Thorac Surg, **70**(4): pp 1275–1280.

[41] Sabbah, H.N., 2005, "Global left ventricular remodeling with the Acorn cardiac support device: hemodynamic and angiographic findings in dogs with heart failure," Heart Fail Rev, **10**(2): pp109–115.

[42] Raman, J.S., Byrne, M.J., Power, J.M., and Alferness, C.A., 2003, "Ventricular constraint in severe heart failure halts decline in cardiovascular function associated with experimental dilated cardiomyopathy," Ann Thorac Surg, **76**(1): pp141–47.

[43] Pilla, J.J., Blom, A.S., Brockman, D.J., Bowen, F., Yuan, Q., Giammarco, J., Ferrari, V.A., Gorman, J.H., 3rd, Gorman, R.C., and Acker M.A., 2002, "Ventricular constraint using the Acorn cardiac support device reduces myocardial akinetic area in an ovine model of acute infarction" Circulation, **106**(12 Suppl 1): pp1207–1211.

[44] Blom, A.S., Mukherjee, R., Pilla, J.J., Lowry, A.S., Yarbrough, W.M., Mingoia, J.T., Hendrick, J.W., Stroud, R.E., McLean, J.E., Affuso, J., Gorman, R.C., Gorman, J.H. 3rd., Acker, M.A., and Spinale, F.G., 2005, Cardiac support device modifies left ventricular geometry and myocardial structure after myocardial infarction. Circulation, **112**(9): pp 1274–1283.

[45] Cheng A, Nguyen TC, Malinowski M, Langer, F., Liang, D., Daughters, G.T., Ingels, N.B. Jr., and Miller, D.C., 2006, "Passive ventricular constraint prevents transmural shear strain progression in left ventricle remodeling," Circulation, **114**(1 Suppl): pp 179–186.

[46] Raman, J.S., Hata, M., Storer, M., Power, J.M., Buxton, B.F., Alferness, C., and Hare, D., 2001, "The mid-term results of ventricular containment (Acorn wrap) for

end-stage ischemic cardiomyopathy," Ann Thorac Cardiovasc Surg, **7**(5): pp 278–281.

[47] Mann, D.L., Acker, M.A., Jessup, M., Sabbah, H.N., Starling, R.C., Kubo, S.H., Acorn Investigators and Study Coordinators, 2004, "Rationale, design, and methods for a pivotal randomized clinical trial for the assessment of a cardiac support device in patients with New York heart association class III–IV heart failure," J Card Fail, **10**(3): pp 185–192.

[48] Shelton, R.J., Velavan, P., Nikitin, N.P., Coletta, A.P., Clark, A.L., Rigby, A.S., Freemantle, N., Cleland, J.G., American Heart Association, 2005, "Clinical trials update from the American Heart Association meeting: ACORN-CORCAP, primary care trial of chronic disease management, PEACE, CREATE, SHIELD, A-HeFT, GEMINI, vitamin E meta-analysis, ESCAPE, CARP, and SCD-HeFT cost-effectiveness study" Eur J Heart Fail, **7**(1): pp 127–135.

[49] Sabbah, H.N., 2003, "The cardiac support device and the Myosplint: treating heart failure by targeting left ventricular size and shape," Ann Thorac Surg, **75**(6 Suppl): pp S13–S19.

[50] Hamner, C., Ruth, G., Raffe, M., Schoen, F.J., and Schaff, H., 2004, "Safety and biocompatibility of the Myosplint system—a passive implantable device that alters ventricular geometry for the treatment of heart failure," ASAIO J, **50**(5): pp 438–443.

[51] Fukamachi, K., and McCarthy, P.M., 2005, "Initial safety and feasibility clinical trial of the Myosplint device," J Card Surg, **20**(6): pp S43–S47.

[52] Liel-Cohen, N., Guerrero, J.L., Otsuji, Y., Handschumacher, M.D., Rudski, L.G., Hunziker, P.R., Tanabe, H., Scherrer-Crosbie, M., Sullivan, S., and Levine, R.A., 2000, Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3-dimensional echocardiography. Circulation, **101**(23): pp 2756–2763.

[53] Inoue, M., McCarthy, P.M., Popovic, Z.B., Doi, K., Schenk, S., Nemeh, H., Ootaki, Y., Kopcak, M.W., Jr, Dessoffy, R., Thomas, J.D., and Fukamachi, K., 2004, "The Coapsys device to treat functional mitral regurgitation: in vivo long-term canine study," J Thorac Cardiovasc Surg, **127**(4**)**: pp 1068–1076.

[54] Fukamachi K, Popovic ZB, Inoue M, Doi, K., Schenk, S., Ootaki, Y., Kopcak, M.W. Jr., and McCarthy, P.M., 2004, "Changes in mitral annular and left ventricular dimensions and left ventricular pressure-volume relations after off-pump treatment of mitral regurgitation with the Coapsys device," Eur J Cardiothorac Surg, **25**(3): pp 352–357.

[55] Fukamachi, K., Inoue, M., Popovic, Z.B., Doi, K., Schenk, S., Nemeh, H., Ootaki, Y., Kopcak. M.W. Jr., Dessoffy, R., Thomas, J.D., Bianco, R.W., Berry, J.M., and McCarthy, P.M., 2004, "Off-pump mitral valve repair using the Coapsys device: a pilot study in a pacing-induced mitral regurgitation model," Ann Thorac Surg, **77**(2): pp 688–692.

[56] Mishra, Y.K., Mittal, S., Jaguri, P., and Trehan. N., 2006, "Coapsys mitral annuloplasty for chronic functional ischemic mitral regurgitation: 1-year results," Ann Thorac Surg, **81**(1): pp 42–46.

[57] Grossi, E.A., Saunders, P.C., Woo, Y.J., Gangahar, D.M., Laschinger, J.C., Kress, D.C., Caskey, M.P., Schwartz, C.F., and Wudel, J., 2005, "Intraoperative effects of the coapsys annuloplasty system in a randomized evaluation (RESTOR-MV) of functional ischemic mitral regurgitation" Ann Thorac Surg, **80**(5): pp 1706–1711.

[58] Magovern, J.A., 2005, "Experimental and clinical studies with the Paracor cardiac restraint device," Semin Thorac Cardiovasc Surg, **17**(4): pp 364–368.

[59] Starling, R.C., and Jessup, M., 2004, "Worldwide clinical experience with the CorCap cardiac support device," J Card Fail, **10**(6 Suppl): pp S225–S233.

[60] Lembcke, A., Dushe, S., Dohmen, P.M., Hoffmann, U., Wegner, B., Kloeters, C., Enzweiler, C.N., Hamm, B., and Konertz, W.F., 2006, "Early and late effects of passive epicardial constraint on left ventricular geometry: ellipsoidal re-shaping confirmed by electron-beam computed tomography," J Heart Lung Transplant, **25**(1): pp 90–98.

[61] Rayburn, B.K., Aranda, J.M., Boehmer, J.P., 2006, "The Paracor ventricular support system: initial US experience [abstract]," Circulation, **114**(18 Meeting Abstracts): pp II–710-b.

[62] Aranda, J.M., Klodell, C.T., Rayburn, B.K., 2006, "Early worldwide experience with the Paracor HeartNet™ elastic restraint device [abstract]," J Card Failure, **12**(6): pp S46.

[63] Vasan, R. S., and Levy, D., 2000, "Defining diastolic heart failure: a call for standardized diagnostic criteria," Circulation, **101**(17): pp 2118-2121.

[64] Senni, M., Redfield, M.M., 2001, "Heart failure with preserved systolic function. A different natural history?" J Am Coll Cardiol, **38**(5): pp 1277-1282.

[65] Vasan, R.S., Larson, M.G., Benjamin, E.J., Evans, J.C., Reiss, C., and Levy, D., 1999, "Congestive heart failure in subjects with normal versus reduced left

ventricular ejection fraction: prevalence and mortality in a population-based cohort," J Am Coll Cardiol, **33**(7): pp 1948–1955.

[66] Tsutsui, H., Tsuchihashi, M., and Takeshita, A., 2001, "Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function," Am J Cardiol, **88**(5): pp 530 -533.

[67] Zile, M.R., Baicu, C.F., and Bonnema, D.D., 2005, "Diastolic heart failure: definitions and terminology," Prog Cardiovasc Dis, **47**(5): pp 307-313.

[68] Bursi, F., Weston, S.A., Redfield, M.M., Jacobsen, S.J., Pakhomov, S., Nkomo, V.T., Meverden, R.A., and Roger, V.L., 2006, "Systolic and diastolic heart failure in the community," JAMA, **296**(18): pp 2209 -2216.

[69] Liao, L., Jollis, J.G., Anstrom, K.J., Whellan, D.J., Kitzman, D.W., Aurigemma, G.P., Mark, D.B., Schulman, K.A., Gottdiener, J.S., 2006, "Costs for heart failure with normal vs reduced ejection fraction," Arch Intern Med, **166**(1): pp 112-118.

[70] Yancy, C.W., Lopatin, M., Stevenson, L.W., De Marco, T., and Fonarow, G.C., 2006, "Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database [published correction appears in J Am Coll Cardiol, **47**(1): pp 76 -84.

[71] Tsutsui, H., Tsuchihashi, M., and Takeshita, A., 2001, "Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function," Am J Cardiol, **88**(5): pp 530 -533.

[72] Senni, M., Tribouilloy, C.M., Rodeheffer, R.J., Jacobsen, S.J., Evans, J.M., Bailey, K.R., Redfield, M.M., 1998, "Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991," Circulation, **98**(21): pp 2282-2289.

[73] Kitzman, D.W., Gardin, J.M., Gottdiener, J.S., Arnold, A., Boineau, R., Aurigemma, G., Marino, E.K., Lyles, M., Cushman, M., and Enright, P.L; Cardiovascular Health Study Research Group, 2001, "Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol, **87**(4): pp 413-419.

[74] MacCarthy, P.A., Kearney, M.T., Nolan, J., Lee, A.J., Prescott, R.J., Shah, A.M., Brooksby, W.P., Fox, K.A., 2003, "Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study" BMJ, **327**(7406): pp 78-79.

[75] Vasan, R.S., Larson, M.G., Benjamin, E.J., Evans, J.C., Reiss, C.K., and Levy, D., 1999, "Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort," J Am Coll Cardiol, **33**(7): pp 1948 -1955.

[76] Aurigemma, G.P., Gottdiener, J.S., Shemanski, L., Gardin, J., Kitzman, D., 2001, "Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study" J Am Coll Cardiol, **37**(4): pp 1042 -1048.

[77] Kitzman, D.W., Little, W.C., Brubaker, P.H., Anderson, R.T., Hundley, W.G., Marburger, C.T., Brosnihan, B., Morgan, T.M., and Stewart, K.P., 2002, "Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure" JAMA, **288**(17): pp 2144-2150.

[78] Tardif, J.C., and Rouleau, J.L., 1996, "Diastolic dysfunction," Can J Cardiol, **12**(4): pp 389 -398.

[79] Zile, M.R., Baicu, C.F., and Gaasch, W.H., 2004, "Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle," N Engl J Med, **350**(19): pp 1953-1959.

[80] Zile, M.R., Brutsaert, D.L., 2002, "New concepts in diastolic dysfunction and diastolic heart failure: part II. Causal mechanisms and treatment," Circulation, **105**(12): pp 1503-1508.

[81] Gandhi, S.K., Powers, J.C., Nomeir, A.M., Fowle, K., Kitzman, D.W., Rankin KM, et al., 2001, "The pathogenesis of acute pulmonary edema associated with hypertension," N Engl J Med, **344**(1): pp 17-22.

[82] Kitzman, D.W., Higginbotham, M.B., Cobb, F.R., Sheikh, K.H., and Sullivan, M.J., 1991, "Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism," J Am Coll Cardiol, **17**(5): pp 1065-1072.

[83] Litwin, S.E., and Grossman, W., 1993, "Diastolic dysfunction as a cause of heart failure," J Am Coll Cardiol, **22**(4): pp 49A -55A.

[84] Apstein, C.S., Morgan, J.P. Cellular mechanism underlying left ventricular diastolic failure. In: Gaasch WH, Lewinter MM, eds. 1994, "Left ventricular diastolic dysfunction and heart failure. Philadelphia, Pa: Lea & Febiger; pp 3-24.

[85] Angeja, B.G., and Grossman, W., 2003, "Evaluation and management of diastolic heart failure," Circulation, **107**(5): 659-663.

[86] Froehlich, J.P., Lakatta, E.G., Beard, E., Spurgeon, H.A., Weisfeldt, M.L., Gerstenblith, G., 1978, "Studies of sarcoplasmic reticulum function and contraction duration in young adult and aged rat myocardium" J Mol Cell Cardiol, **10**(5): pp 427-438.

[87] Tokushima, T., Reid, C.L., and Gardin, J.M., 2001, "Left ventricular diastolic function in the elderly," Am J Geriatr Cardiol, **10**: pp 20 -29.

[88] R. Lower.,1669, *Tractatus de Corde*., Oxford University Press, London.

[89] Arts, T., Hunter, W.C. and Douglas, A.S., Muijtjens, A.M., Corsel, J.W., Reneman, R.S., 1993, "Macroscopic three-dimensional motion patterns of the left ventricle," Adv Exp Med Biol, **346**: pp 383–392.

[90] Hansen, D.E., Daughters, G.T. 2nd., Alderman, E.L., Ingels, N.B. and Miller D.C., 1988, "Torsional deformation of the left ventricular midwall in human hearts with intramyocardial markers: regional heterogeneity and sensitivity to the inotropic effects of abrupt rate changes," Circ Res, **62**(5): pp 941–952.

[91] Bell, S.P., Nyland, L., Tischler, M.D., McNabb, M., Granzier, H., LeWinter M.M., 2000, "Alterations in the determinants of diastolic suction during pacing tachycardia," Circ Res, **87**(3): pp 235–240.

[92] Gorman, J.H., Gupta, 3rd, K.B., Streicher, J.T., Gorman, R.C., and Jackson, B.M., 1996, "Dynamic three-dimensional imaging of the mitral valve and left ventricle by rapid sonomicrometry array localization," J Thorac Cardiovasc Surg, **112**(3): pp 712–726.

[93] Gibbons Kroeker, C.A., Ter Keurs, H.E., Knudtson, M.L., Tyberg, J.V., and Beyar R., 1993, "An optical device to measure the dynamics of apex rotation of the left ventricle," Am J Physiol, **265**(4 Pt 2): pp H1444–H1449.

[94] Marcelli, E., Plicchi, G., Cercenelli, L., and Bortolami, F., 2005, "First experimental evaluation of cardiac apex rotation with an epicardial coriolis force sensor," ASAIO J, **51**(6): pp 696–701.

[95] Buchalter, M.B., Weiss, J.L., W.J. Rogers, W.J., Zerhouni, E.A., Weisfeldt, M.L., et al., 1990, Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging, Circulation, **81**(4): pp 1236–1244.

[96] Buchalter, M.B., Rademakers, F.E. Weiss, J.L., Rogers, W.J., Weisfeldt, M.L., et al., 1994, "Rotational deformation of the canine left ventricle measured by magnetic

resonance tagging: effects of catecholamines, ischaemia, and pacing," Cardiovasc Res, **28**(5): pp 629–635.

[97] Lorenz, C.H., Pastorek, J.S. and Bundy, J.M., 2000, "Delineation of normal human left ventricular twist throughout systole by tagged cine magnetic resonance imaging," J Cardiovasc Magn Reson, **2**(2): pp 97–108.

[98] Kim, H.K., Sohn, D.W., Lee, S.E., Choi, S.Y., Park, J.S., et al., 2007, "Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography," J Am Soc Echocardiogr, **20**(1): pp 45–53.

[99] Y. Notomi, P. Lysyansky and R.M. Setser et al., 2005, Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging, J Am Coll Cardiol, **45**(12): pp. 2034–2041.

[100] Notomi, Y., Setser, R.M., and Shiota, T., Martin-Miklovic M.G., Weaver, J.A., et al., 2005, "Assessment of left ventricular torsional deformation by Doppler tissue imaging: validation study with tagged magnetic resonance imaging," Circulation, **111**(9): pp 1141–1147.

[101] Helle-Valle, T., Crosby, J., and Edvardsen, T., 2005, "New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography," Circulation, **112**(20): pp 3149–3156.

[102] Arts, T., Veenstra, P.C., and Reneman, R.S., 1982, "Epicardial deformation and left ventricular wall mechanisms during ejection in the dog," Am J Physiol, **243**(3): pp H379–H390.

[103] Beyar, R. and Sideman, S., 1986, "Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall," Circ Res, **58**(5): pp 664–677.

[104] Rebecca, P., Carmine G. De Pasquale, Derek P., and Majo X.J., 2008, " Assessment of early diastolic left ventricular function by two-dimensional echocardiographic speckle tracking," Eur J Echocardio, **9**(6): pp 791–795

[105] Allen, K. B., Matheny, R. G., Robinson, R. J., Heimansohn, D. A., Shaar, C. J., 1997, "Minimally invasive versus conventional reoperative coronary artery bypass," Ann Thorac Surg, **64**(3): pp 616-622.

[106] Tuula, S. O., Kurki, T. S., Kataja, M., 1996, "Preoperative prediction of postoperative morbidity in coronary artery bypass grafting," Ann Thorac Surg, **61**(6): pp 1740-1745.

[107] Christenson, J. T., Schmuziger, M., Simonet, F., 1997, "Reoperative coronary artery bypass procedures: risk factors for early mortality and late survival," Eur J Cardiothoracic Surg, **11**(1): pp 129-133.

[108] Nkere, U. U., Whawell, S. A., Sarraf, C. E., Schofield, J. B., Thompson, J. N., Taylor, K. M., 1995, "Pericardial trauma and adhesions in relation to reoperative cardiac surgery," Thorac Cardiovasc Surg, **43**(6): pp 338-346.

[109] Novez, L., Skotnick, S. H., and Lacquet, L. K., 1997, "Morbidity and mortality in 200 consecutive coronary reoperations," Eur J Cardiothoracic Surg, **11**(3): pp 528-532.

[110] The society of thoracic surgeons. 1998, "Data analysis of the society of thoracic surgeons national cardiac surgery database: the seventh year," summit medical Minnetonka, MN.

[111] Seeger, J. M., Kaelin, L. D., Staples, E.M., Yaacobi, Y., Bailey, J. C., Normann, S., Burns, J. W., Goldberg, E. P., 1997, "Prevention of postoperative pericardial adhesions using tissue-protective solutions," J Surg Res, **68**(1): pp 63-66.

[112] Hurle, A., de la Vega, M., Feijoo, J.J., Ray, V. G., Abad, C. Ponce, G., Perez-Arellano, J.L., 1997, "Effect of physical protection on the mesothelial integrity of the pericardium," Ann Thorac Surg, **63**(4): pp 1091-1094.

[113] Duvernoy, O., Maim, T., Ramstrom, J., Bowald, S., 1995, "A biodegradable patch used as a pericardial substitute after cardiac surgery: 6- and 24-month evaluation with CT," Thorac Cardiovasc Surg, **43**(5): pp 271-274.

[114] Weber, K. T., Sun, Y., Katwa, I.C., 1997, "Myofibroblasts and local angiotensin II in rat cardiac tissue repair," Int J Biochem Cell Biol, **29**(1): pp 31-42.

[115] Ou, R., Sun, Y., Ganjam, V. K., Weber, K. T., 1996, "In situ production of angiotensin II by fibrosed rat pericardium" J Mol Cell Cardiol, **28**(6): pp 1319-1327.

[116] Weber, K. T., Anversa, P., Armstrong, P. W., Brilla, C. G., Burnett, J.C., Cruickshank, J. M., Devereux, R. B., Giles, T. D., Korsgaard, N., Leier, C. V., Mendelsohn, F. A. O., Motz, W. H., Mulvany, M. J., and Strauer B. E., 1992, "Remodeling and reparation of the cardiovascular system," J Am Coll Cardiol, **20**(1): pp 3-16.

[117] Reves, J. G., Karp, R, B., Buttner, E. E., Tosone, S., Smith, L. R., Samuelson, P. N. Kreusch, G.R., Oparil, S., 1982, "Neuronal and adrenomedullary catecholarnine release in response to cardiopulmonary bypass in man," Circulation, **66**(1): pp 49-55.

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