

**REVERSING HEART FAILURE: DIASTOLIC RECOIL IN A
PROPOSED CARDIAC SUPPORT DEVICE**

An Honors Fellows Thesis

by

TIMOTHY DANIEL SNOWDEN

Submitted to the Honors Programs Office
Texas A&M University
in partial fulfillment of the requirements for the designation as
HONORS UNDERGRADUATE RESEARCH FELLOW

April 2010

Major: Biomedical Engineering

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ABSTRACT

Reversing Heart Failure: Diastolic Recoil in a Proposed
Cardiac Support Device. (April 2010)

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Congestive heart failure (CHF) holds millions in the grip of an endless cycle of decreased cardiac output and degenerative remodeling, often with little hope of recovery. Diastolic dysfunction, or failure of the heart to properly fill, is a contributing factor to all cases of CHF and is the sole cause of many cases. By storing energy during systole that can be released during diastole, the addition of a diastolic recoil component to an existing systolic support device could aid in inducing restorative remodeling and, thus, interrupt the downward spiral of heart failure.

In this study we use an indicator of diastolic function—the end-diastolic pressure-volume relationship (EDPVR)—to demonstrate in vitro the ability of a prototype device to positively impact the entire heart cycle. The support device alone shifts the EDPVR of a model heart towards smaller volumes. When the diastolic recoil component is employed, the EDPVR is shifted towards lower pressures at low volumes, indicating

stiffer diastolic recoil. We conclude the device provides bi-phasic support of our model heart, constraining over-filling of the ventricles and augmenting ventricular recoil.

DEDICATION

In the sense that it is mine to give, I dedicate this work to my parents and siblings. A source of encouragement and guidance, it is largely due to my family that I have had the opportunities that enabled me to undertake this project. My five siblings are a boundless joy to me with their love, assistance and encouragement, especially as I have had the rare privilege of continuing to reside with my family during my undergraduate career. My father, Chip Snowden, continues to influence and motivate me through his example as a father who places his priorities on God and family, and I can scarcely aspire to surpass the level of commitment, responsibility and love he displays. His unfailing confidence in my abilities and pride in my accomplishments has urged me towards loftier goals and levels of excellence. My mother, Phyllis Snowden, has shaped and educated me spiritually and academically since birth, instilling the fear and love of God that radiates outward to illuminate every aspect of life. She continues to influence me with her example as a godly woman, wife, and mother.

In another sense, this work can be dedicated to none other than God. His love, grace, and mercy continue to amaze me, His beauty and majesty blind me, and His power and righteousness awe me. I can ask for no greater privilege than to walk in His presence, and to spend my life in praising and glorifying Him, spreading the wonders of His love and works of His hands to “every kindred, and tongue, and people, and nation” (Rev. 5:9). All glory to His precious name!

ACKNOWLEDGMENTS

In my engineering education, it has been emphasized that the most productive, most intelligent, and most successful engineers work in teams. This thesis, and the research project it is detailing, is an excellent example of that principle. Numerous people have aided in this work directly and indirectly, and I would like to take this opportunity to personally name some of them.

It should not be surprising that my advisor, Dr. John Criscione, has been integral to the project. His piercing comprehension of the foundations and nuances of biomechanics, his passion for the field and for accuracy and preciseness in conversation and writing, and his ability to imbue his students with his knowledge and enthusiasm, myself in particular, has catalyzed a refinement of this project and my approach to mechanics and research.

I thank Saurabh Biswas, who was both my supervisor and colleague, for his endless supply of patience with delays and revisions, and his encouragement in research and personal matters. Christina Nazzal and Matt Jackson have played an important role in this project, from building the initial prototypes to graciously working without mysteriously disappearing models and vacuum pumps. Dr. Michael Moreno has served in a largely invisible part of this project, collaborating with Dr. Criscione, developing new ideas – and device changes – and reviewing and fine-tuning posters.

I owe a large debt to my mother, Dr. Phyllis Snowden, for it is largely due to her patient efforts in proofreading countless versions of manuscripts, articles, and presentations that this thesis is comprehensible to anyone other than me. I also appreciate the help of my brother, Seth Snowden, in construction of heart models and device prototypes.

Finally, I thank Dr. Ritter and Dr. Louis for their help in the Fellows process, and the Honors Department for their funding of this effort through both the Summer University Undergraduate Research Fellowship and the Fellows program.

NOMENCLATURE

Afterload	The force which the heart must work against to eject blood, determined by the amount of blood in the ventricles prior to contraction.
Akinetic myocardium	Myocardium that is not contracting.
Cardiomyopathic	Harmful to the heart muscle.
CAO	<i>Coronary Artery Occlusion</i> . Complete blockage of one of the blood vessels feeding the myocardium.
CHD	<i>Coronary Heart Disease</i> . A disease of the coronary arteries that can lead to arterial occlusion and myocardial infarction. Also known as CAD or <i>Coronary Artery Disease</i> .
Coronary	Pertaining to the heart.
Dyskinetic myocardium	Myocardium that is contracting abnormally or bulging.
Edema	Swelling or inflammation resulting from accumulation of fluid in a tissue, organ, or body region.
EDPVR	<i>End-Diastolic Pressure-Volume Relationship</i> . An indicator of the heart's diastolic properties.
Fibroblasts	Cells that produce collagen and other extracellular matrix 'fibers.'

Hyperplasia	Abnormal enlargement of a tissue or organ due to replication of its cells, which are maintaining a relatively constant size; as opposed to hypertrophy.
Hypertrophy	Abnormal enlargement of a tissue or organ due to enlargement of its cells; as opposed to hyperplasia.
Hypotension	Low blood pressure.
Ischemia	Restricted blood flow to a tissue, organ, or region of interest.
Innervation	Stimulation of a nerve.
Manometer	A pressure gauge consisting of a column of liquid displaced by changes in pressure.
MI	<i>Myocardial Infarction</i> , commonly known as a heart attack.
Myocardium	Heart muscle.
Myocyte	Muscle cell.
Neurohumor	Biochemical produced by a neuron to affect a neuron, muscle, or gland.
Perfusion	Blood flow to a tissue, organ, or region of interest.
Pericardium	A membrane that surrounds the heart and roots of the major blood vessels.
Resection	Surgical removal of a section of a tissue or organ.
Systemic	Pertaining to the body as a system.
Tachycardia	Abnormally rapid heart rate.

Vasoconstriction	Decrease in diameter of blood vessels due to contraction of the smooth muscle cells in the vessel wall.
Vasodilation	Increase in diameter of blood vessels due to relaxation of the smooth muscle cells in the vessel wall.

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CHAPTER I

INTRODUCTION

Credited with 7.2 million deaths across the globe each year, coronary heart disease (CHD) possesses the dubious honor of being the world's leading killer [1]. Narrowing of the lumen of coronary arteries reduces blood supply to the heart, leading to ischemia, injury, and infarction. It is not hard to imagine the level of damage that can be done by restricting the nutrient delivery to and waste removal from one of the body's most vital organs. An 'index event' such as coronary artery occlusion (CAO) can set off one of the best known results of CHD: myocardial infarction (MI).

Those who escape the 'silent killer's' initial attack rarely realize the consequences of survival. The localized necrosis of myocardial cells, from which myocardial infarction derives its name, naturally results in a decrease of the cardiac muscle's capabilities and, thus, decreased cardiac output. Decreased cardiac output triggers the body's compensatory mechanisms, placing elevated demands on the heart. The continuous level of mechanical strain on the heart resulting from its attempts to meet these elevated demands is thought to induce degenerative left ventricular remodeling, and ultimately alter the left ventricle's shape and structure. Cardiac function, in turn, is negatively

This thesis follows the style of Journal of Medical Devices.

impacted, resulting in systolic and diastolic dysfunction and further output reduction, creating a vicious downward cycle illustrated in Figure 1. Ultimately, this unceasing cycle causes congestive heart failure (CHF) to develop, the term used to describe insufficient blood output from the heart and corresponding reduced blood flow, a compensating increase in blood volume, and the resulting congestion of the veins and lungs, leading to further deterioration of the heart.

It should be noted that while, for very good reason, CAOs and MIs are well known, and were used here to illustrate the genesis of the heart failure cycle, they are by no means the only pathway followed by CHD or the sole means of initiating heart failure. Additionally, although CHD is one of the major culprits in heart failure, any disease that results in a continually depressed level of cardiac output can serve to begin the cycle.

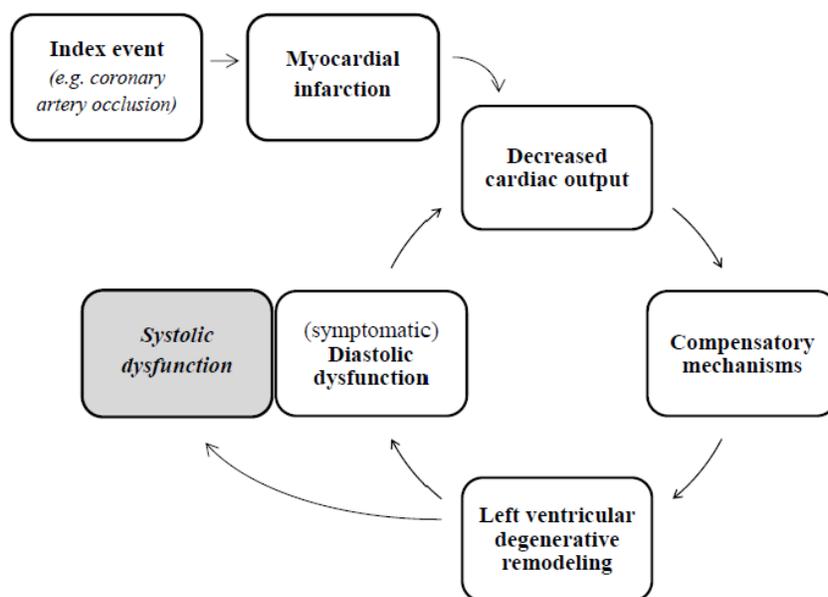


Fig. 1 Heart failure and degenerative remodeling cycle with example index event.

CHF is classified as either systolic dysfunction (failure of the ventricles to adequately eject blood) CHF or diastolic dysfunction CHF. Diastolic dysfunction—or failure of the ventricles to properly fill—is the sole cause of CHF for 40-60% [2] of the nearly 5 million Americans suffering from the disease [3], and is a contributing factor in all cases [2]. Current treatments for heart failure do not fully exploit the mechanics involved for either systolic or diastolic dysfunction, leaving a key component of disease and recovery unaddressed. A device developed to induce restorative remodeling by providing both active compression assistance and systolic support has been prototyped in John Criscione's cardiac mechanics lab at Texas A&M University. The device is intended to be implanted in a minimally invasive surgery—eliminating the need for open-heart surgery—adjusted during healing, and ultimately explanted once the heart is normal.

The latest conception of this device includes the addition of a flexible metal alloy frame that stores energy during systole and releases it during diastole, serving to strengthen diastolic recoil and address diastolic dysfunction. With systolic and diastolic components, the device provides support for the entire heart cycle, and is intended to induce restorative remodeling of the left ventricle by partially relieving the abnormal mechanical loads on the heart. By preventing further degenerative remodeling while reversing existing damage, the device would interrupt the malicious cycle described previously, and could be used in conjunction with therapies designed to treat the initial condition to eventually restore normal heart function. In what follows, we use the end-diastolic pressure-volume relationship (EDPVR), a known indicator of diastolic heart

function, to provide an initial proof of concept of the diastolic recoil component and the device's ability to provide biphasic modulation of the entire heart cycle.

CHAPTER II

BACKGROUND AND MOTIVATION

Physiological motivation

Initial adaptation

The example in the previous chapter in which coronary heart disease led to coronary artery occlusion and myocardial infarction illustrates one of the many possible index events or processes leading to CHF. In reality, any disease or condition that damages myocytes or negatively affects the contractile ability of the myocardium could serve as a factor leading to CHF. In addition to CHD, these risk factors include hypertension, diabetes mellitus, congenital heart disease, valvular heart disease, viral infections, infiltrative disease processes, or genetic cardiomyopathies [4, 5]. The members of this wide range of disorders share very little in common; some strike rapidly, others gradually; some primarily affect the cardiovascular system, while others primarily target other organs or regions of the body. Regardless of their diversity, one essential characteristic is shared by each of these varying disorders: suppressed heart function and the resulting reduction in cardiac output.

As cardiac output diminishes, compensatory cascades are activated in an attempt to restore proper perfusion and maintain homeostasis. Decreased stroke volume and cardiac output naturally reduces blood pressure, resulting in suppressed coronary and systemic perfusion. Insufficient systemic perfusion causes vasoconstriction and fluid

retention as the renin-angiotensin-aldosterone (RAA) pathway upregulates angiotensin II (the most potent human vasoconstrictor known), vasopressin and aldosterone (both of which increase fluid reabsorption in the kidneys) in an attempt to restore adequate blood flow [6, 7]. Vasoconstriction ameliorates hypotension, and elevated blood volume increases cardiac output via increased preload and afterload of the heart. Intensified sympathetic stimulation elevates norepinephrine levels, reinforcing vasoconstriction through increased binding to α receptors [8], and activating β_1 receptors responsible for upregulating calcium ion activity in the myocardium, effectively increasing contractile force and frequency [9]. Together, these responses serve as an acute adaptation to stabilize cardiac output.

Persistent maladaptation

In addition to their stabilizing effects, these adaptive mechanisms also bring about negative consequences. The adrenergic response, for example, one of the strongest of the body's compensatory cascades, also induces cardiomyocyte hypertrophy and apoptosis, myocyte damage, and fibroblast hyperplasia [4]. In the short term, these effects are overshadowed by the immediately beneficial effects previously described. If these adaptive processes persist, however, the good effects gradually are subdued by those harming the heart, and the response becomes *maladaptive* and cardiomyopathic. Increased peripheral resistance due to vasoconstriction combines with greater afterload to elevate the load on the left ventricle, exacerbating the reduced myocardial functionality caused by decreased coronary perfusion. As the increased workload of the

heart under suboptimal conditions continues, the myocardium begins to structurally change in an effort to reduce the abnormal stresses it is experiencing. The myocytes themselves lose myofilaments, adjust the relative expressions of heavy myosin chain types, alter cytoskeletal proteins, alter excitation contraction coupling, and become less responsive to adrenergic stimulation. The left ventricle particularly alters geometry, as it dilates and begins shifting from a prolate ellipsoid to a spherical shape, thinning its wall in the process [4].

The structural changes to the ventricles and myocardium, referred to as *degenerative (or maladaptive) remodeling*, further aggravate the problem. These alterations further increase the burdens on the heart, triggering intensified neurohormonal compensatory mechanisms, resulting in increased loads on the heart and escalated degenerative remodeling [4, 5]. For a time symptoms may be suppressed by the compensatory effects of the temporary adaptive mechanisms; however, as the cycle continues to progress unheeded and the heart becomes increasingly dysfunctional, symptoms begin to present [4].

As the cycle continues and the disease progresses, damage reaching throughout the body ensues. Continued dilation and distortion of the ventricle, for instance, affects the papillary muscles attached to the mitral valve via the chordae tendinae. Enlargement of the ventricles displaces the papillary muscles, distorting the mitral valves and resulting

in mitral regurgitation (MR) [10]. Mitral regurgitation further diminishes cardiac efficiency, compounding the already heightened demand on the heart.

Another common and important symptom is blood congestion in the pulmonary system, caused by increased pressure in the left ventricle from greater blood volume and degenerative remodeling-induced weakening. The lungs and airways become edematous, reducing compliance, obstructing airways, and reducing lung capacity: all factors contributing to magnify the work required to breathe and, thus, the demand for blood flow to the muscles responsible for breathing. The altered distribution of blood to critical organs particularly impacts the renal system; increased demand from respiratory muscles combines with high sympathetic nervous system tone to seriously reduce renal perfusion and lead to renal dysfunction [6].

Diastolic dysfunction

The impact of these various adaptations and maladaptations on systolic function is intuitive. As output decreases, directly affecting the myocardium through decreased coronary perfusion, and indirectly affecting the heart by various mechanisms designed to restore systemic perfusion, the heart is placed under increasing stresses. It is not hard to visualize the myocytes in the ventricles laboring under increased demands and decreased supplies.

What is much harder to comprehend is the effect of the various maladaptations on diastolic function. To the untrained enquirer, it would almost seem as if the increased pressures and loads would ensure excellent diastolic function by filling, if not overfilling, the ventricular chambers. Such is obviously not the case, however, when it is considered that diastolic dysfunction dominates approximately half of the heart failure cases and is evident to some extent in all cases. Diastolic dysfunction is described by Gaasch and Zile as implying “that the myofibrils do not rapidly or completely return to their resting length; the ventricle cannot accept blood at low pressures, and ventricular filling is slow or incomplete unless atrial pressure rises”[11].

As should be expected, a multitude of factors are known to influence diastolic dysfunction. Underlying mechanisms can affect the active relaxation process and the passive stiffness properties of the heart muscle. One common mechanism affecting the cardiomyocyte is altered calcium ion homeostasis – possibly partially resulting from increased sympathetic tone – in which amplified calcium activity increases contractility, extending myocardial relaxation time [12, 13].

Another mechanism affects the viscoelasticity of the cardiomyocytes. Titin is a cytoskeletal protein that acts as a viscoelastic spring to store energy during myocyte contraction and release it during relaxation. Abnormal titin isoforms and distribution, possibly coupled with elevated microtubule (another cytoskeletal component) density

and distribution, adversely affect diastolic recoil by behaving as a viscous load and increasing viscoelastic stiffness [12, 13].

Alteration of the extracellular matrix (ECM) is a third major mechanism. Interstitial fibrosis is often associated with hypertrophy, as cardiac fibroblasts, activated in part by the RAA system, increase fibrillar collagen deposition and eventually lead to increased myocardial stiffness and reduced reserve flow in the coronary arteries. Load and neurohumoral activation also increase collagen synthesis, in conjunction with a shift in the synthesis/degradation balance. While not thought to be an initial cause, excessive sympathetic innervations increasing heart rate may induce tachycardia, reducing myocyte relaxation time and exacerbating existing diastolic dysfunction [12, 13].

These are only a few of the partially understood mechanobiological factors underlying the onset and progression of diastolic dysfunction. Many more alterations have been identified and tentatively linked to diastolic dysfunction – shifts in the ADP/ATP ratio affecting the energetics of myocyte relaxation, effects of matrix metalloproteinases on collagen synthesis/degradation balance, or changes to the cyclic release of nitric oxide responsible for modulating myocardial relaxation and stiffness [13]. Regardless, from our sampling of the vast array of convoluted mechanisms controlling and impacting diastolic function we can gather that diastolic dysfunction is associated with degenerative remodeling of the left ventricle, particularly hypertrophy, and is likely caused, at least in part, by myocardial fibrosis and abnormal loads [14].

Current approaches

Almost as numerous as the mechanisms underlying heart failure are the approaches that have been developed to directly or indirectly address them. Pharmacological treatments, surgical therapies, and mechanical devices are constantly being proposed, improved, or abandoned as our understanding of the heart and the plethora of associated systems and processes is expanded. A number of relevant approaches are summarized in Figure 2.

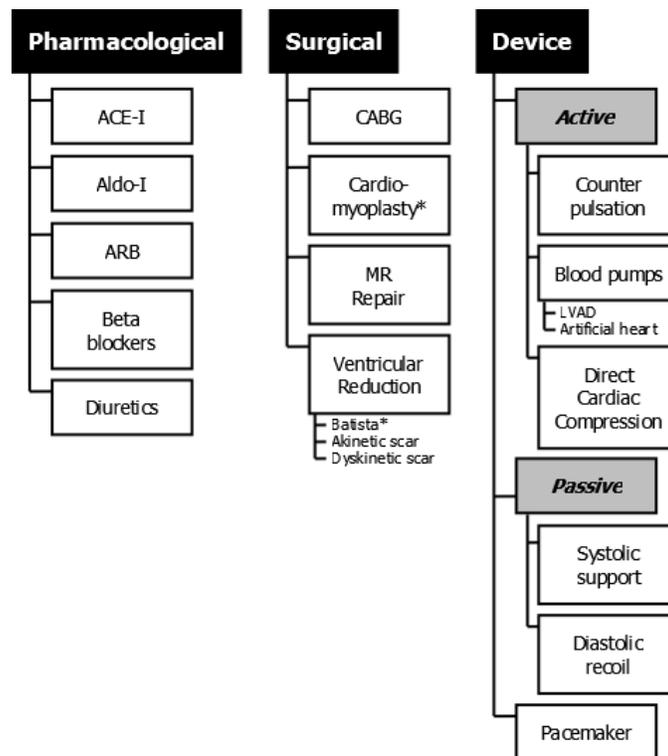


Fig. 2 Approaches to remediating heart failure.
 (* Denotes a largely obsolete approach)

Pharmacology

Pharmacological therapies are usually employed as the first line of defense against decreased cardiac function in an effort to interrupt the adverse neurohormonal cascades. Beta-blockers are used to reduce elevated sympathetic tone; angiotensin II receptor blockers (ARB), angiotensin converting enzyme (ACE-I) inhibitors, and aldosterone (Aldo-I) inhibitors to combat upregulation of the RAA system; and diuretics to reduce fluid retention. While these therapies, and others, have demonstrated a significant positive effect on morbidity and mortality, the extent to which they can retard disease progress is limited before the body begins desensitization to their actions and their side-effects begin proving detrimental [4, 5, 15-17]. Current understanding of the mechanisms involved indicates that the limitations of pharmacological therapies is strongly linked to their failure to halt or reverse adverse structural and mechanical changes that are stimulating maintenance and escalation of the problematic neurohormonal cascades.

Surgery

It is not surprising, then, that surgical techniques designed to amend underlying structural and mechanical problems have proliferated. Ventricular reduction surgeries encompass several techniques designed to restore the ideal size and shape of the left ventricle in an effort to reduce stress and dyssynchrony and improve myocardial contraction. The Batista procedure is one of the earlier attempts to restore cardiac function by surgically reshaping the left ventricle. Batista removed a section of

functional myocardium in the left ventricular free wall, returning the left ventricle to a more ellipsoid shape. Unfortunately, high failure rates and a failure to improve overall pump function led to an abandonment of this procedure by most hospitals [16, 18, 19].

Removal of dyskinetic scars (bulging regions of injured, dysfunctional tissue, often resulting from myocardial infarction), or aneurysmorrhaphy, has become widely accepted, and is reported to consistently improve ventricular shape and function. The resected area is often replaced with a patch in a technique called endoventricular patch plasty, or the 'Dor procedure'. Akinetic scars (regions of non-functioning tissue) are also removed using this approach, but the benefits are much more controversial, as CABG and/or other surgery is normally performed simultaneously, eliciting doubt as to the role akinetic scar resection had in positive results [10, 16, 18].

Dynamic cardiomyoplasty is an obsolete surgery in which the latissimus dorsi muscle is wrapped around the heart and stimulated in synchrony with it in an effort to provide systolic support. Although the technique was a failure in the sense that the skeletal muscle fatigued and was unable to maintain a significant level of systolic augmentation, it motivated the creation of an entire class of heart failure devices. During trials, it was noticed that, regardless of synchronized stimulation of the skeletal muscle, that diastolic properties were improved, sometimes also enhancing cardiac performance, leading Kass, et al to postulate that the longissimus dorsi was actually acting as an elastic girdle and passively constraining the ventricles [17, 20].

Coronary artery bypass graft (CABG) surgery is used for heart failure patients with significant coronary artery stenosis and ample viable myocardium. Although not directly addressing size or shape of the heart, CABG surgery can remove a problem triggering biochemical cascades – stenosis – and reverse left ventricular dilation, provided enough dysfunctional but still viable myocardium is present. Mitral regurgitation repair or replacement is another common surgery performed simultaneously with ventricular repair, alteration, or device implantation [10].

Devices

While providing valuable options for interrupting the destructive neurohormonal pathways and degenerative remodeling cycle, the surgeries just discussed have several disadvantages. The Dor procedure, for example, has a wide variability in its effectiveness due to the highly subjective nature of determining the amount of tissue to remove and the final shape and size of the left ventricle. Nearly all of the surgeries are major interventions that inherently carry a relatively high risk of mortality, and so are not undertaken lightly or immediately upon detection of remodeling and dysfunction. Neither do any of the surgeries directly address improvement of blood circulation, although several of the pharmacological therapies do – such as the vasodilators. Finally, any combination of pharmacological and surgical intervention requires the failing heart to have the capability of maintaining adequate heart function while healing. This leaves

several windows of opportunity for approaches that are minimally invasive, directly improve blood circulation, and/or support or replace heart function during healing.

Active assist

We have classified the most common classes of devices into two main groups: active and passive. Active assist devices provided pumping energy to the heart. This subclass contains one of the most widely used and well known group of heart devices – blood pumps. This ubiquity should not be surprising, considering that their functions range from augmentation to replacement of the heart’s primary responsibility of pumping blood. Counter-pulsation assist devices, or intra-aortic balloon pumps (IABP) are catheter based pumps placed into the descending aorta, inflated during diastole, and deflated at the beginning of systole. Providing mechanical support of circulation, they serve to increase coronary perfusion, balance myocardial oxygen supply and demand, and increase cardiac output and ejection fraction [6].

When IABPs fail to satisfactorily augment circulation, ventricular support is often employed as the next logical step. Left ventricular assist devices (LVAD) are employed to improve hemodynamic flow, although VADs can be classified as intra-, para-, and extracorporeal based on their implantability, and into pulsatile or continuous flow, and then further subdivided by the mechanism utilized. LVADs have an impressive history of improving circulation and heart function, serving as both bridges to transplant and permanent support [6, 10, 16]. LVADs were one of the first devices recognized to

induce restorative remodeling; hemodynamic unloading was found to reverse ventricular dilation [21] as well as molecular remodeling, upregulating gene expression related to myocardial activity and increasing contractile strength of cardiomyocytes [22]. Hetzer, et al demonstrated that structural improvements and restored cardiac function could persist after gradual weaning from the LVAD [23], leading to both occasional implementation as bridges to recovery and development of newer devices based on the knowledge accumulated from their widespread investigation and use. An 'extreme version' of VADs, implantable total artificial hearts have been attempted, and marginally successful, but are indicated only in the most desperate cases [17].

The Anstadt cup is a device for direct cardiac compression, and consists of a rigid shell lined with a flexible diaphragm which is only fixed at the rim and the apex. The diaphragm is then cyclically pressurized and physically compresses the heart, pumping blood and improving circulation while avoiding the problems associated with direct blood contact with the device. Despite its apparent advantages, few long term trials have been performed and the device has not gained widespread usage [24, 25].

Passive support

Passive support devices are fairly self-explanatory – a passive device constrains the heart, limiting growth and adverse remodeling, and possibly inducing restorative remodeling. The motivation for these devices stems from the discovery that despite its purpose of augmenting systolic function, cardiomyoplasty provided passive elastic

support for the heart [20, 26]. The most direct application is a synthetic wrap for the ventricles, such as Acorn Cardiovascular's™ CorCap™, which was demonstrated to prevent progressive LV dilation and dysfunction, to decrease sphericity, and to limit functional mitral regurgitation [10, 16, 27]. The Myosplint® was another device which attempted to passively alter ventricular shape, but through flexible cords bisecting the ventricle and reducing sphericity, wall stress and mitral valve distortion [17]. Unfortunately, the parent company, Myocor™, closed in 2008 and sold the rights to the device to a company with no plans for further development [28].

Diastolic recoil components are also passive, in the sense that they do not provide additional energy to the heart cycle; their purpose is to store energy during systole and return it to the heart during diastole to improve the decreased diastolic suction due to convective deceleration and diminished elastic recoil brought about by chamber remodeling [29]. The only currently known device is the ImCardia™ device developed by CorAssist Cardiovascular Ltd. This device basically consists of springs implanted in the ventricular wall to augment recoil, and has demonstrated an ability to induce restorative remodeling [30].

Cardiac resynchronization

Another therapy seeing increasing usage is cardiac resynchronization therapy (CRT), which uses a pacemaker to address electrical activation delays of the left ventricular free wall. This delay causes portions of the ventricle to act against other portions, sloshing

blood horizontally rather than properly ejecting it. CRT coordinates the septum and free wall by stimulating multiple loci – or *resynchronizing* the left ventricle. While not directly modulating mechanics, this approach has been shown to improve ventricular performance and result in reduction of left ventricular size [17].

CHAPTER III

PROPOSED SOLUTION

Ultimately, the ideal therapy or combination of therapies would not only interrupt, but also reverse the progress of the disease process by removing the mechanisms that underlie neurohormonal cascades mediating the stabilizing responses responsible for long-term maladaptation and degenerative remodeling. That is the aim of the proposed device.

A prototype device developed by Dr. John Criscione and others couples a passive support device with an active assist component. The device consists of a conical chamber that can be variably inflated with a fluid to reduce the size of the chamber's interior. This chamber fits snugly over the ventricles. A separate inflatable jacket fits around this device and is cyclically inflated in synchrony with systole. Unpublished preliminary preclinical trials established the potential of this device to improve systolic performance by addressing the mechanical loads triggering biochemical processes inducing structural remodeling through a dual action of both supporting the ventricles with the passive chamber, constraining them from overfilling, and augmenting contraction of the heart with the pulsatile component, increasing cardiac output.

The solution proposed consists of expanding this device's support activity to the entire heart cycle through the addition of a diastolic recoil component. A flexible alloy frame

that compresses during systole and acts to transfer energy to the beginning of diastole is inserted into the systolic support chamber, creating a negative pressure gradient in the left ventricle that assists relaxation and augments ventricular filling. Figure 3 pictures a prototype of this frame.

Altogether, this device aims to address many of the problems with previous technologies. By directly addressing the mechanics responsible for the neurohormonal pathways, it avoids the negative effects and reduced efficacy associated with prolonged pharmacological inhibition. A collapsible device that can be implanted in a minimally invasive surgery, it eradicates the need for the major surgeries that so negatively impact the survival of patients with advanced heart failure. The device is adjustable pre- and post-implantation, allowing the device to follow the shrinking size of the heart as proper size and shape are restored, maximizing efficacy and potential for final recovery. Because the device is implanted inside the pericardium, and so is secured to the



Fig. 3 Recoil frame made of shape memory alloy.

ventricles by the vacuum existing between the pericardium and the heart, the device is not physically secured to the heart and can be removed once ventricular function is adequately restored. Although some level of fibrosis is unavoidable, the multiple layers of the device should maintain the free movement of the heart by preventing the same surface from fibrosing to both the epicardium and pericardium.

The project described in the following chapters is designed to demonstrate the ability of the support components of this device to simultaneously: 1) shift the filling curve of a laboratory model of the ventricles towards lower volumes (constriction), and 2) induce negative pressures at low volumes, modeling the initial portion of the filling cycle. Figure 4 conceptually illustrates this response. Demonstrating this bi-phasic action would indicate that the device holds great promise for modulating pathological mechanical loads on the ventricles and inducing restorative remodeling.

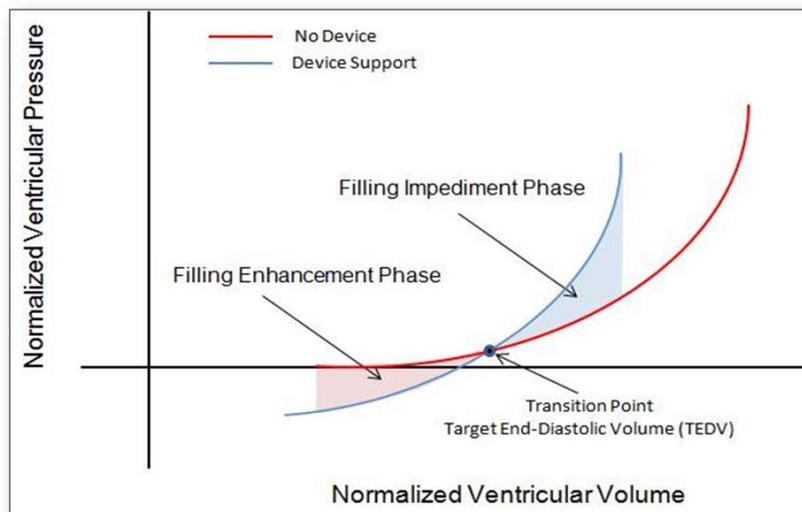


Fig. 4 Conceptual EDPVR illustrating proposed bi-phasic response.
 Courtesy of Michael Moreno.

CHAPTER IV

METHODS AND EXPERIMENTAL SETUP

As can be inferred from the research goals, the entire focus of the laboratory portion of the project was to obtain EDPVR's from a model heart alone and with the two support 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 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.

The experimental setup is conceptually very 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 5 and 6 illustrate this setup.

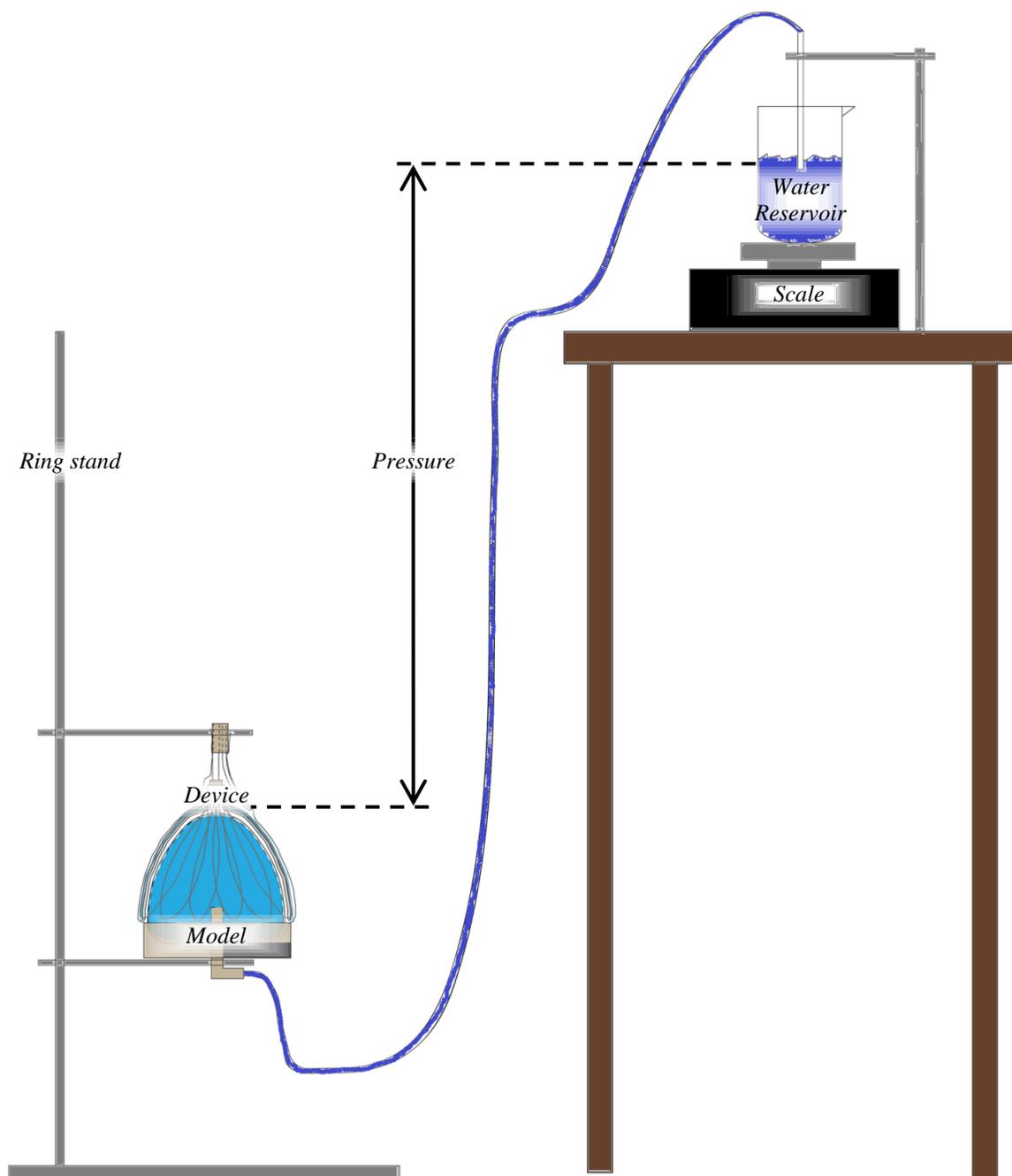


Fig. 5 Experimental setup.

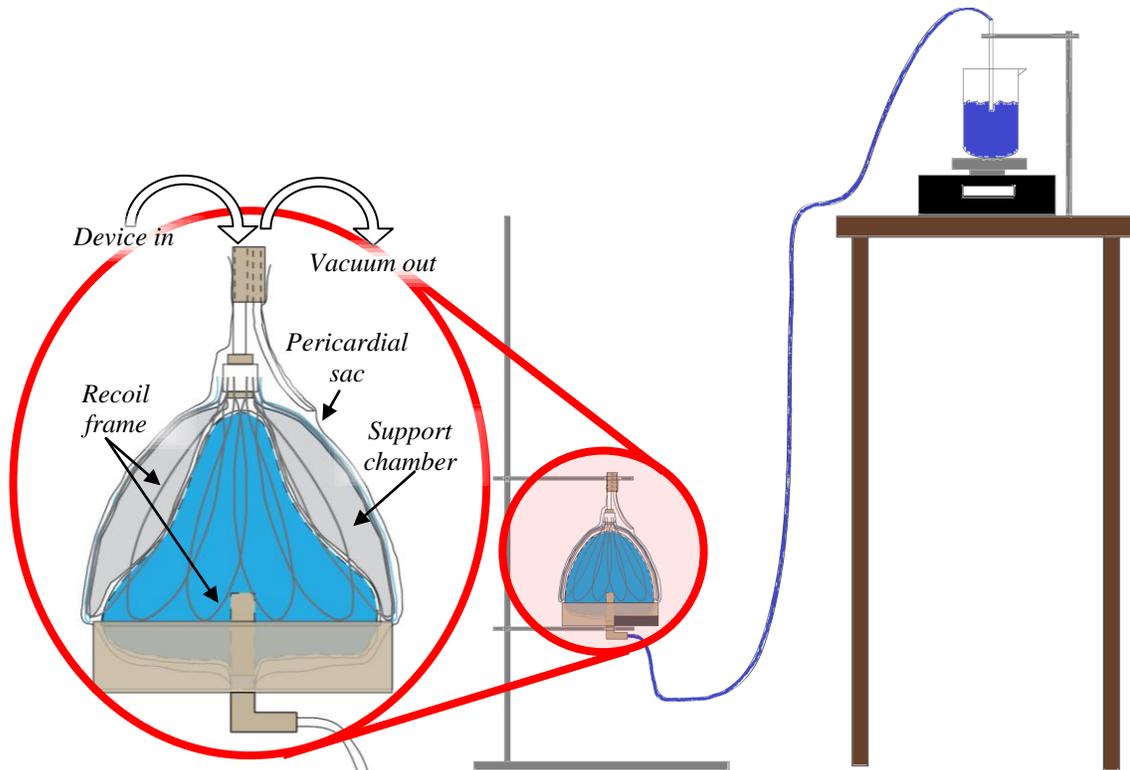


Fig. 6 Close-up illustration of heart model, pericardial sac model, and cutaway device with diastolic recoil frame and inflated passive support chamber.

Pressure readings were taken at 5 cmH₂O intervals. The heart has a normal left ventricular end-diastolic pressure of approximately 15 mmHg [31], or 20 cmH₂O; 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 without the

recoil component. Finally, the recoil component was inserted in the passive support device. The three 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. In this experimental setup, the pericardial sac was modeled by a vacuum drawn in a sac placed around the heart model and device.

CHAPTER V

RESULTS

Initial model

An initial heart model, which Figure 7 depicts, utilized an internal solid plug to mimic the heart's shape and a compliant bladder surrounding the plug to mimic the heart's compliance and volume range. This model yielded an EDPVR with a pressure range of about 16cmH₂O over a 350mL volume range, as the plot in Figure 7 illustrates. Employing the empty support and recoil device caused the EDPVR to shift to the left,

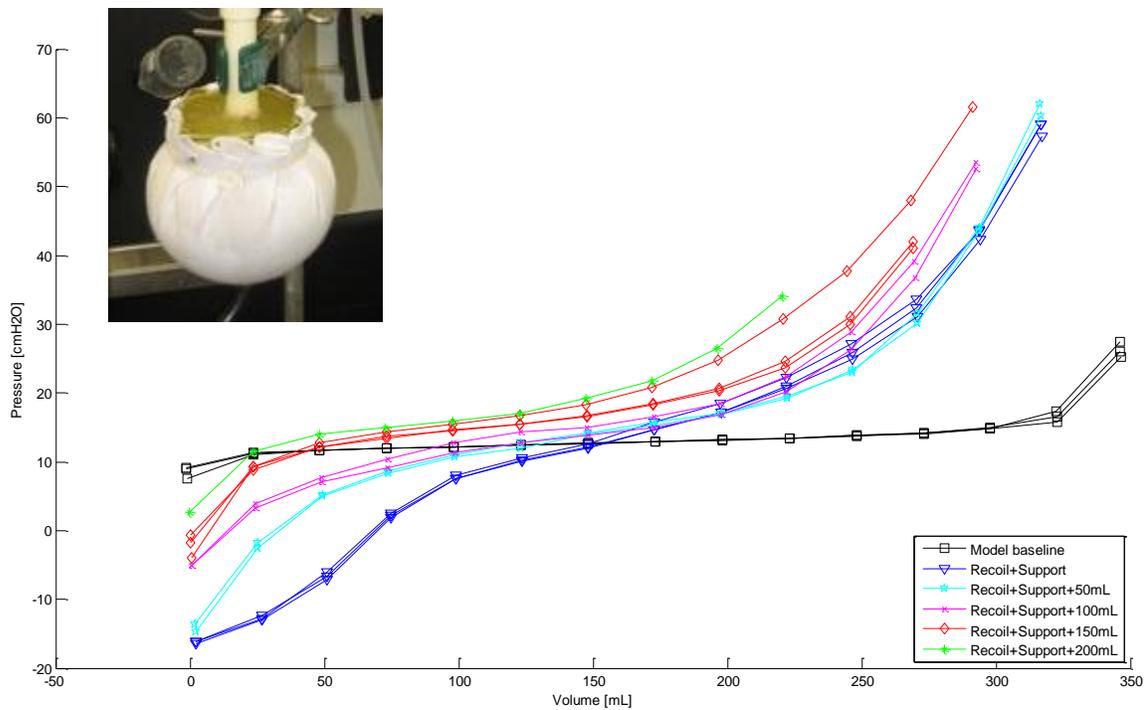


Fig. 7 EDPVR's and inset photograph (top left) of the initial heart model. Note the non-physiological spherical shape.

towards smaller volumes. Increasing the volume in the systolic support chamber from 50-100mL resulted in little response of the maximum heart volume. Increasing the volume in the support chamber to 150mL and 200mL caused further leftward shifts of the EDPVR, ultimately reducing the volume at 25cmH₂O by approximately 150mL. The device also modulated the small volume portion of the EDPVR, creating a maximum drop of about 25cmH₂O from the model baseline. This drop was reduced as the EDPVR was shifted leftward by the increased constraint of the support chamber. It should be noted that the device used was a previous version of the current design, in which the recoil frame was in a separate chamber surrounding the support chamber. This chamber required pressurization to keep the diastolic recoil frame taut, in these tests 160mL of air was used. Additionally, the data was taken using the original method described in the previous chapter, in which volume was altered and the resulting pressure change was recorded.

Current model

The first model was replaced because its shape distorted into a sphere as it was filled. The new model consisted of a flexible, non-elastic shell that modeled both the shape and compliance of the heart, shown in Figure 8. Figures 9 and 10 both contain baseline results of the new model, which show an EDPVR shape satisfactorily close to the ideal relationship.



Fig. 8 Current heart model.

Tests of the efficacy of the diastolic recoil component are contained in Figure 9. The support device used in this trial, when empty, was the same size as the model heart; therefore, no constraint was expected, allowing the diastolic recoil component alone to be tested. Additionally, in this trial the support chamber held only very low pressures, causing the only changes in volume between the unfilled and filled (20mL) support chamber to be at low pressures. The experimental method used was the second method described in the previous chapter, in which pressure was incremented and the corresponding volume response was recorded. Employment of the recoil device caused the beginning volume to increase by approximately 200mL.

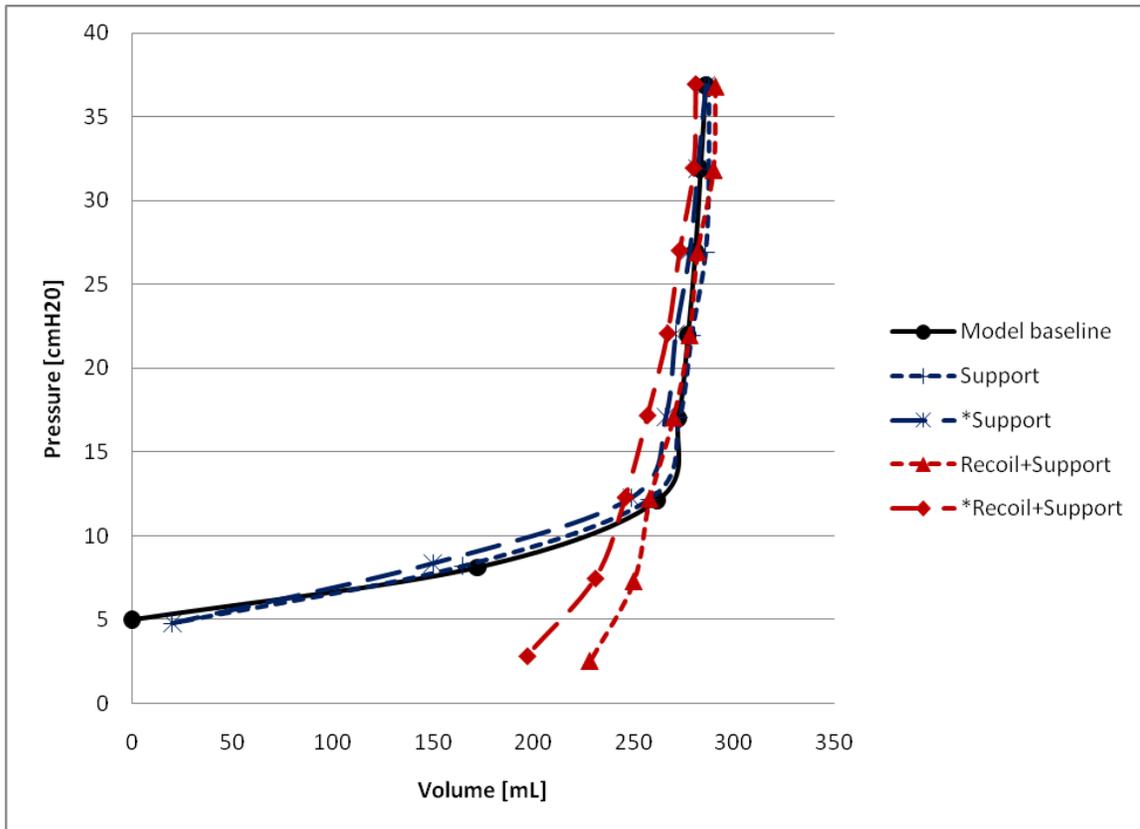


Fig. 9 EDPVR of recoil component. Trials denoted by a (*) were run with 20mL of air in the systolic support chamber.

The biphasic response of the combined support and recoil device is shown in Figure 10. In these trials, which used the same method as the previously described experiments, employment of the empty support and recoil device caused a small leftward shift of approximately 20mL. Filling the support chamber with 40mL of air further constrained the heart model, shifting the EDPVR leftward by about 100mL. The low volume side of the EDPVR was consistently shifted downward by approximately 8cmH₂O.

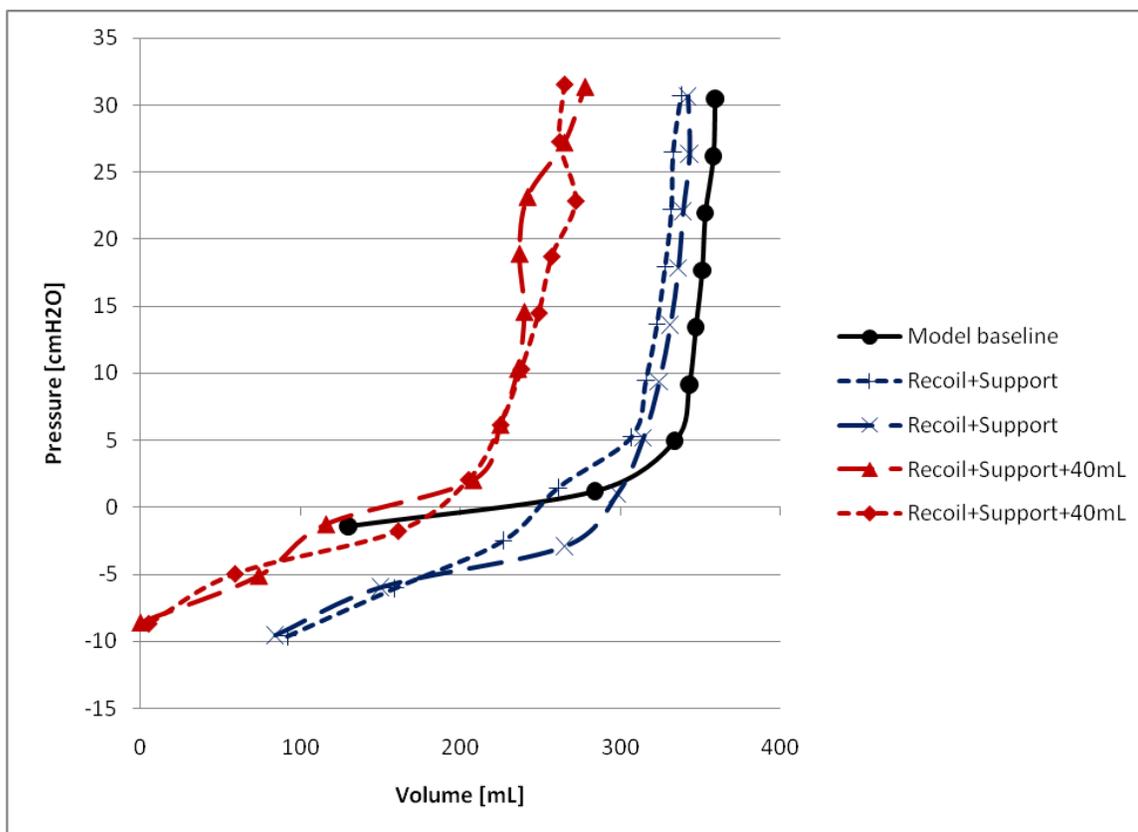


Fig. 10 EDPVR of biphasic modulation - support and recoil components.

CHAPTER VI

DISCUSSION

The results in the previous chapter clearly demonstrate the ability of the proposed combination support device to biphasically modulate the EDPVR of a model normal heart. The diastolic recoil frame, the particular interest of this study, consistently created negative pressures at low volumes in all heart models used. 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. The constraint of the passive systolic support device on maximum filling volumes was also shown 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.

The responses of the two models were very similar, although the maximum pressure obtained by the second model was higher because the non-elastic shell is rigid when pressurized, much like myocardium. The volume limit of the heart model varied somewhat (250-350mL) between models, and even between trials as the model was often repaired or adjusted, affecting its size slightly. Nevertheless, the shape of the EDPVR remained similar, and the responses to modulation by the device were consistent; therefore, although slight changes in model and prototype construction are

required to gain entirely consistent results, the goal of the bench-top study to provide a proof of the recoil augmentation concept was accomplished.

During the study, it became evident that the support chamber cannot be simply secured at the top and bottom of the device and then allowed to freely inflate. This configuration causes the chamber to fill unevenly, changing the shape of the cavity for the ventricles, and pushing the device off the ventricles. The presence of the diastolic recoil frame largely negates this problem by maintaining the shape of the device. This problem can be completely avoided by securing the inner wall to the outer wall along the arc length of the device at regular intervals, thereby forcing the inner chamber to maintain its shape during inflation.

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 of 25 cm, and had no fluid between the device, model and sac. Postoperatively, the vacuum in the pericardial sac is maintained mechanically until the entrance hole in the pericardial sac heals and it can maintain a vacuum on its own. The pericardial sac is lubricated, which may substantially change the shear stresses acting on the device and holding it in place. Additionally, substantial fibrosis is expected to occur. As discussed previously, the two layer design of the device allows 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.

CHAPTER VII

CONCLUSION

Heart failure is a disease with a plethora of initial causes that ultimately result in a progressive failure cycle of decreased cardiac output, prolonged compensatory mechanisms, degenerative remodeling, and dysfunction. The details of these steps vary based upon the cause of the disease, and the type of heart failure that develops, but the general cycle is the same. Complete therapies for heart failure must not only address the underlying cause initiating this cycle, but must interrupt the self-perpetuating cycle itself. The various pharmaceuticals, surgeries and devices each have their own purpose and results, and may be combined to create a complete therapy. Because of their ability to directly modulate the adverse mechanical loads the heart is experiencing and to indirectly affect the biochemical compensatory mechanisms, devices are an increasingly attractive and popular component of heart failure treatments.

This investigation studied *in vitro* the addition of a recoil component to a passive systolic support device. In a bench-top model of the ventricles, the device demonstrated an ability to provide bi-phasic modulation of the heart cycle. At low volumes, corresponding to beginning diastole, the diastolic recoil component releases energy stored during compression to augment ventricular filling. At high volumes, corresponding to end diastole, the systolic support component constrains the ventricles, preventing overfilling and allowing the myocardium to function more effectively. The

diastolic recoil component prevents exacerbation of diastolic dysfunction by the constraint of the systolic support component. The combined device provides passive support of the entire heart cycle. Together with an active component that was not studied in these trials, the three main classes of cardiac devices synergistically combine to assist and support the heart. This approach promises to induce restorative remodeling, increase cardiac output, reduce the compensatory response, and reduce diastolic and systolic dysfunction, reversing heart failure and leading to restoration of the heart.

Further preclinical studies are required to study the efficacy and safety of the device in live animal models and the effects of the pericardium, fibrosis, and right ventricular dampening. Results from these studies can then be used to refine the device prototype and lead into future clinical studies.

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