5-2022

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Recommended Citation

Ledbetter, Harley D., "Structural and Functional Myocardial Adaptations to Task-Specific Epidural Stimulation in Chronic Spinal Cord Injury." (2022). *Electronic Theses and Dissertations.* Paper 3872.
https://doi.org/10.18297/etd/3872

STRUCTURAL AND FUNCTIONAL MYOCARDIAL ADAPTATIONS TO TASK-SPECIFIC EPIDURAL STIMULATION IN CHRONIC SPINAL CORD INJURY

By

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B.S. University of Louisville 2019

A Thesis
Submitted to the faculty of the
College of Education and Human Development of the University of Louisville
in Partial Fulfilment of the Requirements
for the Degree of

Master of Science in Exercise Physiology

Department of Health & Sport Sciences
University of Louisville
Louisville, Kentucky

May 2022

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A Thesis Approved on

March 31, 2022

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ACKNOWLEDGEMENT

ABSTRACT

STRUCTURAL AND FUNCTIONAL MYOCARDIAL ADAPTATIONS TO TASK-SPECIFIC EPIDURAL STIMULATION IN CHRONIC SPINAL CORD INJURY

Harley D. Ledbetter

March 15, 2021

Cardiovascular disease is a leading cause of mortality, and this is especially true in individuals with spinal cord injury. Decreased systemic blood pressure leads to cardiac deconditioning, thought to be related to the increased cardiovascular morbidity and mortality in this population. This study investigates effects of myocardial loading from epidural stimulation in a group of individuals with spinal cord injury to understand how changes in preload and afterload could lead to beneficial myocardial remodeling. The study conducted echocardiograms to describe the myocardial changes after training with two different types of epidural stimulation intervention: one designed to facilitate movement (Voluntary) and one targeted to maintain systolic blood pressure within a target range of 110-120 mmHg (Cardiovascular). The study showed significant increases in SBP (31 ± 4mmHg) and DBP (17 ± 3mmHg) values with the use of Cardiovascular stimulation compared with Voluntary stimulation. Changes in blood pressure did not, however, lead to significant changes in cardiac structure or function outcomes.

iv

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The cardiovascular system is composed of the heart, lungs and the vasculature that delivers blood and nutrients to the rest of the body. At the center of this system, the force driving all functions is the heart.

The heart is comprised of a left and a right side, and each side has an atrium and a ventricle(Felner, 1990). The right atrium receives deoxygenated blood from the venous circulation, blood then flows into the right ventricle and is ejected to the pulmonary artery. In the lungs, blood is oxygenated and travels to the pulmonary vein where it drains into the left atrium. Blood drains into the left ventricle and it is then ejected into the aorta where it will be distributed to the systemic arterial blood vessels. Blood flows through heart in one direction and opening of the valves to allow blood to fill and be ejected from the ventricles is dependent on pressure differences between the chambers. Left ventricular contraction during systole will close the mitral valve, but the aortic valve will not open until the pressure generated by the left ventricle exceeds the pressure in the aorta(Felner, 1990). Similarly, during diastole, as the left ventricle expands and relaxes pressure will drop. Once pressure in the left atrium exceeds pressure in the left ventricle, the mitral valve will open and blood will fill the left ventricle again. Systemic blood pressure is thus a reflection of arterial resistance and the volume of blood entering the left ventricle right before systole(Felner, 1990). These two parameters equate to afterload (i.e., systemic pressure the heart must work against) and preload (i.e., the volume of blood at end-diastole), respectively, which determine how the heart adapts following exercise, altitude, and even injury. Since the cardiovascular system is a closed loop

1

system, changes in afterload and preload will result in immediate changes in function, which, if maintained, lead to changes in structure(Felner, 1990). For example, when the preload on the heart is increased, there is an increase in blood volume inside the left ventricle during diastole and diastolic function outcomes increase. In this condition, a larger volume of blood will need to be ejected from the left ventricle so force of contraction will need to increase as well, leading to increased systolic function outcomes. Long term exposure to these conditions would result in myocardial adaptations, like larger left ventricle dimensions during diastole and systole and increased wall thickness, that ultimately change how the heart functions long-term.

Cardiac Remodeling

The workloads that lead to either increases or decreases in cardiac output, heart rate and stoke volume can be described as preload and afterload. Preload is defined as the tension or load placed on the walls of the left ventricle at end-diastole, just before systole(Norton, 2001). The pressure that is exerted on the walls creates a stimulus that tells the myocardium how far it is stretched. If preload in the left ventricle is increased repeatedly eventually the heart adapts and stroke volume will increase up to a certain point. End-diastolic volume is a clinical surrogate for pre-load due to its similar effects on stroke volume and cardiac remodeling, and the fact that stretch of the sarcomeres cannot be determined without damaging cardiac tissue. Preload and end-diastolic volume correlate to diastolic function of the heart or the ability of the heart to relax and fill with blood. Impaired diastolic function occurs when elasticity of the left ventricle decreases,

leading to progressive decreases in end-diastolic volume and preload(Nagueh et al., 2016).

Afterload is described as the pressure or load that the heart must overcome to open the aortic valve and eject blood into the systemic circulation(Norton, 2001). Afterload is directly correlated to systolic function of the heart or the ability of the heart to contract(Chengode, 2016). If afterload is increased, then the myocardium must generate more force to eject blood. Central blood pressure or systemic vascular resistance are synonymous for afterload. Impaired systolic function from cardiac myocyte damage or atrophy is evident in progressive decreases in ejection fraction, as the left ventricle is progressively unable to generate enough force to overcome afterload. Based on these definitions it is easy to relate the workload of the myocardium to the volumes inside the left ventricle and systemic resistance in the cardiovascular system.

There are a multitude of factors that can lead to cardiovascular disease, but the most significant factor is blood pressure, specifically high blood pressure or hypertension(Hegde & Solomon, 2015; Kou et al., 2014; Mavrogeni, Bacopoulou, Markousis-Mavrogenis, Chrousos, & Charmandari, 2021; Nadruz, 2015). Chronic hypertension has been reported to cause CVD via changes of the left ventricle and is the most common reason for left ventricular hypertrophy (LVH). Hypertrophy of the chamber increases wall thickness as well as chamber dimensions that lead to cardiac dysfunction because the left ventricle becomes increasingly inefficient. The heart is like any other muscle in the body that requires oxygen through blood transport to operate. When there are increases in blood pressure the workload placed on the heart also increases so the heart must work harder to maintain ample blood flow throughout the

body. Is has been shown that when an increase stress on the left ventricle occurs, such as

hypertension, the heart adapts to maintain constant blood flow(Kenchaiah & Pfeffer,

2004). The heart does this by thickening its myocytes to increase force of contraction and

eject blood against an increasing afterload. Unfortunately, this increase in myocyte

thickness does not mean the heart is more efficient: when cardiac myocytes thicken, the

left ventricle dimension decreases, resulting in less blood volume at end-diastole and less

blood pumped out to the body with each cardiac cycle. This becomes a positive-feedback

loop: the heart to works harder to eject blood into the systemic circulation against an

increasing afterload, further thickening its myocytes and decreasing left ventricle

dimension, leading to eventual CVD and heart failure.

A similar but less common situation is also possible. When blood pressure is

chronically decreased the workload placed on the heart is also decreased and once again

the heart must adapt to these changes. In this case, rather than cardiac myocytes

thickening, they atrophy or get smaller. When atrophy of cardiac myocytes occurs, it is

seen to show decreases in cardiac output because the heart is now too weak to eject blood

out to the body (Perhonen, Zuckerman, & Levine, 2001). In the eventual case, the heart

can no longer sufficiently pump blood to the body and can go into hypovolemic shock.

The ideas of decreasing and increasing the workload of the heart have more

practical examples that occur in everyday life. There is a large amount of research that

has been conducted into the adaptive capabilities of the heart at high altitudes, during

exercise as well as during bed rest and most of the results conclude that short term

adaptations of cardiac function are due to volume changes. In high elevations research

has shown that there is an immediate decrease in oxygen supply to the body, so the heart

begins to work harder to meet the demand(Naeije, 2010). Short term this can cause shortness of breath, lightheadedness and in some cases nausea but these symptoms are not present very long since the heart begins to acclimate and adapt. The same study examining the prolonged effects on the cardiovascular system of high altitudes saw that though there was an increase in heart rate, a decrease in stroke volume, a decrease in volumes of the left and right ventricles, but no change in ejection fraction, indicating that cardiac contractility was preserved.

Individuals that are native to high altitudes also present with reduced left ventricle volumes with preserved ejection fraction, indicating these changes are an adaptation to long term exposure to hypoxia and decreases in peripheral arterial resistance or blood pressure rather than maladaptive remodeling that leads to cardiac dysfunction. In high altitude conditions similar results have been seen in individuals who live there and individuals who are studied there (Naeije, 2010). In these studies, the researchers concluded that with acute and prolonged exposure to higher altitudes there are decreases in left and right ventricular volumes, increased heart rate, decreased stroke volume, but increased systolic function outcomes like ejection fraction and contractility. They attributed the cardiac changes to afterload increases and hypovolemia in both populations. Afterload increases being an increase in blood pressure and hypovolemia being decreased blood volume in the heart. In this case, higher altitudes lead to decreased blood oxygen saturation which causes the myocardium to contract harder and faster in order to maintain a stable delivery of oxygen to peripheral tissues. Increased contractility due to afterload and oxygen demand causes myocyte hypertrophy and decreased chamber dimensions.

Exercise is a similar condition that causes increases in cardiac workload. Studies have shown that increases in heart rate and systolic blood pressure during exercise increase maximal cardiac output significantly (Evans, 1985; Khan, Safi, & Wood, 2016; Weiner & Baggish, 2012). During exercise, increased heart rate means less time for the heart to fill, but increased metabolic demand means the same or even a greater volume of oxygenated blood must still be delivered to the periphery. This demand is compensated for by increasing blood pressure to fill the ventricles quickly. Following exercise, the heart rate and blood pressure drop to below pre-exercising levels and allow for recovery.

With chronic exercise, cardiac myocytes will hypertrophy to allow for a higher capacity of work and result in remodeling of the cardiac chambers. When the blood pressure increases throughout the body so does central blood pressure, or the pressure behind the aortic valve the myocardium must overcome to eject blood into the aorta. Here, increased afterload forces the myocardium to generate more force in a shorter amount of time, leading to beneficial adaptations such as increases in chamber volume and hypertrophy of cardiac muscle. Since heart rate is also increasing under these conditions, decreasing time for left ventricle filling, there is not an increase in preload. A study from (Nishimura, Yamada, & Kawai, 1980), looked at left ventricular hypertrophy in professional bicyclists and age-matched controls and found that, though the left ventricle end-diastolic volume had not increased, the septal wall and posterior wall thickness increased significantly. It was attributed to the need for the myocardium to contract harder at higher intensities.

As stated earlier, the heart can adapt to decreased workload as well. This is evident in microgravity studies where individuals are chronically supine or in studies

done on astronauts (Gaffney et al., 1985; Perhonen et al., 2001). With less gravity acting

upon the heart while tilted at 6° for two weeks, decreases in cardiac output and stroke

volume were evident in non-injured males. This was because tilt led to decreases in

stroke volume, decreases in left ventricle end diastolic volume, and decreased blood

pressure (Gaffney et al., 1985; Guensch et al., 2019; Perhonen et al., 2001). These

changes were attributed to decreased venous return from being tilted rather than the lack

of activity from bed rest because ejection fraction was preserved, indicating no changes

in myocardial contractility: preload decreases while tilted 6° and blood pressure is also

decreased, thus less forceful contraction of the myocardium is required. In these studies,

chronically decreased workload ultimately led to decreased performance of the heart.

Physiological Changes Following Spinal Cord Injury

Spinal cord injury (SCI) leads to long-term disability and immobilization that

drastically alters an individual's life. Reports estimate that spinal cord injury affects

10,000 Americans annually, meaning there is great need for therapeutic interventions to

mitigate or prevent maladaptive adaptations after injury (Jacobs & Nash, 2004). In the

event of traumatic injury, disruption of neural transmission can cause a myriad of

functional and physiological adaptations to occur in cardiac myocytes. Hemodynamic

changes in the body influence the severity of myocardial adaptions. Changes in blood

pressure cause unloading of the heart, changes in stroke volume decrease chamber

dimension, while decreased physical activity and sympathetic activity result in a

multitude of blood flow and catecholamine changes.

A spinal cord injury is a chronic injury that is either a complete or incomplete lesion to the spinal cord. The severity of the lesion itself will have different results in each individual. With a complete lesion of the spinal cord there are no connection of nerves from the point of injury meaning no function below the level of injury is possible. While an incomplete lesion means that some of the nerves are still intact so some sensory or motor function may still be present. The level at which the lesion occurs will also produce different deficits throughout the body. Cervical level injuries produce the most physiological deficits since it is higher up on the spinal cord meaning more nerves and subsequently processing centers are disconnected from the nervous system. This means that the cardiovascular regulating center of the spinal cord is not able to send efferent signals to the brain to adjust heart rate and blood pressure. A thoracic level injury will produce also produce various deficits based on where in the thoracic region the lesion is. If the lesion is below the T6 level the cardiovascular regulating center is still connected to the functioning nervous system.

In humans and rats, chronic hypotension is a common secondary consequence of SCI and is known to cause structural adaptations in the heart. Studies report that following SCI in rodents there are significant decreases in BP as well as reductions in LV mass and LV end diastolic volume (Poormasjedi-Meibod et al., 2019; Squair et al., 2018); similar results are seen in humans as well (B. L. Ditterline et al., 2020; Sharif, Wainman, O'Leary, & Ditor, 2017). The reduction in blood pressure also leads to a decreased loading of the heart, and thus, hypovolemia can be seen in tandem. The effects of reduced blood volume in the heart have been shown to cause decreases in LV chamber dimension (Kessler et al., 1986). Decreases in chamber dimension also result in decreases

in end-diastolic volume (EDV), which is seen to cause a down and rightward shift in the frank-starling curve (Perhonen et al., 2001). Subsequently, in the same study, stroke volume (SV) is also decreased due impaired contractility. Studies also show LV mass was significantly decreased following SCI compared to non-injured (NI) individuals, which is a cardiac response to the decrease in blood pressure and volume (de Groot, van Dijk, Dijk, & Hopman, 2006).

As mentioned above, the Frank-Starling mechanism helps explain the force of contraction of the heart and uses SV and EDV to calculate the curve. Current research shows that following SCI, bed rest, and space flight, SV and EDV decrease (Kessler et al., 1986; Maggioni et al., 2012; Perhonen et al., 2001). Decreases in end-diastolic volume decrease preload, decreasing contractility and resulting in a smaller volume of blood ejected with each heartbeat. Chronic unloading ultimately decreases left ventricular dimension and decrease the tension on the heart. As the myocardium thickens LV dimension decreases, ultimately decreasing end-diastolic volume and stroke volume. Untreated increases in LV mass in these populations lead to decreased efficiency and contribute to overall cardiac dysfunction.

Decreases in sympathetic activity and physical activity following SCI decreases blood flow below the level of injury and a reduction in circulating neurotransmitters. Rodent models of SCI have demonstrated that decreased sympathetic activity is coupled with reductions in blood volume, leading to significant unloading of the heart that expectedly results in cardiac atrophy (Poormasjedi-Meibod et al., 2019). With decreased sympathetic activity following SCI there are less circulating plasma catecholamines, specifically epinephrine, norepinephrine, and dopamine, which modulate cardiovascular

activity. The nervous system must adapt, and begins to rely heavily on the renin-angiotensin-aldosterone system in order to control cardiovascular activity and maintain blood pressure (Schmid et al., 1998). This is also relevant in rats with SCI, where loss of sympathetic control decreases catecholamines and results in cardiac atrophy (Squair et al., 2018; Wakeno et al., 2006).

Effects of Aging and Level of Injury on Cardiac Outcomes

Since SCI is an injury to the nervous system and neuron wiring in the body is so intricate, different levels or locations of injury will result in different changes in physiology. In SCI populations, the highest cause for mortality is CVD, and the effects of aging on cardiac tissue are accelerated. It has been shown that chronic hypotension and skeletal muscle unloading can decrease pressure and volume inside the heart leading to cardiomyocyte atrophy. In SCI, it has been speculated that this atrophy is what leads to cardiac dysfunction and is the reason for decreased ejection fraction and diastolic filling velocities. This demonstrates the importance of deterring these changes and potentially reversing some of this remodeling to decrease the risk of developing CVD.

It is seen in normal individuals the advancement of aging causes increases in loading of the heart which in turn lead to increases in cardiac mass. With SCI the opposite has been seen: increasing age following injury results in greater decreases in LV mass and wall stress (Eysmann, Douglas, Katz, Sarkarati, & Wei, 1995). The increased effects of atrophy due to aging is of concern because it leads to decreased systolic and diastolic function and increases the risk that CVD will occur sooner. These individuals experience cardiovascular dysfunction younger than sedentary, NI individuals (Matos-

Souza et al., 2011). The most common levels of injury studied for cardiovascular outcomes are cervical, high thoracic, and low-mid thoracic, each offering different levels of dysfunction but commonly known that higher levels of injury result in the most dysfunction. It has been shown in multiple studies, both humans and rat models, that higher levels of injury result in significantly greater increases in cardiac atrophy, evident in LV mass and wall thickness compared with non-injured controls (Schmid et al., 1998; West, Mills, & Krassioukov, 2012). Significant differences in catecholamines have also been shown between levels of injury, where cervical levels release the least amount of epinephrine, norepinephrine and dopamine during exercise while the lower thoracic injuries had decreased but close to normal levels of the same catecholamines (Schmid et al., 1998). As mentioned earlier, this will change the sympathetic modulation of the heart causing different amounts of adaptation to occur. This is evidence for the increased cardiac atrophy that occurs in higher level injuries and how each level of injury can affect the cardiac outcomes.

<center>Reversal of Maladaptive Cardiac Remodeling</center>

As stated previously, many individuals suffer from CVD in the United States which leads to a plethora of research being done. Knowing that CVD results from cardiac remodeling there is lots of speculation and research into how to prevent or even reverse these changes. Some therapies that have been studied in obese individuals and hypertensive individuals has been the use of diet, exercise, and antihypertensive medication. In sedentary populations, both human and rats, studies look at how aerobic

<center>11</center>

exercise training could offer therapy. In SCI research the predominate method of therapy to restore cardiovascular function has been scES.

Changes in SV and EDV can result from adaptations in the cases of hypertension and obesity. Data collected in individuals with obesity and hypertension show increases in SV and LV mass that likely result from chronic increases in afterload that require the myocardium to thicken in order to generate more force (Aurigemma, de Simone, & Fitzgibbons, 2013; Kenchaiah & Pfeffer, 2004; Peterson et al., 2004). Concentric hypertrophy of the LV is seen in obese individuals, characterized by increases in LV mass as well as stroke volume and cardiac output. This occurs due to the increase metabolic demand of the cardiac tissue and the surrounding adipose tissue (Aurigemma et al., 2013). One study specifically noted that in young women with obesity, concentric hypertrophy was associated with decreases in systolic and diastolic function (Peterson et al., 2004). The results of these studies suggest that by increasing exercise and thus decreasing the cardiac output at rest for individuals, concentric hypertrophy can be reversed. This was seen to be affective across multiple studies (Arbab-Zadeh et al., 2014; Khan et al., 2016; Nishimura et al., 1980). In hypertensive populations the extreme and constant load on the heart increases LV mass. Research that has been done in animals has shown that mechanically returning BP to normal regresses the remodeling as do some antihypertensive drugs such as angiotensin-converting enzyme inhibitors, methyldopa, and guanethidine (Kenchaiah & Pfeffer, 2004). In another study the ability to generate pressure was returned in rats with SCI via the use of dobutamine (Squair et al., 2018). Studies in humans with hypertension have showed beneficial reductions in LV mass in response to therapies such as dietary restriction of sodium, antihypertensive medication,

and exercise for weight loss (Kenchaiah & Pfeffer, 2004), indicating the ability of the myocardium to reverse maladaptive remodeling by changing loading conditions.

However, challenges arise for these pharmacological therapies to be used in SCI due to severe immobility and chronic blood pressure instability. The benefit of aerobic exercise on cardiac remodeling is only effective when a large load can be placed on the heart and the individual is able to sustain exercise for more than 30 minutes (Gibbons, Stock, Andrews, Gall, & Shave, 2016). SCI individuals usually suffer from low blood pressure and random episodes of autonomic dysreflexia, or abnormally high blood pressure elicited by sensory stimuli. Therefore, the use of antihypertensive drugs tends to be ineffective due to the lack of chronic hypertension and presence of unstable blood pressure in individuals with SCI. Most commonly, the use of electrical stimulation to facilitate lower-limb movement has seen improvements to cardiac remodeling in SCI. In mice with SCI, vagal nerve stimulation was used to increase heart rate and help improve chronic heart failure by decreasing LV end-diastolic pressure. Following stimulation, the blood pressure was seen to decrease significantly compared to those that did not receive stimulation (Li et al., 2004).

Preliminary studies in electrical stimulation in humans have found positive cardiac adaptations in SCI populations. Functional electrical stimulation (FES) in humans helps increase lower limb activity to assist with rowing which can increase the workload of the heart and help individuals sustain that workload for 30 or more minutes. This study showed improvements in resting blood pressure of resting 98mmHg before training to 114mmHg following 6 months of FES training, leading the authors to speculate that beneficial cardiac remodeling occurred (Gibbons et al., 2016). Another study observed

the changes in cardiac structure following passive FES cycling and found increases in LV mass, internal septal thickness, posterior wall thickness, and LV diameter during diastole which is beneficial to reverse the atrophy that occurs in SCI (Nash et al., 1991). This shows that the structure of the heart was able to change following exercise training but not function. Robotic exoskeletons to facilitate body weight supported stepping have also been introduced and seen to cause improvements in cardiac remodeling by significantly increasing the ejection fraction, end diastolic volume, and end systolic volume of participants following a training intervention (Turiel et al., 2011). This demonstrated the ability of robotic bodyweight supported treadmill stepping to increase the function of the LV with no significant changes in structure reported.

There is current data that demonstrates spinal cord epidural stimulation (scES) can be used to mitigate the chronic hypotension that occurs following SCI, which could potentially reverse the structural and functional changes seen in individuals with SCI and be used slow the onset of CVD. Data collected at Frazier Rehabilitation Center utilizes lumbosacral scES. Immediate use of stimulation led to restoration of voluntary movement of the lower extremities and movement was not possible in the absence of stimulation (S. Harkema et al., 2011). The center primarily investigates the effects of scES on motor behaviors and autonomic function. Studies have demonstrated the ability for scES to facilitate voluntary movement of the lower extremities (Knikou, Angeli, Ferreira, & Harkema, 2009), facilitate overground standing and stepping (Rejc, Angeli, Bryant, & Harkema, 2017), and elicit sustained increases in systolic blood pressure (S. J. Harkema et al., 2018). Two smaller studies were conducted by the center, one was the use of cardiovascular scES to increase blood pressure without contraction of skeletal muscle. In

this study, individuals with SCI and chronic hypotension utilized scES to increase and sustain systolic blood pressure within 110-120 mmHg without activation of skeletal muscle, indicating the restoration of cardiovascular autonomic reflexes. The center also studied the use of voluntary scES which facilitated the voluntary flexion and extension of the trunk and lower extremities against gravity while in a supine or seated position. The data in this study shows activation of the lower extremity muscles, a greater force generated by the lower extremity muscles, and coordinated flexion and extension occurs only with scES and only while the individuals intend to move. Given that these task-specific interventions change motor function and hemodynamics below the level of injury, a pilot study was performed to investigate benefits of epidural stimulation on cardiac function. This study showed significant increases in LV mass, ejection fraction, SV, and left ventricular diameter during diastole (B. E. L. Ditterline et al., 2020). This indicates reversal of cardiac atrophy is possible in SCI. However, the results of the pilot study raise the question of which scES paradigm is most effective at reversing the cardiac atrophy that occurs.

The literature suggests that immediate changes in blood pressure, such as those that occur in scES targeted for cardiovascular function, should cause an increase in afterload of the heart as afterload directly relates to arterial blood pressure and cardiovascular scES does not cause skeletal muscle contraction(Norton, 2001). Conversely, coordinated movement of the trunk and lower limbs facilitated by voluntary scES should increase preload, as contraction of lower limb and trunk muscles facilitate venous return via the skeletal muscle pump(Norton, 2001; Sharif et al., 2017). So, we wanted to investigate cardiac effects of targeted epidural stimulation in order to better

understand the mechanism of how stimulation affects loading conditions through blood pressure and how that leads to changes in cardiac function. The goal was to use epidural stimulation to differentially change preload and afterload in individuals with spinal cord injury and see how the heart adapts in response.

RESEARCH METHODS

We wanted to investigate cardiac effects of targeted epidural stimulation in order to better understand the mechanism of how cardiac function can be changed after SCI by using stimulation to differentially affect preload and afterload and determine how the heart adapts in response.

Eight individuals with SCI were recruited for a task specific epidural stimulation interventional study (6 male and 2 female). Participants have high levels of injury at the cervical region and chronic duration of injury (1+ years). AIS levels varied from A to C. This thesis contributes to the current literature of echocardiography in SCI by offering an interventional study of epidural stimulation in SCI.

Study Aims

The first aim of the study is to compare the acute effects of cardiovascular scES with voluntary scES on blood pressure and heart rate in individuals with SCI. Manual blood pressure measurements from the brachial artery were used to determine effects of scES on blood pressure and heart rate. Three manual blood pressures (MBP) were measured from participants before scES and three MBP were measured during active scES. To establish how scES affects blood pressure, we compared MBP between individuals with SCI that used scES targeted to increase systolic blood pressure (cardiovascular scES) with those that used scES targeted only to facilitate voluntary movement (voluntary scES). Since cardiovascular scES is targeted to increase blood pressure without skeletal muscle activation (S. J. Harkema et al., 2018), and voluntary scES is targeted to facilitate lower extremity movement (Angeli, Edgerton, Gerasimenko,

& Harkema, 2014), we hypothesize cardiovascular scES will significantly increase systolic and diastolic blood pressure and decrease heart rate compared with voluntary scES.

The second aim of the study is to compare long-term cardiac effects of cardiovascular scES with voluntary scES. The participants underwent echocardiograms before and after training interventions to see if chronic changes in workload led to structural or functional changes of the myocardium. Increasing systolic blood pressure increases afterload, and we hypothesize individuals in the cardiovascular scES group will significantly improve their systolic function outcomes and significantly increase myocardial dimensions compared with voluntary scES(B. L. Ditterline et al., 2020). By contrast, By contrast, non-weight bearing exercise increases preload, and as such we hypothesize individuals in the voluntary scES group will significantly increase diastolic function outcomes compared with cardiovascular scES(Gibbons et al., 2016; Turiel et al., 2011).

Interventions

Eight individuals were randomly assigned toto 2 task-specific interventions: cardiovascular scES and voluntary scES.

Cardiovascular scES parameters were designed to maintain systolic blood pressure between 110 and 120 mmHg without the activation of skeletal muscle.

Participants with an epidural stimulator implanted onto their spinal cord are mapped to find stimulation parameters to control and sustain blood pressure in the normative range of ~120/80 without causing muscle activity. Once the participants were

mapped, they had their baseline echocardiogram performed. Next, they began training six hours a day for a total of 80 sessions. Training sessions involved daily use of cardiovascular scES to maintain systolic blood pressure within 110-120 mmHg. Systolic blood pressure was measured from the brachial artery with an ambulatory blood pressure monitor to ensure systolic blood pressure was maintained within the target range throughout the 6 hours. Following80 sessions they had their post intervention echocardiogram performed and compared to baseline.

Voluntary scES parameters were designed to facilitate the coordinated movement of the trunk and lower extremities:

- Participants with an epidural stimulator implanted onto their spinal cord are mapped for voluntary motor function of the trunk and lower extremities. Voluntary scES facilitates coordinated, intentional movement of the lower extremities and trunk. Once the participants were mapped, they had their baseline echocardiogram performed. Next, they began voluntary stimulation training six hours a session for a total of 80 sessions. During voluntary scES, individuals lay supine and would extend and flex the ankles, knees, and hips, or they would sit upright and move the trunk without support from their hands. Following the 80 sessions they had their post intervention echocardiogram performed and compared to baseline.
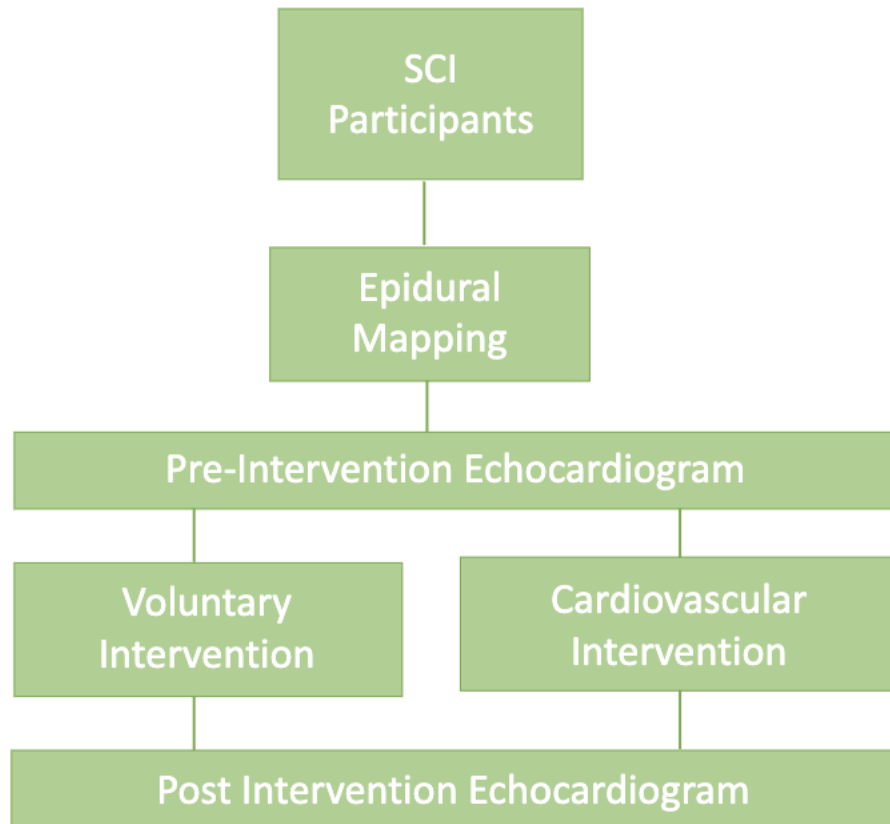
Figure 1: Intervention Design

Participants

8 individuals with SCI participated in this study as part of a larger efficacy clinical trial. To be enrolled in the larger clinical trial the participants needed be at least 18 years of ages, 2 years post injury and have cardiovascular dysfunction including presence of persistence resting low blood pressures and/or symptoms of autonomic dysreflexia, orthostatic hypotension, dysregulation in repones to postural changes or highly variable blood pressures in a 24hr period.

Data Acquisition

Aim 1: Brachial blood pressures were measured with a sphygmomanometer and stethoscope using the auscultatory method while the participant was seated in their personal wheelchair. A baseline heart rate and blood pressure were manually recorded without stimulation; three measurements were obtained with two to five minutes between measurements. Afterwards, scES was turned on and heart rate and blood pressure were measured again three times. Pre-stimulation blood pressure and heart rate were compared to blood pressure and heart rate values obtained during scES between the cardiovascular scES and voluntary scES groups.

Aim 2: Echocardiography is the method that is used to determine cardiac structure, systolic function, and diastolic function; all three of which have a different set of images and measurements that are set by the American Society of Echocardiography to determine normal and healthy values.

Cardiac structure is described in Table 1:

	Normative range
LVIDd	3.5-5.6 cm
LVIDs	2.0-4.0 cm
LV Mass	43-115 g/m^2
LVOTD	2.0-2.2 cm
LVSD	0.6-1.1 cm
LVPWD	0.6-1.1 cm
LVOT Area	2.3-2.6 cm^2

Table 1: Normative reference values for cardiac structure. LVIDd, left ventricle internal dimension during diastole; LVIDs, left ventricle internal diameter during systole; LV, left ventricle; LVOTD, left ventricle outflow tract diameter; LVSD, left ventricle septal wall dimension; LVPWD, left ventricle posterior wall dimension
*all normative values are referenced from the American Society of Echocardiograph

Systolic function outcomes are described in Table 2:

	Normative Range
EF	53-73%
CO	4.0-8.0 L/min

SV	60-100 mL
MPI	0.39±0.05
LVOT VTI	18-22 cm

Table 2: Normative reference values for systolic function. EF, ejection fraction; CO, cardiac output; SV, stroke volume; MPI, myocardial performance index; VTI, velocity time integral
*all normative values are referenced from the American Society of Echocardiography

Diastolic function outcomes are described in Table 3:

	Normative Range
EDV	59-120 mL
Peak E Wave Vel	42-115 cm/s
Peak A wave Vel	25-93 cm/s
MV Deceleration Time	140-240
IVRT	70-100

Table 3: Normative reference values for diastolic function EDV, end-diastolic volume; MV, mitral valve; IVRT, isovolumic relaxation time
*all normative values are referenced from the American Society of Echocardiography

Participants provided their own control as measurements are taken pre- and post-intervention. Effects of cardiovascular scES and voluntary scES on cardiac structure were assessed with echocardiography (figure 7). For the echocardiogram, research participants were positioned on an echocardiography table in the left-lateral decubitus position. This position is the best position for collecting ultrasound images of the heart. In this position the participant is laying supine on their left side with their arm in front of them. From here, the heart falls closer to the rib cage due to gravity, rotates to be more vertical to the ultrasound probe and the lungs are no longer in the way which can make image acquisition harder. There was a 3 lead ECG during procedure connected to participant as well as a blood pressure cuff. The use of the ECG was to ensure that the systolic and diastolic phases of the images are correct based on the cardiac cycle. The participant's BP was taken 5 -6 times throughout procedure to ensure that they are within their resting range. If the blood pressure was too high, data collection paused until the blood pressure returned to resting values. This is important since the values being collected for structure

and function are load depending meaning deviations of blood pressure values from the resting values would cause error. A variety of standard, non-invasive echocardiographic measurements, set by the American Society of Echocardiography was performed. Views were be taken in the parasternal long axis (PLAX) showing the left ventricle, the mitral valve and the aortic valve; the apical 4 chamber (A4C) showing the right and left atria and ventricles; the apical 2 chamber (A2C) showing just the left atria and ventricle; and from the apical 5 chamber (A5C) showing all four chambers of the heart plus the aorta. Five consecutive cardiac cycles were recorded at the end of a tidal expiration and the mean value was recorded for each parameter. Frame rate and imaging depth was kept constant during within-subject acquisition. Four consecutive cardiac cycles were recorded for off-line analysis. Echocardiogram images were recorded with state-of-the-art echocardiography equipment Philips X5-1 MHz xMATRIX array transducer on a Philips EPIQ 7 ultrasound system already owned by the center and collected by a registered diagnostic cardiac sonographer. Standard dimensions, wall thickness, chamber volumes, systolic and diastolic function parameters were be calculated using the Philips EPIQ 7 machine.

Data Analysis:

Participants served as their own control as measurements are taken pre- and post-intervention. Effects of cardiovascular scES and voluntary scES on cardiac structure were assessed with echocardiography (figure 7). For the echocardiogram, research participants were positioned on an echocardiography table in the left-lateral decubitus position. This position is the best position for collecting ultrasound images of the heart. In this position

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systolic and diastolic function parameters were be calculated using the Philips EPIQ 7 machine.

Statistical Analysis

Demographics and injury continuous characteristics were summarized with mean with standard deviation, median with 1st and 3rd quartiles, and maxima's (minimum and maximum). Categorical characteristics were summarized with frequency count and associated percentage. Blood pressure outcomes were compared between CV stim and VOL stim using linear mixed model with random intercept and slopes for stimulation (on/off) and repetition (3 repetitions). The model included independent variables stimulation type (CV, VOL), stimulation (on/off) and their interaction. Echo outcomes were compared with mixed linear models with random intercept. independent variables were stimulation type, time point, and their interaction. The model included Estimates were presented with least square means with associated standard errors. Linear contrasts were built on the interaction terms to evaluate within group changes and across group differences of those changes. All tests were 2 sided. The significance level was corrected with Bonferroni method (Bland & Altman, 1995) and set to 0.001 (= 0.05/36 outcomes).

RESULTS

This chapter shows the results of epidural stimulation changes in the myocardium on individuals with SCI. Each participant acted as their own control for this study therefore blood pressure and echo outcomes of structure and function can be averaged between each individual and reflect average changes in the SCI population. Demographics are described in Table 4 below. There were no significant demographic differences between groups. We can see that the mean age for the CV group is 33±7 years of age and 37±10 years of age for the Vol group. Half of the population were men and half of the population were women. Body surface area (BSA) was used for this study instead of body mass index (BMI) because BSA is more accurate to individuals and it takes into account the overall size of the individual which can heavily influence LV structural outcomes and functional outcome. No significant differences between demographic characteristics of the cardiovascular scES and voluntary scES groups

indicate significant differences found in Aim 1 and Aim 2 are unlikely to result from demographics of the population.

| | | Total n = 8 | Stimulation Type | | p-value |
			CV n = 4	VOL n = 4	
Age	Mean ± SD	35 ± 9	33 ± 7	37 ± 10	
	Median [Q1-Q3]	35[29-40]	31[28-38]	36[35-40]	0.6918
	Range, Min to Max	22 to 51	27 to 43	22 to 51	
Sex	Male, n (%)	4 (50%)	2 (50%)	2 (50%)	
	Female, n (%)	4 (50%)	2 (50%)	2 (50%)	0.7642
Height	Mean ± SD	172 ± 13	177 ± 9	168 ± 15	
	Median [Q1-Q3]	173[160-183]	178[169-184]	160[160-180]	0.1621
	Range, Min to Max	152 to 188	165 to 185	152 to 188	
Mass	Mean ± SD	73 ± 14	78 ± 17	69 ± 12	
	Median [Q1-Q3]	70[65-77]	71[69-88]	65[61-77]	0.3488
	Range, Min to Max	57 to 104	68 to 104	57 to 85	
Years since injury	Mean ± SD	8 ± 4	6 ± 3	9 ± 3	
	Median [Q1-Q3]	8[6-10]	6[4-9]	8[7-13]	0.7493
	Range, Min to Max	3 to 13	3 to 10	6 to 13	
AIS	A, n (%)	6 (67%)	2 (50%)	4 (80%)	
	B, n (%)	2 (22%)	1 (25%)	1 (20%)	0.7642
	C, n (%)	1 (11%)	1 (25%)	0 (0%)	
BSA	Mean ± SD	1.86 ± 0.23	1.95 ± 0.23	1.78 ± 0.23	
	Median [Q1-Q3]	1.86[1.63-2.03]	1.87[1.81-2.08]	1.63[1.62-2.03]	0.3488
	Range, Min to Max	1.59 to 2.28	1.77 to 2.28	1.59 to 2.05	

Table 4: Population Demographics

Aim 1 investigated effects of cardiovascular scES on blood pressure and heart rate compared with voluntary scES to better understand cardiac loading. In Table 5 we see that use of cardiovascular scES significantly increased systolic blood pressure with on overall change of 31±4mmHg compared with no scES. Similarly use of cardiovascular scES led to a significant increase in diastolic blood pressure with an overall increase of 17±3mmHg compared with no scES. Cardiovascular scES led to a significant decrease in heart rate of 9±3 BPM compared with Voluntary scES. Voluntary scES did not

significantly change systolic or diastolic blood pressure following the activation of the voluntary stimulation.

		CV				VOL				
		Stim OFF	Stim ON	Change [2]	p-value	Stim OFF	Stim ON	Change [1]	p-value	Effect Size
Blood Pressure	SBP, Mean ± SE	86 ± 4	116 ± 4	31 ± 4	<.0001	107 ± 4	111 ± 4	4 ± 4	0.3088	2.305
	DBP, Mean ± SE	54 ± 3	71 ± 3	17 ± 3	<.0001	62 ± 4	67 ± 4	5 ± 3	0.0984	1.44
	HR, Mean ± SE	74 ± 5	66 ± 5	-9 ± 3	0.012	74 ± 5	69 ± 5	-5 ± 3	0.1696	0.38

Table 5: Stimulation effects on BP and Heart Rate

One way to describe cardiac health is to look at the overall structure of the chambers, specifically in the left ventricle, because this chamber is the final stop for blood before existing to the body. Aim 2 investigated the long-term effects of voluntary and cardiovascular stimulation training on myocardial structure and function. Table 6 shows changes in LV structure outcomes from pre to post training. In this study we do not see any significant changes in structure following cardiovascular scES nor voluntary scES interventions. Structure of the LV thus remained stable from pre- to post-intervention.

	CV			Vol			
	Pre Train Mean ± SE	Post Train Mean ± SE	p-value	Pre Train Mean ± SE	Post Train Mean ± SE	p-value	Effect Size
LV mass (g)	166.83 ± 28.57	173.33 ± 28.57	0.6089	119.23 ± 28.57	112.08 ± 28.57	0.5745	0.4
LVIDd (cm)	4.61 ± 0.24	4.7 ± 0.24	0.6485	4.18 ± 0.24	4.18 ± 0.24	1	0.17
LVIDs (cm)	3.09 ± 0.14	3.1 ± 0.14	0.9628	2.73 ± 0.14	2.7 ± 0.14	0.8765	0.075
LVSD (cm)	0.94 ± 0.09	0.98 ± 0.09	0.6622	0.88 ± 0.09	0.88 ± 0.09	1	0.16
LVPWD (cm)	1.07 ± 0.08	1.05 ± 0.08	0.6107	0.9 ± 0.08	0.85 ± 0.08	0.134	0.425

Table 6: Changes in structural outcomes following interventional training in each group

Figure 2 illustrates LV chamber dimensions from pre- to post-intervention in the cardiovascular scES and voluntary scES groups. Here we can see that in both groups there were no significant differences in left ventricle mass. We did see some increases in LV mass of the CV group which shows that for these individuals there were increases in LV mass. The left ventricle diameter during diastole did not change significantly either but we do see some increase in 3 individuals in the voluntary group showing that preload was increasing for these individuals.
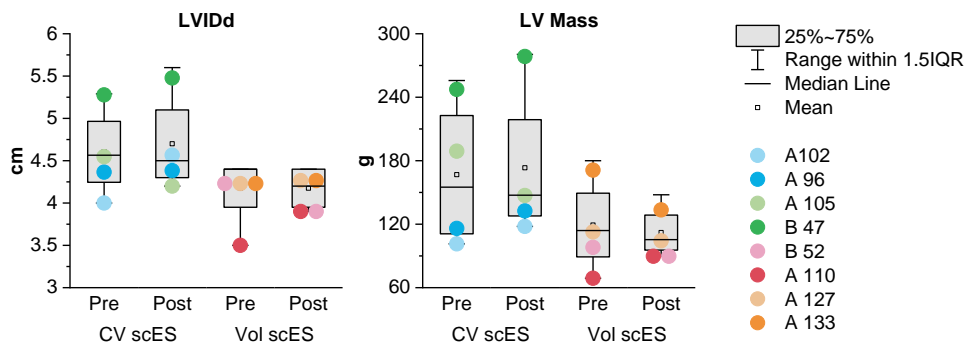

Figure 2: Changes in left ventricle dimensions following interventional training

Systolic function of the heart reflects strength and contractility of the myocardium. Table 7 shows changes in LV systolic function outcomes from pre to post

| | CV | | | Vol | | | |
| | Pre Train | Post Train | | Pre Train | Post Train | | |
	Mean ± SE	Mean ± SE	p-value	Mean ± SE	Mean ± SE	p-value	Effect Size
EDV (ml)	95.45 ±11.75	92.98 ±11.75	0.5478	73.95 ±11.75	78.58 ±11.75	0.279	0.645
ESV (ml)	37.73 ±4.53	34.88 ±4.53	0.3616	27.38 ±4.53	28.9 ±4.53	0.6162	0.535
EF (%)	60.03 ±1.09	62.63 ±1.09	0.1437	63.23 ±1.09	63.43 ±1.09	0.9013	0.55
CO (l/min)	4.48 ±0.46	5.43 ±0.46	0.1948	3.95 ±0.46	4.43 ±0.46	0.4931	0.26
Vmean (cm/s)	72.28 ±3.55	75.2 ±3.55	0.4983	61.5 ±3.55	62.13 ±3.55	0.8827	0.2
VTI (cm)	25.33 ±2.27	23.03 ±2.27	0.3259	20.7 ±2.27	20.25 ±2.27	0.8412	0.305

Table 7: Changes in systolic function following interventional training of the two groups

training. In this study we do not see any significant changes in systolic function following cardiovascular scES nor voluntary scES interventions. Systolic function of the LV thus remained stable from pre- to post-intervention.

Figure 3 illustrates LV systolic function outcomes from pre- to post-intervention in the cardiovascular scES and voluntary scES groups. We did not see significant changes in either group following training but in the CV group we can see that those individuals did have decreases in EDV and ESV which would normally be bad but their individual ejection fractions increased. that increase but their ejection fraction stayed virtually the same. This is another way that we can confirm preload is increasing for this group.
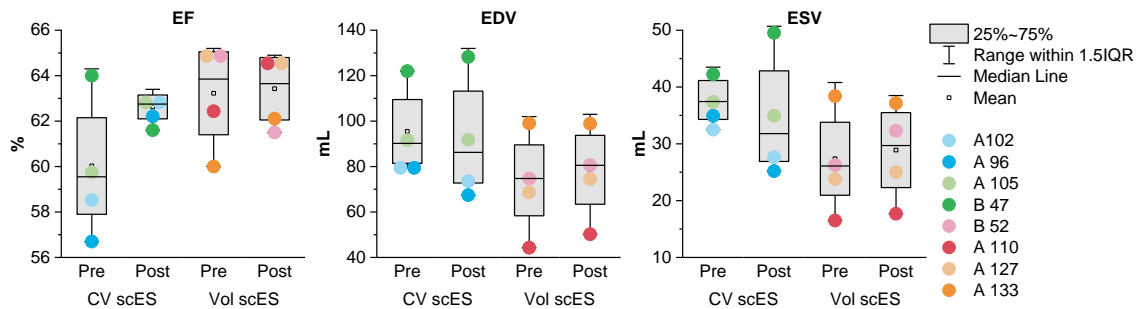

Figure 3: Left Ventricle Volumes and Systolic Function Outcomes

Table 8 shows changes in LV diastolic function outcomes from pre to post training. In this study we do not see any significant changes in diastolic function following cardiovascular scES nor voluntary scES interventions. Diastolic function of the LV thus remained stable from pre- to post-intervention.

	CV Pre Train Mean ± SE	CV Post Train Mean ± SE	p-value	Vol Pre Train Mean ± SE	Vol Post Train Mean ± SE	p-value	Effect Size
Mitral Valve							
E wave (cm/s)	82 ±11	75 ±11	0.39	83 ±11	82 ±11	0.93	0.29
A wave (cm/s)	46 ±5	55 ±5	0.10	47 ±5	47 ±5	0.86	**0.74**
Decel time (ms)	227 ±17	253 ±17	0.22	191 ±17	196 ±17	0.77	0.38
IVRT (ms)	91 ±5	83 ±5	0.17	81 ±5	75 ±5	0.28	0.135

Table 8: Changes in diastolic function following interventional training of the two groups

The diastolic filling pattern of the heart has two phases – early, or passive, filling and late, or active, filling. Figure 4 illustrates LV systolic function outcomes from pre- to post-intervention in the cardiovascular scES and voluntary scES groups. We did not see any significant changes to the E wave velocity/ early diastole, the A wave velocity/ late diastole, the mitral valve deceleration time and the isovolumic relaxation time (IVRT). However, IVRT is a subclinical indicator for diastolic dysfunction and the IVRT did decrease for nearly all individuals.
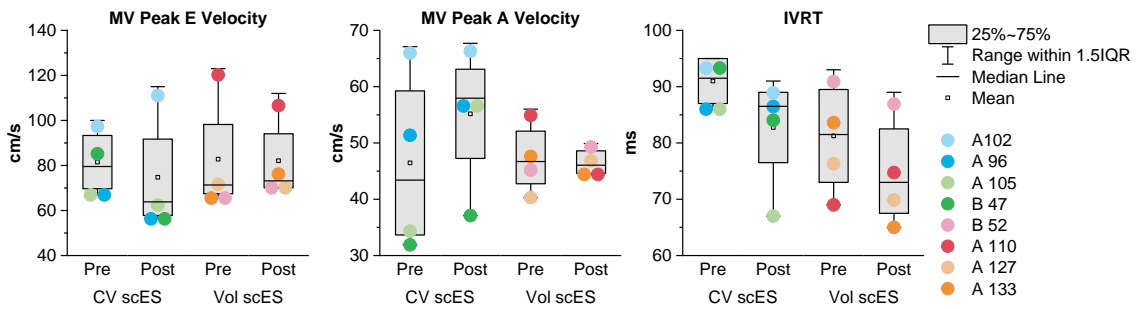

Figure 4: Left Ventricle Diastolic Outcomes

The overall health and performance of the heart can be described using a ratio of contraction time and relation times. This outcome is measured as the MPI which is a calculation of MCOT – LVET/ LVET. Table 9 shows the results of MPI following pre- and post-interventional training. In this study both groups do not show significant changes in MPI. The cardiovascular group did however show significant decreases in LVET ($\Delta 47.5\pm11.43$ ms) and MCOT ($\Delta 53.75\pm14.29$ ms). Likewise, MCOT decreased significantly in the cardiovascular scES group indicating more efficient relaxation.

| | CV | | | Vol | | | |
| | Pre Train | Post Train | | Pre Train | Post Train | | |
	Mean ± SE	Mean ± SE	p-value	Mean ± SE	Mean ± SE	p-value	Effect Size
MPI	0.29 ± 0.05	0.32 ± 0.05	.62	0.33 ± 0.05	0.38 ± 0.05	.36	0.17
MCOT (ms)	430 ± 25	376 ± 25	**.01**	432 ± 25	428 ± 25	.81	**1.25**
LVET (ms)	334 ± 21	286 ± 21	**.01**	325 ± 21	313 ± 21	.34	**1.11**

Table 9: Myocardial Performance Index changes following interventional training of the two groups

Figure 5 depicts the outcomes of MPI and the components of the value. We did indeed see significant decreases in the MCOT and LVET in the CV group which meant the timing of the heart is improving. Though the MPI did not significantly increase in either group there still was an increase which indicated that the individual's hearts were indeed becoming more efficient.
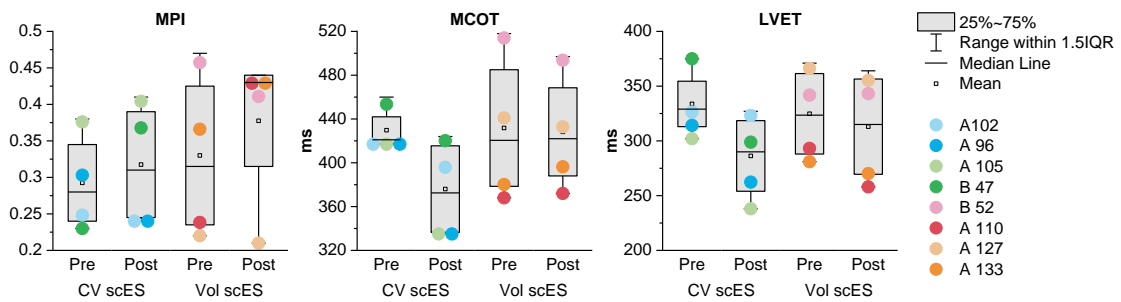

Figure 5: Myocardial Performance Outcomes

DISCUSSION & CONCLUSION

The current study reports that use of cardiovascular scES leads to significant increases in SBP and DBP, while the use of voluntary scES to facilitate trunk and lower extremity movement causes no significant changes in SBP or DBP. This supports the first hypothesis that cardiovascular scES significantly increases BP while voluntary scES does not. In the cardiovascular scES group there were also significant decreases in MCOT and LVET compared with voluntary scES. Despite significant increases to SBP and DBP (indicating increased afterload) in the cardiovascular scES group, as well as significant decreases to MCOT and LVET, there were no significant changes in cardiac structure or systolic function outcomes. Similarly, while lower extremity movement in the voluntary scES group led to changes in preload, there were no significant changes to diastolic function outcomes. This contradicts the second hypothesis of the study that following 80 sessions of CV training or Vol training there will be changes see in the cardiac myocyte structure and function. In the case of both time points, all values for both groups still fall into normative ranges for non-injured individuals.

Blood Pressure Measurements

In this study, the cardiovascular scES group did have significant increases in SBP and DBP of 31±4 mmHg and 17±3 mmHg, respectively, associated with a significant decrease in heart rate of 9±3 BPM. This differs from the Vol training group who only saw an average increase of 4±4 mmHg in SBP and 5±3 mmHg in DBP. The exact cause of increased blood pressure is not known but is speculated to result from sympathetic nervous system activation. These results do not show long term increases in SBP and

33

DBP but rather show the immediate effects of stimulation. In interesting point to note is that SBP and DBP changes are not due to increases in heart rate, as evident in the 9±3 BPM decrease in heart rate with the use of cardiovascular scES. This is of interest because, under exercising conditions, the heart rate would increase along with total peripheral resistance(Felner, 1990), resulting in increased SBP and DBP. This could mean that increases in sympathetic nervous system activity are not solely causing SBP and DBP to increase but are possibly also related to acute increases in volume of the ventricles or the contractility of the myocardium increasing volume in the systemic circulation.

Structural Measurements

The measurements taken for left ventricle structure reflect preload, afterload, and thickness of the myocardium. The dimensions and mass of the left ventricle allows us to look at LV hypertrophy. Increases in LV mass and decreases in LVIDd illustrate concentric hypertrophy, while increases in LV mass and LVIDd illustrate eccentric hypertrophy. In this study we do not see any significant changes in structure following cardiovascular scES nor voluntary scES interventions. Similarly, there are no significant differences between training groups. We did see some individual increases in LV mass in the cardiovascular scES group which moved those individuals closer to the middle of the healthy range even though the group changes were not significant. The left ventricle diameter during diastole did not change significantly, either, but we do see some increase in 3 individuals in the voluntary group indicating that preload could be increasing in these individuals.

The prevalence of CVD in the world reflects the importance of preventative therapies: cardiovascular disease leads to decreased wall thickness, decreased chamber dimension, and can lead to eventual systolic and diastolic dysfunction. Though the individuals of this study do not have manifest CVD, their outcome measures are decreased and on the low-end of normative values. These changes following injury can be attributed to a decrease in sympathetic activity, decreased physical activity and acute hypovolemia following injury. Studies have shown exercise, high altitudes and head down tilted bed rest can change the loading on the heart and result in structural changes of the myocardium (Evans, 1985; Gaffney et al., 1985; Naeije, 2010; Perhonen et al., 2001).

In SCI populations, research into how to prevent atrophy of the myocardium has used the modalities of FES-rowing, robotic stepping, and scES. These studies show prove that increasing physical activity can be beneficial to preventing further myocardial atrophy (Gibbons et al., 2016; S. Harkema et al., 2011; Turiel et al., 2011). The changes in these studies can be attributed by the increase in preload and afterload on the heart. The difference between this study and previous exercise-related SCI research is previous research that demonstrates significant changes to LV structure are subsequent to skeletal muscle loading and potential changes to metabolic activity. It is possible significant structural effects would be seen with a weight-bearing Voluntary scES group.

Systolic Function

Systolic function outcomes show the left ventricles ability to generate enough contractile force to overcome central blood pressure and supply blood to the rest of the

35

body. When systolic function begins to decline it is observed in decreases in ejection fraction, SV, CO, and VTI concurrent with increases in end-systolic volume(Douglas et al., 2019). The decreased values are due to the myocardium becoming too weak to force sufficient blood out of the heart. CO illustrates systolic function quantifying the amount of blood that the heart can eject each minute, calculated by multiplying the amount of blood ejected during a single cardiac cycle (stroke volume, or SV) by the heart rate. SV reflects the strength of each contraction by describing how much blood can be ejected in single cardiac cycle. There happens to be a sweet spot of how much blood is ejected in a cardiac cycle out of the total blood that was able to fill the ventricle (EDV) and what remains after contraction (ESV), this is known as the EF or ejection fraction. EDV and ESV or the amount of blood remaining at end-diastole and end-systole respectively, are the measurements that determine EF. EF and SV both illustrate the strength of the myocardium, and greater numbers indicate greater force of contraction. One interesting point to note is, though minimal stroke volume decreases were observed in both groups, the cardiovascular scES group demonstrated slight increases in cardiac output which were also associated with decreased heart rates. This could potentially be related to the slight increases in ejection fraction seen in the cardiovascular scES group. With an increased afterload, like that seen in the cardiovascular scES group, it is still beneficial that EF and CO remained the same because it demonstrates the heart could adapt to the immediate changes even if neither group showed significant changes from pre- to post-intervention.

In the SCI population systolic dysfunction is not apparent but decreased volumes inside the ventricles lead to the subsequent decreases in systolic function outcomes. One

study saw the compounded effects of scES in SCI individuals from CV stimulation to Vol stimulation to weight bearing standing stimulation and saw significant increases in SV and EF (B. E. L. Ditterline et al., 2020). The results of this study do not show similar results possibly due to differences in study design. Compounding interventions in the previous study allow the participants in the study to stim for longer and longer periods of time, increasing not only the hours of scES each day but the duration of each intervention. Additionally, the use of fully weight-bearing standing seen in the previous study would lead to not only activation of the skeletal muscle pump, as the lower extremities are forced to contract against gravity, but potentially long-term adaptation to changes in metabolic demand from skeletal muscle hypertrophy. In the current study, voluntary scES, being supported, is not as metabolically demanding as overground standing and could possibly account for why there were no significant changes.

Though the use of 6 hours of either Vol or CV stimulation is a majority of the day for SCI individuals, it is possible that in order to see long term significant changes in systolic function, the duration of stimulation and thus load on the heart would need to increase to a majority of the day.

Diastolic Function

Diastolic function reflects cardiac health and elasticity of the left ventricle by describing the filling volumes and pressures of the ventricles. Decreased diastolic function in CVD manifests as the inability of the LV to fill from pressure gradient between the LA and LV but instead relies on LA contraction to push blood into the ventricle(Lang et al., 2015). Similarly, the relaxation time is prolonged causing the LA to

37

continue to do most of the work during diastole leading to LA enlargement. SCI individuals are seen to have increased Peak A wave velocities that reflect the late diastolic workload of the LA. This is seen in the pre training time points of the current studies with decreased velocities compared with normative values. In early diastole, negative pressure in the LV acts as suction, passively drawing in blood from the LA due to this pressure gradient. In late diastole the LA contacts (the active portion) to finish ejecting all the blood out once the pressure gradient has minimized. The velocities of blood through the mitral valve during each phase describes phase the heart is relies on for diastolic filling. The IVRT quantifies how efficiently the heart is relaxes, too slowly and the MV opens late and too quickly the MV opens early. MV deceleration time is a measure of how long it takes for the pressure gradient in the LA and LV to equalize(Nagueh et al., 2016).

In the current study, preload increases would be apparent in diastolic function outcomes by increased Peak E wave velocity following intervention, but this was not seen. However, IVRT is a subclinical indicator for diastolic dysfunction, meaning IVRT will start to prolong and lengthen prior to development of manifest diastolic dysfunction that eventually lead to heart failure(Nagueh et al., 2016). This study showed IVRT did decrease for both groups, even though it was not significant between groups, which is still beneficial because that means that the time it takes for the myocardium to fully relax and be prepared to expand and suck in blood is decreased leading to a more efficient and synchronous diastolic phase in the LV.

Myocardial Performance Index

For myocardial performance index we wanted to look at the global function of the heart. The MPI is a ratio that describes the efficiency of the heart in a better way than just EF and CO because it considers both systolic and diastolic function(Abuomara, Hassan, Rashid, & Baraka, 2018). This measurement provides a subclinical performance value which has been set to have normative values by the ASE. We expected to see significant increases in the MPI and significant decreases in the MCOT and LVET for the cardiovascular scES group due to an increase in afterload, but no significant changes in the voluntary scES group. MCOT is the total time that is takes for the MV to close and then open. By subtracting the LVET the result becomes the IVRT and the isovolumic contraction time (IVCT) combined. Dividing this value by the LVET allows the diastolic timing of the heart compared to the systolic timing of the heart.

We did indeed see significant decreases in the MCOT and LVET in the cardiovascular scES group which means the synchrony of the heart is improving. Though the MPI did not significantly increase in either group there still was an increase which indicated that the individuals' hearts were indeed becoming more efficient. The greater decreases of MCOT and LVET in the cardiovascular scES group compared to the voluntary scES group could be attributed to the afterload increase in the CV group. Since the myocardium is having to work harder against a new pressure but maintain efficiency, the timing of the heart contracting and relaxing both improve compared with the myocardium in the voluntary scES group adapting only to increased preload.

Limitations

As it stands, comparative data in cardiac structure and function research done following human SCI is very limited, and even more so in interventional studies. The research found in this project fills in the deficit seen in the literature. The previous study done by our center showed increases in LV mass and EF which was much longer of an intervention than the current study. In that study, 80 sessions of training were added after each intervention and the linear model showed increases in those values. The use of scES to potentially facilitate cardiac remodeling, also creates more opportunities in future research investigating metabolic and hemodynamic effects of scES on cardiac function, among others. As we expected to see acute changes in blood pressure and heart rate caused by scES, this shows how differences in load can determine cardiac remodeling following SCI. No observations of quantifiable differences in cardiac remodeling between cardiovascular and voluntary scES demonstrated potentially due to the lack of a standing intervention or from compounding the interventions.

The SCI studies that looked at robotic stepping and FES cycling also saw significant changes in structure and functional outcome, but those studies also were longer than 6 months. Whereas our current study may have been limited by only 80 sessions of training taking roughly three months. The effect sizes of this study show that with a larger population, such as in the previous SCI studies, significant values may have been observed. The length of time that stimulation is on could also be increased such as in the case of our centers previous study the time of stimulation was close to 12 hours of stimulation per session with significant structural and functional outcomes noticed. The current mechanism of how epidural stimulation is increasing blood pressure or allowing

for voluntary movement is unknow, but speculation could lead us to think there is a sympathetic response to where the stimulation is increasing the contractility of the myocardium or decreasing the activation energy required to fire the muscle or these changes could just be due to increases in physical activity levels or something unrelated all together. These questions will hopefully be studied in the future.

The use of a homogenous group of SCI with respect to level and severity of injury in this study prevents generalization to the entire SCI population, though it does have the potential to apply to individuals with severe cardiovascular deficits (i.e., those that would be most at risk for development of CVD). Since SCI individuals spend most of their day seated upright and the echocardiograms in the study are taken in the supine position, the insight offered into the hemodynamics is slightly restricted as this isn't representative of their daily hemodynamics. This is a contribution to the current literature related to cardiac function in SCI, as it helps future research determine more appropriate interventions and fill in the sparse literature related to cardiac function in SCI.

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APPENDIX

Acronyms

A2C	Apical 2 Chamber
A3C	Apical 3 Chamber
A4C	Apical 4 Chamber
AIS	Abbreviated Injury Scale
CO	Cardiac Output
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EDV	End Diastolic Volume
EF	Ejection Fraction
ESV	End Systolic Volume
IVRT	Isovolumic Relaxation Time
LA	Left Artria
LV	Left Ventricle
LVH	Left Ventricle Hypertrophy
LVIDd	Left Ventricle Internal Diameter during Diastole
LVIDs	Left Ventricle Internal Diameter during Systole
LVOT	Left Ventricle Outflow Tract
LVOTD	Left Ventricle Outflow Tract Diameter

LVPWD	Left Ventricle Posterior Wall Dimension
LVSD	Left Ventricle Septal Wall Dimension
MBP	Manual Blood Pressure
MCOT	Mitral Valve Opening to Closure Time
MPI	Myocardial Performance Index
MV	Mitral Valve
PLAX	Parasternal Long Axis
RA	Right Atria
SBP	Systolic Blood Pressure
scES	Spinal Cord Epidural Stimulation
SCI	Spinal Cord Injury
SubC	Subcostal
SV	Stroke Volume
Vol	Voluntary
VTI	Velocity Time Integral

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