CARDIAC CONSEQUENCES AND EFFECTS OF EXERCISE INTERVENTIONS FOLLOWING SPINAL CORD INJURY IN HUMANS

by

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ABSTRACT

Individuals with chronic motor-complete spinal cord injury experience reduced cardiac function compared to non-injured individuals. Findings of cardiac deconditioning are not uncommon in this unique population and contribute to the increased risk of developing cardiovascular disease. In addition, disruption of descending autonomic pathways can cause abnormalities in cardiac function due to an intact parasympathetic (vagal) control and decreased sympathetic activity. The lack of research assessing cardiac outcomes during the first year following spinal cord injury limits the knowledge of time course changes and effective clinical therapies. Further investigation using different modalities of exercise as a therapeutic strategy are warranted, as the benefits of aerobic exercise to mitigate health complications associated with spinal cord injury have been well documented. In this thesis, I initially used a cross-sectional design assessing echocardiographic measures for left ventricular structure, systolic function, diastolic function, and mechanics, in individuals with sub-acute (i.e., three months) and chronic (i.e., > one year) cervical spinal cord injury to a non-injured control group. The results showed no differences between the non-injured group and the sub-acute group, though there was a decline in left ventricular indices for the chronic group. Upon further investigation of cardiac consequences, Holter monitoring showed the occurrences of arrhythmias up to six months post-injury in individuals with cervical and thoracic spinal cord injury. Next, echocardiography was used in a longitudinal design to track the changes in left ventricular structure, function, and mechanics within a six-month period for individuals with cervical and thoracolumbar injuries. The results show changes in left ventricular volumes and function occur only months after cervical injury. Finally, to explore cardiac rehabilitation through exercise strategies for this population, echocardiography was used to show that arm cycle ergometry may be more beneficial than body weight supported treadmill training for individuals with cervical or high-thoracic spinal cord injury to improve cardiac mechanics. Overall, the work presented in this thesis explored clinically relevant data that 1) increases our understanding of cardiac function in the months following a spinal cord injury and 2) investigates the efficacy of therapeutic exercise interventions to mitigate the long-term cardiac consequences of spinal cord injury.

LAY SUMMARY

Spinal cord injury damages the fragile nerve connection from brain to body and can alter the function of the heart. However, the timeline of when these changes occur are not well understood. Furthermore, strategies to improve the heart continue to be explored. We used ultrasound to investigate the differences in heart structure and function in people with short-term and long-term spinal cord injury, to people who are not injured, and how heart function is different for people with upper- or lower-level spinal cord injury. We explored the effect of exercise strategies to improve these devastating changes to the heart. My results show a short window of opportunity to best prevent these changes. Results of my thesis also show that heart size and function can change within months after injury. Finally, my studies found that active upper-body exercise may be better for the heart than passive leg movement after long-term injury.

PREFACE

Experimental chapters of this thesis (Chapters 5, 6, 7, and 8) were approved by the University of British Columbia clinical research ethics board (H12-02945, H13-03072, H21-01274). Data collection for experimental Chapter 6 was completed at the University of Copenhagen (Denmark), and this study was approved by The Health Sciences Research Committee of Denmark (region umbrella j.nr.2007-58-0015, secretariat 30-0392). The work is generally presented in the form presented for publication, therefore some repetition of introductory statements in chapters is anticipated. I would like to acknowledge and thank all of the participants (individuals with spinal cord injury and control group) for dedicating their time to these studies. I would like to acknowledge the contributions of these numerous collaborators in my research and outline my contributions for each of the projects that were conducted and included in my thesis here.

Chapter 4 is based on a manuscript currently under preparation for submission. As the lead author for this chapter, I was involved in conceptualization and interpretation of the data, I developed the search strategy with Dean Giustini (biomedical librarian and researcher, UBC), systematically performed the literature search and data extraction, synthesized the selected literature, wrote the initial drafts, and participated in the manuscript editing process. Nathan Hitchman performed the literature search and data extraction alongside me to ensure accuracy, and participated in the manuscript editing process. Dr. Tom Nightingale and Dr. Matthias Walter provided input on conceptualization, expert opinion throughout, and were involved in the editing process. Dr. Andrei Krassioukov is the corresponding author and was involved in conceptualization, results interpretation, and was the main author responsible for editing and reviewing.

Chapter 5 is based on a manuscript currently undergoing revisions following peer-review (Fossey MPM*, **Balthazaar SJT***, Squair JW, Williams AW, Poormasjedi-Meibod MS, Nightingale TE, Erskine E, Hayes B, Ahmadian M, Currie KD, Walter M, Krassioukov AV[#], West CR[#]. Spinal cord injury impairs cardiac function due to impaired bulbo-spinal sympathetic control); changes have been made for continuity and coherence in this thesis. The final

manuscript was a collaboration of clinical and pre-clinical studies between the laboratories of Dr. Andrei Krassioukov and Dr. Christopher West, respectively. For this chapter, I was responsible for conceptualization, participant recruitment, echocardiography data collection and analysis. I was responsible for the interpretation of all clinical data, initial drafting, final editing of the manuscript, and completed the final submitted work. Mary Fossey was responsible for the pre-clinical data collection, analysis, interpretation (not included in this chapter), drafting and editing of the manuscript, and completed the final submitted work. Dr. Alexandra Williams acquired the images for the control group, performed the clinical mechanics data analysis, provided expert opinion, and was involved in the editing process. Dr. Tom Nightingale was involved in conceptualization, provided expert opinion, and was involved in the review and editing process. Dr. Matthias Walter provided expert opinion, and was involved in the review and editing process. Dr. Katharine Currie was involved in the review and editing process. Dr. Andrei Krassioukov was involved in supervision, clinical data collection, interpretation of clinical data, drafting and final editing of the manuscript, and provided expert opinion. Dr. Christopher West was involved in supervision, pre-clinical data collection and interpretation, drafting and final editing of the manuscript, and provided expert opinion. I would like to acknowledge Dr. Guillermo Adrian Alanis for his assistance in recruiting the clinical control group. Dr. Jordan Squair, Dr. Malihe-Sadat Poormasjedi-Meibod, Brian Hayes, and Mehdi Amadian were involved in pre-clinical data aspects of the manuscript (not included in this chapter). Clinical data from this chapter was presented at the 2019 American Spinal Injury Association Annual Scientific Meeting (Honolulu, Hawaii, USA), winning a third-place presentation award.

Chapter 6 has been published and peer-reviewed in *The Journal of Spinal Cord Medicine* (**Balthazaar SJT**, Sengeløv M, Bartholdy K, Malmqvist L, Ballegaard M, Hansen B, Svendsen JH, Kruse A, Welling KL, Krassioukov AV, Biering-Sørensen F, Biering-Sørensen T. Cardiac arrhythmias six months following traumatic spinal cord injury. *J Spinal Cord Med* 2021). I was a visiting student at Copenhagen University Hospital for this secondary project. This project was not originally part of my PhD project. For this chapter, I initiated the collaboration of institutions on the study, performed data analysis, interpretation, and statistics. I drafted the initial manuscript, edited the manuscript for journal submission, and completed the final submitted

work. Dr. Morten Sengeløv, Dr. Kim Bartholdy, Dr. Lasse Malmqvist, Dr. Martin Ballegaard, Dr. Birgitte Hansen, Dr. Jesper Hastrup Svendsen, Dr. Anders Kruse, and Dr. Karen-Lise Welling were involved in data collection, interpretation, and editing of the manuscript. Dr. Andrei Krassioukov, Dr. Fin Biering-Sørensen, and Dr. Tor Biering-Sørensen were involved in supervision, data collection and interpretation, drafting and final editing of the manuscript, and provided expert opinion. This work was in collaboration with researchers and clinicians affiliated with the University of Copenhagen.

Chapter 7 is based on a manuscript currently under peer-review (**Balthazaar SJT***, Walter M*, Nightingale TE, Currie KD, West CR, Tsang TSM, Krassioukov AV. Temporal changes of cardiac structure, function, and mechanics during sub-acute cervical and thoracolumbar spinal cord injury in humans). For this chapter, I was responsible for conceptualization, participant recruitment, echocardiography data collection and interpretation, statistics, drafting, final editing, and completion of the submitted work. Dr. Matthias Walter was involved in the conceptualization, interpretation, drafting and final editing of the manuscript, and provided expert opinion. Dr. Tom Nightingale was involved in the conceptualization, interpretation, drafting and final editing of the manuscript, and provided expert opinion. Dr. Katharine Currie was involved in the interpretation and final editing of the manuscript, and provided expert opinion. Dr. Christopher West was involved in the interpretation and final editing of the manuscript, and provided expert opinion. Dr. Teresa Tsang was involved in the interpretation and final editing of the manuscript, and provided expert opinion. Dr. Andrei Krassioukov was involved in the supervision, clinical data collection, interpretation of clinical data, drafting and final editing of the manuscript, and provided expert opinion. I would like to acknowledge Nathan Hitchman for his assistance with data collection. Data from this chapter was presented at the 2021 International Collaboration On Repair Discoveries (ICORD) Annual Research Meeting (Vancouver, British Columbia, Canada), winning a top poster presentation award.

Chapter 8 will be submitted for publication (**Balthazaar SJT***, Nightingale TE*, Currie KD, Krassioukov AV. Effects of active arm-cycling versus passive leg exercise interventions on

left ventricular structure, function, and mechanics of individuals with chronic motor-complete spinal cord injury: An exploratory randomized clinical trial). This chapter is part of a larger, multi-centre, randomized control trial. For this chapter, I was involved in the participant training and data collection. I was responsible for echocardiography data collection and interpretation, and data analysis. I drafted the initial manuscript, edited the manuscript for journal submission, and completed final revision of the manuscript. Dr. Tom Nightingale was involved in participant training, data interpretation, analysis, statistics, drafting and final revision of the manuscript, and provided expert opinion. Dr. Katharine Currie was involved in the participant training, data collection, analysis, and final revision of the manuscript. Dr. Andrei Krassioukov was involved in the supervision, clinical data collection, interpretation of clinical data, drafting and final editing of the manuscript, and provided expert opinion. I would like to acknowledge Abdullah Alrashidi for his time and assistance with the participant data, training, and recruitment in this part of the chapter. This trial is registered with ClinicalTrials.gov (NCT0178977). Data from this chapter has been nominated for an award-winning presentation at the International Spinal Cord Society (ISCoS) Annual Scientific Meeting 2021 (Virtual).

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LIST OF ABBREVIATIONS

2D	two-dimensional
A	atrial diastolic filling velocity
A’	atrial diastolic tissue velocity
ABT	activity-based therapy
ACET	arm cycle ergometry training
AD	autonomic dysreflexia
AIS	American Spinal Injury Association impairment scale
ANS	autonomic nervous system
ASIA	American Spinal Injury Association
B-mode	brightness mode
BMI	body mass index
BSA	body surface area
BWSTT	body weight supported treadmill training
CN	cranial nerve
CNS	central nervous system
CON	control
CVD	cardiovascular disease
DBP	diastolic blood pressure
E	early diastolic filling velocity
E’	early diastolic tissue velocity
EDV	end-diastolic volume
EF	ejection fraction

ESV	end-systolic volume
HR	heart rate
IQR	interquartile range
ISNCSCI	international standards for neurological classification of spinal cord injury
IVS	intraventricular septal wall thickness
LV	left ventricle
LVIDd	left ventricular internal diameter during diastole
LVIDs	left ventricular internal diameter during systole
MAP	mean arterial pressure
OH	orthostatic hypotension
PWT	posterior wall thickness
Q	cardiac output
S’	systolic tissue velocity
SBP	systolic blood pressure
SCI	spinal cord injury
SV	stroke volume
STE	speckle tracking echocardiography
UEMS	upper extremity motor score

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DEDICATION

THE BALTHAZAAR FAMILY

&

THE DE LIMA FAMILY

CHAPTER 1. BACKGROUND

1.1 Introduction

Spinal cord injury (SCI) is a severe neurological disorder commonly known to result in motor and sensory deficits (i.e., paralysis)[1] but also a myriad of autonomic dysfunctions (i.e., cardiovascular consequences, sexual functions, urinary tract/bowel impairments).[2] In fact, people with SCI consider these disturbances in the autonomic nervous system even more devastating than paralysis.[3] Individuals with SCI develop cardiovascular disease (CVD) at an increased pace, with a greater rate of occurrence and an earlier onset compared to the non-injured population.[2,4] Studies have demonstrated that this increased risk is more prevalent in individuals with more severe and more rostral neurological levels of injury (NLI).[5,6] Both low levels of physical activity[7] and profound blood pressure (BP) instability,[8] commonly experienced by individuals with injuries at or above the sixth thoracic level,[9] likely explains this heightened risk.

Relative to the cardiovascular system, the two major automatic nervous system branches are the parasympathetic nervous system and the sympathetic nervous system.[10] The parasympathetic neurons originate from the cranial and sacral nerves. Cranial nerves do not communicate with the spinal cord, therefore following SCI, vagal regulation of the heart remains intact.[11] Sympathetic nervous outflow emerges from the T1-L2 segments into the sympathetic chain ganglia.[12] Cervical and high thoracic SCI (at or above T6) are associated with diminished supraspinal control over the heart and splanchnic blood vessels,[13] which are both necessary for effective cardiovascular regulation.[14]

The autonomic dysfunction caused by diminished supraspinal control, bring about consequences of low resting BP, low BP during an orthostatic challenge, dramatic bursts of increased BP (i.e., autonomic dysreflexia).[11] Unfortunately, autonomic dysreflexia (AD) and

orthostatic hypotension (OH) occur regularly in individuals with SCI, affecting up to 90%[15] and 74%[16] of individuals above the sixth thoracic level, respectively. The resulting cardiovascular dysfunction[17] can be accompanied by bradycardia and splanchnic venous pooling,[11] hence affecting the blood redistribution from the lower limbs and splanchnic area.[18] Combined with the reduced venous muscle pump activity below the lesion,[19] the compromised venous return and cardiac output (Q), ultimately contribute to cardiac atrophy.[20]

To mitigate this cardiac atrophy, exercise training may increase volume loading by stimulating the heart's ability to pump blood to the working muscles.[21] Increasing left ventricular (LV) end diastolic volume (EDV) can result in cardiac muscle fiber lengthening, which increases contraction force.[22] EDV will increase stroke volume (SV) through the Frank-Starling mechanism.[23] Increasing central cardiovascular adaptations are thought to be more successful with the recruitment of larger muscle groups hence creating higher levels of Q.[21] Therefore, central adaptations from training might be a more preferred method compared to peripheral adaptations, to reduce the risk of CVD and improve the capacity of the heart to supply oxygen to functioning tissues.[24]

CVD following SCI has become more prevalent today, as the acute management and rehabilitation for individuals with SCI has evolved. This chapter aims to provide a contemporary review of the epidemiology of SCI, the autonomic influence on the cardiovascular system, the cardiovascular consequences following SCI, the impact of exercise on the heart, and the potential benefits exercise may have on the SCI population. This information will serve as a frame of reference for this thesis.

1.2 Overview

1.2.1 Spinal Cord Anatomy

The spinal cord is the connection from the brain to the body, projecting through the foramen magnum into the vertebral canal, beginning at the caudal end of the medulla and terminating at the first or second lumbar vertebrae. The spinal cord is a cylinder of nerve tissue made up of white and gray matter. The spinal nerve is comprised of motor and sensory nerve fibers that travel to and from various areas in the body.[25] Each segment innervates a region of skin providing peripheral nerve fibres arising from a single dorsal root ganglion called dermatomes. In clinical evaluation of injury, dermatomes can be traced on the surface of the skin, and lack of sensation in a dermatome can signify the extent of spinal cord damage.[26]

There are 31 pairs of nerves leaving the spinal cord, which are divided into 12 thoracic, 8 cervical, 5 sacral, 5 lumbar and 1 coccygeal nerves in the human body. The spinal cord transmits sensory information from the body to the central nervous system (i.e., afferent fibres). Motor neurons in the ventral horn carry axons into the body to innervate skeletal and smooth muscles (i.e., efferent fibres), that are responsible for voluntary and involuntary mechanisms, respectively (**Figure 1-1**).[27]

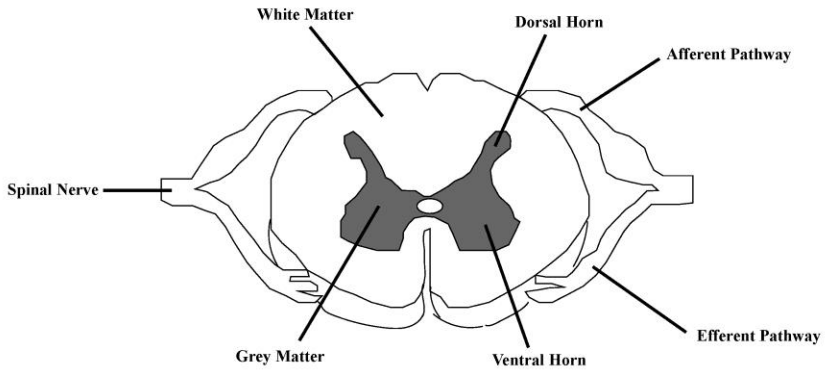


Figure 1-1. Cross-sectional schematic diagram of the spinal cord
The diagram highlights tissue regions and pathways.

1.2.2 Incidence, Prevalence, and Characteristics of Spinal Cord Injury

SCI is a rare and debilitating condition, with more than 27 million people worldwide living with a chronic disability following injury,[28] owing 90% of these cases to traumatic causes. According to estimates, the annual global incidence of traumatic SCI varies from 9 to 216 cases per million people.[29] Specifically, incidence rates of SCI in developed countries range from 13 to 163 per million people while the rates in non-developed countries vary from 13 to 220 per million people,[30] with cervical SCI accounting for 41.6% to 76.0% of all SCI.[31] Males between the ages of 28 to 35 years old are one of the top demographic groups most likely to suffer an injury.[32] Falls and motor vehicle accidents are the most common causes of SCI worldwide.[30]

1.2.3 Incidence in Canada

In 2010, a total of 85,556 cases of SCI in Canada were estimated, where 51% were traumatic and 49% were non-traumatic in nature. The number of new cases was estimated to be 4,071, with 42% of SCI sustained following a traumatic event.[33] From 1995 to 2004, the occurrence of traumatic SCI in British Columbia remained relatively stable,[34] although a study in Ontario found that the rate nearly doubled between 1997 and 2000.[32] With an aging population and a growing prevalence, a rise in incidence over time is possible.[33] In Canada, the lifetime cost per person with SCI is over $1.5 million for a paraplegic SCI and at least $3.0 million for tetraplegic SCI.[35]

1.2.4 Advancements in Care

The first documented text on SCI originated around the sixteenth century BC, when two SCI cases were registered in the ancient Egyptian medical text on trauma, the Edwin Smith

Papyrus, on Plate X and XI.[36] Today, the duration of stay in inpatient recovery centers has declined in Canada and the United States. This is likely attributed to improvements in acute care and technological advancements, as a reduction in mortality after SCI has been regularly recorded in many countries over the last few decades.[37] Spinal immobilization aids in the prevention of secondary cord injuries immediately post-spinal trauma,[38] by stabilizing of the spinal column and early cord decompression.[39] Though much of the focus is on the recovery of locomotor function,[40] it is well understood that this is not a priority for individuals with SCI,[41] and more emphasis should be placed on the chronic secondary complications post-injury.

1.2.5 Secondary Complications of Spinal Cord Injury

With advancements in care following SCI, the difficulties are centered on the secondary complexities. Readmission to the hospital due to secondary problems following injury is common, especially within the first year following the rehabilitation period.[42] Secondary symptoms following SCI are mostly caused by dysautonomia, which results in bladder and bowel instability, genital dysfunction, and altered thermoregulation and metabolism. According to a documented large survey of SCI individuals, autonomic control (including cardiovascular function) has a significant effect on life quality for those living with SCI and should be a research priority.[41]

CVD has an earlier onset and a faster development with SCI in comparison to the majority of the population.[43] The inactive lifestyle associated with motor function loss following injury contributes to high morbidity and mortality.[44] This lifestyle modification leads to increased CVD risk factors (i.e., obesity and metabolic profile).[45] Ultimately, this leads to a higher mortality rate for individuals with SCI compared to the non-injured population, with a

higher relative risk for individuals with a more rostral injury.[46] In chronic SCI, the life expectancy of people with cervical and thoracic SCI is about 70% and 85%, respectively, compared to the general population.[47]

1.3 Autonomic Control of the Cardiovascular System

1.3.1 Overview

The autonomic nervous system is divided into two major components (i.e., parasympathetic and sympathetic), innervating a majority of visceral organs, including the heart.[11] The first set of neurons are the preganglionic neurons. The cell body of the preganglionic neurons are located in the gray matter of the brain or spinal cord. The axons travel to the ventral roots of the spinal cord and synapse on a second group of neurons, the postganglionic neurons. Preganglionic neurons of the sympathetic nervous system are usually found from the T1 to L2 segments of the spine. The postganglionic neurons are found in the peripheral nervous system's autonomic ganglia.[48] A majority of sympathetic postganglionic fibres are adrenergic and release noradrenaline, though the sympathetic fibres innervating sweat glands are cholinergic and release acetylcholine. The parasympathetic neurons are found in cranial nerves III, VII, IX, and X of the brainstem and S2-S4 of the sacral spinal segments.[11] Pre- and post-ganglionic neurons are not organized in a one-to-one ratio; it is a network of neurons as opposed to a direct link from one preganglionic to one particular post ganglionic neuron.[10] This is an important feature of the nervous system as it improves the speed and accuracy of signalling to the target organs.[49]

1.3.2 Cardiovascular Autonomic Pathways

The heart and blood vessels are the two main components of the cardiovascular system. Sympathetic cardiac input originates at levels T1-T5 of the spinal cord, travelling to both the heart and vasculature. Sympathetic input to the lower extremities also originates in the spinal cord at levels T6-L2 via the sympathetic chain ganglia.[50] Sympathetic postganglionic neurons terminate in the cardiac ganglion, to act on the sinoatrial, atrioventricular nodes, and the myocardium. Sympathetic fibers exiting the spinal cord from T1-L2 innervate blood vessels (**Figure 1-2**). The splanchnic bed contains one quarter of the body's total blood volume at rest and therefore plays an important role for cardiovascular control.[10] Parasympathetic input via the vagus nerve, exits from the medulla, and the cardiac ganglion. The baroreceptor afferents, which are important for cardiovascular control, travel through the vagus nerve to the nucleus tractus solitarius.[50]

1.3.3 Cardiovascular Autonomic Pathways and Spinal Cord Injury

Damage to sympathetic pathways may result in a reduction in overall sympathetic function and therefore reduce circulating catecholamine levels (specifically the neurotransmitter noradrenaline). Reduced activity from sympathetic postganglionic axons lead to the reduction of the α-adrenoreceptors,[51] increasing their sensitivity to noradrenaline. For example, people with cervical SCI have a greater pressor response to noradrenaline. The reduction of sympathetic preganglionic neuron soma size that occurs early after SCI recuperates with time. This is possibly due to the primary afferent sprouting in the dorsal root ganglion, which enhances feedback to the sympathetic preganglionic neurons.[52]

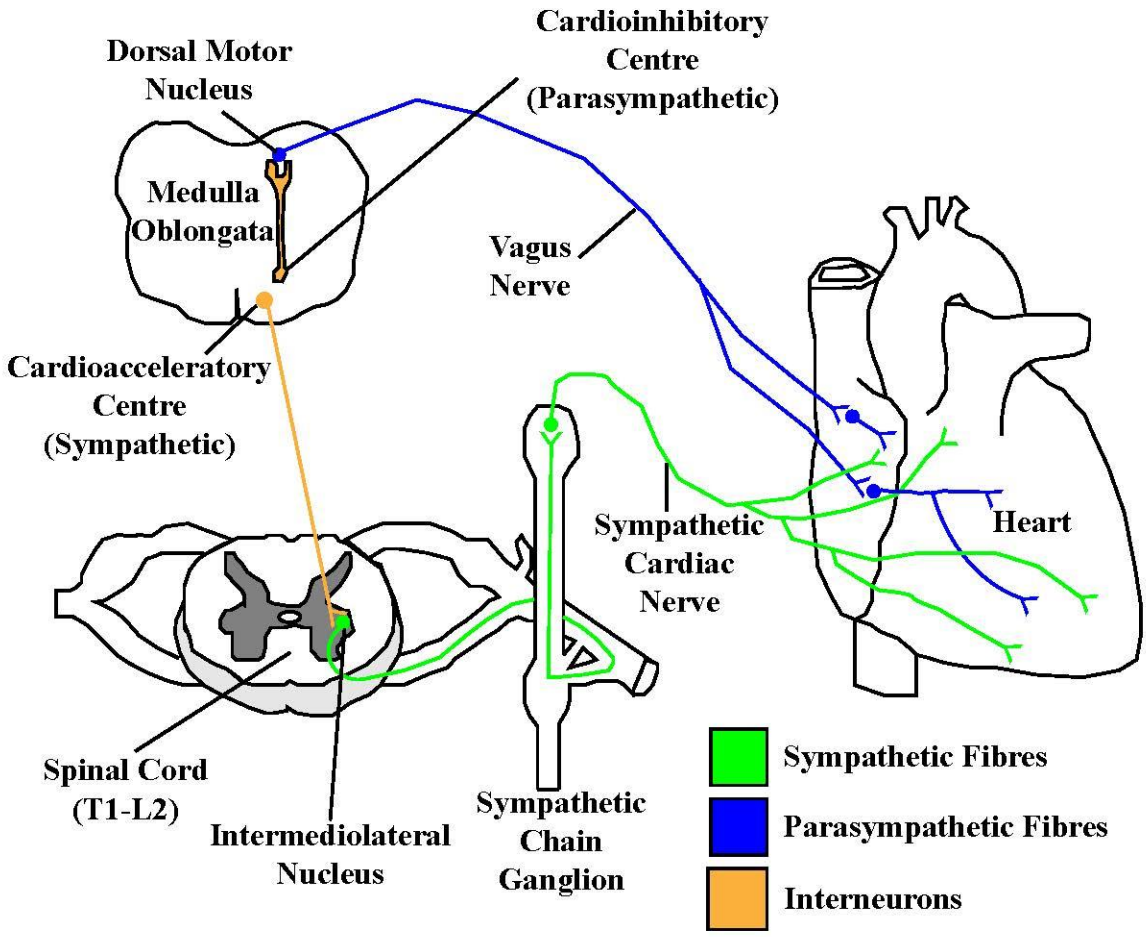


Figure 1-2. Schematic diagram of the autonomic influences on the heart
The medulla oblongata is responsible for regulating autonomic outflow to the heart, both sympathetic and parasympathetic.

1.3.4 Autonomic Imbalance and Cardiovascular Dysfunction

A balanced sympathetic and parasympathetic nervous system will regulate the cardiovascular system in a variety of conditions.[50] While the degree of cardiovascular impairment in SCI can be attributed to injury level and severity,[53] the International Standards for Neurological Classification of Spinal Cord Injuries[26] may not always correlate with the degree of cardiovascular impairment.[54] However, it has been found that non-athletes with motor-complete injuries do demonstrate an association between sensorimotor and sympathetic impairments.[55]

One tool to assess the cardiac autonomic nervous system is heart rate variability (HRV).[56] Individuals with SCI show lower HRV values compared to non-injured individuals in the low frequency band, suggesting a lower sympathetic influence on the heart for individuals with high-level SCI.[57] However, another study has shown the interpretation of HRV indices requires further investigation due to the complexities of cardiac autonomic function, and therefore limits its routine use to help manage cardiac autonomic dysfunction at rest in individuals with chronic SCI.[58] Exercise has been shown to temporarily alter HRV, suggesting chronic exercise may ameliorate the autonomic function following SCI.[59]

1.4 Cardiovascular Consequences following Spinal Cord Injury

1.4.1 Cardiovascular Dysfunction

The improvements in medical care towards the end of the last century have improved the life expectancy of people living with SCI to the point that the major cause of death to date in the chronic SCI population is CVD.[60] Typically, physical inactivity is one of the most important modifiable risk factors for the onset of CVD in non-injured individuals.[61] Given the physical deconditioning of individuals living with SCI over time, CVD is known to occur at an earlier age and has a higher incidence in this population.[62] Furthermore, an injury to the cervical or upper thoracic levels of the spinal cord (i.e., above T6; high-level SCI) can disrupt sympathetic autonomic pathways, putting these people at risk for a variety of health complications described in further detail later on in this chapter.[11]

1.4.2 Prevalence of Cardiovascular Dysfunction following Spinal Cord Injury

A compromised cardiovascular autonomic system is a significant concern following SCI. In theory, individuals with an autonomic complete injury above T1 have a complete absence of supraspinal sympathetic cardiac control, while T1-T5 could have partial or full control, and an injury below T5 would have normal sympathetic control.[6] With high-level lesions, the disrupted descending sympathetic pathways in the spine result in unopposed parasympathetic regulation of the heart (i.e., autonomic imbalance),[63] leading to an increased risk of arrhythmias.[64] In conjunction with this, the heart rate (HR) reached during peak exercise is lower if sympathetic control of the heart is diminished.[65] Furthermore, this lack of sympathetic control over the heart can lead to recurring periods of extreme hypotension during the day,[66] which is described in further detail below.

1.4.3 Acute Cardiovascular Dysfunction following Spinal Cord Injury

Neurogenic shock occurs acutely following SCI above the T6 level.[67] Individuals with neurogenic shock may show various cardiovascular consequences such as hypotension and bradycardia (due to the unaffected parasympathetic influence[12]), which has been reported to last between one and five weeks after injury.[68] These consequences are not surprising given the diminished input to the sympathetic pre-ganglionic neurons.[9] Typically, vasopressor therapy is needed to keep arterial BP stable at this time.[69] Neurogenic shock should be distinguished from spinal shock, which is characterized by a temporary loss of spinal reflex activity below the lesion and generally lasts 4 to 6 weeks.[70]

1.4.4 Clinical Consequences for Cardiovascular Dysfunction after Spinal Cord Injury

The most prominent outcomes to the altered BP control following SCI are: low supine BP, OH, AD.[2]

1.4.4.1 Low Supine Blood Pressure

In people with cervical SCI, sympathetic function at rest is usually low, as measured by low resting plasma noradrenaline and adrenaline levels. Low BP can be found in people with acute or chronic, complete or incomplete cervical SCI. The average supine resting systolic arterial pressures have been found to be between 94 and 114 mmHg.[14] Precautions need to be taken as fainting may occur when individuals transition to an upright position.

1.4.4.2 Orthostatic Hypotension

OH is defined as a decrease in systolic arterial pressure of ≥20 mmHg or diastolic arterial pressure of ≥10 mmHg, within three minutes of moving from a supine to an upright position,[71] though there is a known prevalence of 'delayed' OH in the SCI population.[72] One cause can be attributed to an altered baroreceptor reflex. When a healthy non-injured individual assumes an upright stance, an increase in sympathetic outflow to control BP and cerebral perfusion will occur due to the baroreflex-mediated vasoconstriction response.[73] However, when the reflex loop is interrupted (i.e., as with SCI), the compensatory HR and vascular response can fail, which is the primary cause of OH following high-level SCI.[74] Another factor is the venous pooling caused by decreased skeletal muscle pump function as a result of paralysis.[75] The pumping action of the muscle helps to maintain Q during orthostatic stress in non-injured individuals.[75]

OH can be attributed to the diminished sympathetic control of blood vessels in the splanchnic bed.[13] In conjunction with this, cardiovascular deconditioning[76] and/or altered salt and water balance[77] can contribute to OH. Hypotension is common in acute SCI and multiple episodes of hypotension can impact quality of life, resulting in feelings of general exhaustion,[66] difficulty performing every day activities,[16] and even impaired cognitive function.[78]

A rise in peripheral resistance during an episode of OH, despite the lack of sympathetic influence over certain vessels, may lessen its severity.[79] Individuals with SCI experience frequent spasticity, which has an unknown influence on venous return and OH. Although when at rest, the low levels of plasma catecholamine do not increase with orthostatic stress,[75] the increased sensitivity of the α-adrenoreceptors that occur after SCI induces vasoconstrictive responses to a given plasma catecholamine concentration.[80] In conjunction with this, endothelin-1 and angiotensin II increase the peripheral resistance during orthostatic stress.[81,82]

1.4.4.3 Autonomic Dysreflexia

AD is a potentially life-threatening medical emergency that occurs after SCI and is characterized by a drastic rise in BP (≥ 20-40 mmHg systolic), triggered by a noxious or non-noxious stimuli below the level of injury (i.e., bladder distension, bowel impaction).[83] AD is often accompanied by bradycardia, though instances of tachycardia have been reported.[84] The preserved vagal control to the heart influence this typical bradycardic response.[13] AD generally impacts individuals with an injury above T6,[83] as sympathetic control to the splanchnic vasculature is impaired,[85] though AD has been reported in individuals with a T10 lesion.[86] While AD is most prevalent in the chronic setting, it can be seen in a limited number of individuals in

the acute setting as well.[87] Unfortunately, AD develops in response to stimuli encountered in everyday life, and is therefore unavoidable.

Decreased supraspinal feedback to the spinal sympathetic circuitry, plasticity of autonomic nerve fibres in the spinal cord, and altered spinal reflexes are responsible for the progression of AD.[11] The reflex loop underlying AD involves a sensory stimulus triggering the spinal reflex arc, which induces sympathetic activity.[83] The onset of AD leads to an elevated BP in response to massive vasoconstriction below the lesion, causing extreme hypertension[12] and pilomotor activity, often resulting in a pale skin appearance and goosebumps, respectively.[15] Additionally, the α-adrenergic hyperresponsiveness and inappropriate afferent sprouting is thought to influence the progression of AD along with a reduced reuptake of noradrenaline.[88]

Vasodilation occurs above the lesion, since these areas remain under normal supraspinal regulation, and result in facial flushing and headaches.[15] There have also been reports of individuals who do not show any of these signs during an episode of AD.[89] This can be a dangerous consequence as typical feelings of discomfort due to coronary artery disease may go untreated as a result of absent sensory function.[90] Episodes of AD may have catastrophic effects such as coma, cardiac arrest, myocardial ischemia, or even death.[90–92] Frequent occurrences with extremely high BP may have a detrimental effect on the cardiovascular system since these increased BP measures are in stark contrast to the low resting BP which can damage to the vascular wall's endothelial layer (i.e., increased shear stress).[2] When the AD stimulus is identified and removed, BP rapidly returns to normal.

1.4.5 Etiology of Cardiac Dysfunctions in Spinal Cord Injury

Following SCI, individuals with a lesion T5 and above exhibit cardiac dysfunction,[54] as these individuals may have an impaired ability to increase chronotropy (heart rate), dromotropy (conduction speed), and inotropy (contractility). The unopposed vagal influence leads to low resting HR and a limited HR reserve, ultimately negatively affecting SV and Q.[93] Maximum HR has been shown to be approximately 100 beats per minute (bpm) in the absence of sympathetic activity with maximum vagal withdrawal,[94] which is close to peak HR seen in individuals with cervical SCI.[65] Several reasons for the alterations in cardiac function following SCI include physical inactivity,[95] diminished supraspinal sympathetic control to the heart and vasculature,[64] morphological changes of sympathetic neurons,[96] α-adrenoreceptor hypersensitivity in the vasculature,[13] or decreased cardiac β-receptor density.[97]

1.4.6 Cardiac Structure and Function in Spinal Cord Injury

SCI can induce substantial reductions in LV chamber size and mass, resulting in altered indices of systolic and diastolic activity, according to a recent meta-analysis.[98] Though there was significant variation between studies, significantly lower SV, EDV, end-systolic volume (ESV), and Q were found in comparing individuals with SCI to non-injured individuals (**Figure 1-3**). This impaired systolic function is likely due to a decrease in the pressure and volume loading of the heart as a result of systemic hypotension[13] and an overall reduction in blood volume.[19] In non-injured individuals, the venous muscle pump contributes to the return of blood to the heart, but is compromised in individuals with high-level SCI. In conjunction with this, people with SCI can suffer from extreme physical deconditioning as a result of extended bed rest and a typically extensive use of a wheelchair.[7] Similarly, non-injured individuals undergoing prolonged bed rest

show a reduction in both diastolic and systolic function.[99] As these studies are cross-sectional, the temporal relationship between SCI and altered cardiac indices are unclear. Longitudinal studies to track changes in cardiac structure and function early on following SCI with later follow up are warranted. Furthermore, although time since injury has shown associated reductions in LV structure and systolic function in a recent cross-sectional study,[100] it is not known how these cardiac indices in sub-acute SCI compare to non-injured individuals.

1.4.7 Elevated Risk of Cardiac Arrhythmias

SCI above T6 with known autonomic dysregulation of the cardiovascular system has been linked to electrophysiological changes in the heart and elevated risk of arrhythmias.[101,102] Following SCI, unopposed parasympathetic regulation is thought to trigger repeated bradycardic and asystolic events.[103] Injuries that disrupt the spinal sympathetic pathways are more likely to be accompanied by neurogenic shock and cause HR defects, which may lead to early mortality.[101] Atrial fibrillation is more frequent in people with SCI, especially during AD.[104] The increased ventricular repolarization is distributed between the layers of the heart and can raise the risk of re-entry arrhythmias,[105] which can lead to Torsade des Pointes.[106] Due to the autonomic imbalance that may occur in individuals with high-level SCI, these individuals are more likely to experience arrhythmias the first month post-injury compared to those with thoracolumbar injuries.[107] However, tracking these longitudinal prevalence of arrhythmias into the sub-acute and chronic phases of SCI still needs to be investigated.

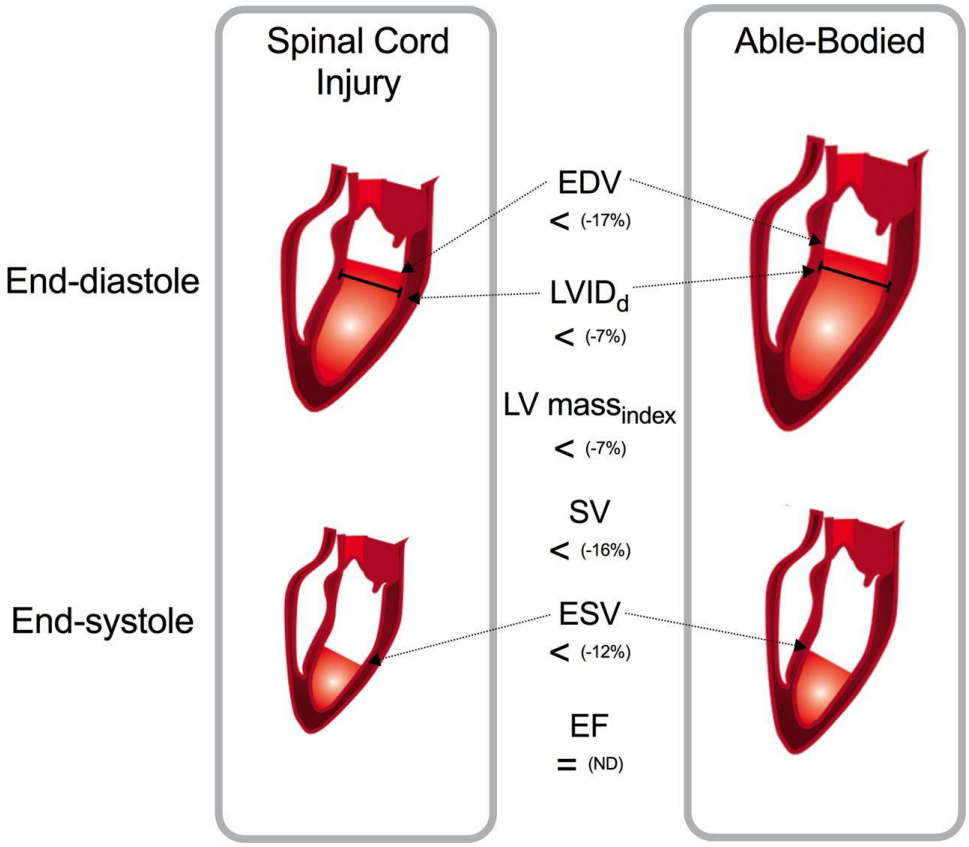


Figure 1-3. Schematic comparison of cardiac indices in chronic SCI to non-injured individuals
A recent meta-analysis revealed significantly reduced end-diastolic volume (EDV), left ventricular internal diameter in diastole ($LVID_d$), left ventricular mass indexed ($LV\ mass_{index}$), stroke volume (SV), and end-systolic volume (ESV) in SCI individuals compared to non-injured individuals. Used with permission.[98]

1.5 Physical Activity after Spinal Cord Injury

1.5.1 The Cardiovascular System during Exercise

The onset of exercise-induced tachycardia in individuals with SCI is brought about by vagal inhibition (i.e., parasympathetic withdrawal) of the sinoatrial node.[108] Typically, further increases to HR are due to increased sympathetic drive, determined by the capabilities of the sympathetic nervous system.[109] The β1-adrenoreceptors on the heart are activated with adrenaline or noradrenaline, which increase chronotropy and inotropy.

A significant amount of blood at rest is stored in the large venous beds of the splanchnic region in non-injured individuals.[110] During exercise, the sympathetic nervous system redirects blood from the splanchnic bed to the periphery in order to supply muscles with oxygen.[110] During exercise, elevation in Q is due to both increased SV and HR.[111] SV increases as EDV increases (i.e., increased preload) and ESV reduces (i.e., increased contractility). The greater venous return is due to altered peripheral circulation, including the directing of blood back to the heart and increased sympathetic neural activity which produce constriction to peripheral vascular beds.[112]

1.5.2 Current Physical Activity Levels in Individuals with Spinal Cord Injury

Individuals with SCI are generally less active and more physically deconditioned compared to the general population.[113] The PARA-SCI (Physical Activity Recall Assessment for People with SCI) provides a general description of individuals' activity and a subjective measure of intensity. Individuals with acute cervical SCI undergoing inpatient rehabilitation may not be performing the required volume of physical activity to improve cardiometabolic health. One study found that individuals undergoing SCI rehabilitation during the acute phase self-reported a median of 20 to 28 minutes total higher-intensity activity outside physical and occupational therapy in a day. The biggest contributor to this time was 7 to 10 minutes of activities of daily living (which does not challenge cardiovascular fitness).[114] Consequently, these individuals are spending a small proportion of time optimizing neurological and cardiovascular health prior to discharge.

More importantly, as individuals integrate themselves back into the community following rehabilitation, physical activity levels are not improved. A study showed that about 50% of

community-dwelling individuals with chronic SCI reported that they do not perform any leisure time physical activity (LTPA).[115] A major finding in this study was that the number of years post-injury negatively correlate with LTPA, suggesting that people injured for a longer period of time were less active than those injured recently. The associated secondary health conditions that occur in chronic SCI may be a reason for the lessened LTPA.[115] Therefore, a greater focus on developing practices of regular exercise during rehabilitation may build habits following discharge to maintain physical activity levels, potentially leading to cardiovascular benefits.

1.5.3 Responses to Exercise in Spinal Cord Injury

The decline in maximal HR during exercise is caused by diminished sympathetic control to the myocardium and a reduction in circulating adrenaline.[116] A study using ultrasound to compare portal vein flow concluded that individuals with high-level SCI could not effectively redistribute blood from the splanchnic bed to the periphery, compared to low-level SCI and non-injured controls.[18] Another study comparing blood flow for different injury levels found enhanced flow to the legs in all the groups from exercise, though significantly lower in individuals with tetraplegia, also reflecting the inability to mobilize splanchnic blood reservoir.[117]

Studies into the possibility of central cardiovascular adaptations in this population have been contentious.[118] Endurance, arm strength, peak power output, and $\dot{V}O_{2peak}$ (i.e., oxygen uptake measured during peak exercise) can improve through upper-body training.[119] However, the potentially limited capacity for aerobic exercise may not have an impact on the heart.[120] The BP responses to exercise are also affected with autonomic complete injuries above T6, as these individuals are not able to increase their BP as high as non-injured individuals.[117]

1.5.4 Cardiac Responses to Training Modalities following Spinal Cord Injury

Arm crank ergometry (ACET) is a common form of exercise for people with SCI. A training period of 16-weeks showed an increase in SV and a trend for increased Q with a higher power outputs eliciting a HR of 130 to 150 bpm in a group of 9 individuals with paraplegia.[121] These improved central adaptations were thought to be attributed to increased myocardial contractility at appropriate intensity, a reduction in cardiac afterload from the muscular recruitment, and possible increased venous return.[121] It is important to note that these individuals had preserved sympathetic control to the heart, and were able to increase their HR to intensities that resulted in cardiac changes.

A group of six individuals with chronic, motor-complete SCI performed four months of body weight supported treadmill training (BWSTT), which was shown to increase femoral artery compliance, suggesting an improvement in vascular health.[122] Due to the large muscle mass involved in this modality of exercise and the cardiovascular challenge of standing, BWSTT may be beneficial for cardiovascular training. Additionally, enhancements were noted in diastolic and systolic function in 14 people with SCI after a six-week robotic aided treadmill training program.[123] However, it is important to note that these individuals had motor-incomplete injuries and a majority of these individuals were paraplegic. A paucity in the literature regarding cardiac indices for individuals with chronic high-level motor-complete SCI following ACET or BWSTT remain.

1.5.5 Physical Activity and Cardiovascular Health following Spinal Cord Injury

Participants engaging in self-reported ≥ 25 minutes/day of mild-to-moderate intensity LTPA were shown to have lower BMI, lower C-reactive protein, and higher percent fat free mass

than the inactive participants (i.e., decreased risk of developing CVD).[124] Another study showed that six weeks of moderate-intensity arm-crank ergometry improved functional ability, fasting insulin concentrations, and hepatic insulin sensitivity in inactive adults with chronic paraplegia. However, no changes were noted in peripheral insulin sensitivity, adipose tissue metabolism, or other biomarkers of CVD risk.[125] It has been shown that adherence to the previous Canadian physical activity guidelines for individuals with SCI[126] did not promote clinically meaningful changes in cardiometabolic health.[127]

1.5.6 Exercise Guidelines for Individuals with Spinal Cord Injury

Exercise guidelines specifically for individuals with SCI were recently updated following a systematic review and participatory process with knowledge users and medical experts.[113] In these updated guidelines, the term 'exercise' focuses on planned and structured physical activity for purposes of fitness, rather than any 'physical activity' by the body requiring energy expenditure. The guideline to improve cardiorespiratory fitness is that adults with SCI should engage in at least 20 minutes of moderate-to-vigorous intensity aerobic exercise twice per week as well as three sets of strength training twice per week. The guideline to improve cardiometabolic health is that adults with SCI should partake in at least 30 minutes of moderate-to-vigorous aerobic activity three times a week. It was concluded that with these guidelines, people with SCI will benefit from comparatively limited amounts of exercise in terms of activity and cardiometabolic well-being, close to what has been seen in a healthy inactive individual, as well as people living with chronic disease.[113] Regardless of activity levels and baseline fitness, autonomic and physiological exercise adaptations can vary between individuals with SCI, especially for individuals with higher-level lesions.[128]

1.5.7 Mechanisms of Exercise Responses and Cardiac Function in Spinal Cord Injury

Individuals with SCI at or above T6 have limited maximal HR due to the diminished sympathetic drive to the heart.[129] This can lead to impaired systolic function[130] and electrocardiogram abnormalities,[131] which can impact how an individual with SCI can actively perform sufficient physical activity in their daily living. Additionally, the blood redistribution from areas of the body lacking sympathetic control reduces preload (i.e., venous return) and limits SV during exercise.[129] The reduced preload from the diminished supraspinal sympathetic control to the vasculature is compounded with immobility,[132] therefore individuals with tetraplegia usually show the most cardiac dysfunction.[133]

The belief that cardiac dysfunction in SCI can be mitigated with exercise[134] has been studied extensively. Pre-clinical models and controlled clinical trials have shown promise in that exercise training can attenuate dysfunction and LV atrophy following SCI.[134,135] In rodent models, passive hind-limb cycling restored SV, but not the pressure-generating potential or contractility.

1.6 Summary

SCI is a rare and debilitating condition, with an annual global incidence of traumatic SCI varying from 9 to 216 cases per million people. Males between the ages of 18 and 35 are an age group most likely to experience SCI, with motor vehicle collisions being the primary cause. Compromised sympathetic pathways between the medulla and the sympathetic preganglionic neurons to the heart and splanchnic vascular bed can result from a cervical or high-thoracic SCI. Individuals with high-level SCI are predisposed to early development of CVD due to abnormal cardiovascular control along with a lack of physical activity. Furthermore, the disrupted

autonomic cardiovascular control leads to irregular BP, predisposing individuals with higher lesions to life threatening episodes of AD and/or venous pooling and impaired venous return. The impaired venous return results in decreased LV loading, therefore decreasing SV and Q. Chronic decreases in volume loading of the heart, as with SCI, may result in cardiac atrophy. There is limited knowledge investigating the temporal progression of cardiac remodelling from acute-to-chronic SCI in humans, perhaps limiting the development of a programme to mitigate decline in cardiac function for individuals with SCI. Despite the fact that pre-clinical and clinical trials indicate that exercise training may partly reverse cardiac dysfunction following SCI, the question of when these changes occur and what exercise rehabilitation strategies are most effective remain to be answered.

In the next chapter, I describe the application of echocardiography as this was the tool used to obtain cardiac measures in experimental chapters 5, 7, and 8.

CHAPTER 2. APPLICATION OF ECHOCARDIOGRAPHY

2.1 Echocardiography Principles and Instrumentation

Since the first ever report of the application of ultrasound for cardiovascular diagnosis in 1954,[136] echocardiography has developed tremendously. Echocardiography is a form of ultrasound imaging used for the non-invasive assessment of cardiac structure and function. The echocardiographic examination has become more integrated and comprehensive with technological advances. This technology has completely replaced old methods in some cases, while being incorporated to enhance current modalities in others. This chapter provides definitions of the derived echocardiographic indices, highlighted from recommendations and guidelines.[137–140] These will be used in later experimental chapters (Chapters 5, 7, and 8) of this thesis. This chapter further highlights the current literature of echocardiographic indices in the SCI population.

2.1.1 Ultrasound Principles

Ultrasound is a form of sound wave (i.e., longitudinal) which undergoes compression and rarefaction as it travels through the body.[141] For clinical imaging, ultrasound waves are generated by a transducer with piezoelectric crystal elements, which convert electrical energy into mechanical energy by electrically stimulating the piezoelectric crystals.[141] Returning ultrasound waves are converted to an electric signal which is interpreted by the system's software (i.e., the piezoelectric effect). Two-dimensional (2D) images are constructed from a series of adjacent scan lines.[141]

2.1.2 Image Acquisition

Individuals being scanned are positioned in the left lateral decubitus position (as much as possible, depending on mobility and support) for the acquisition of image in the apical and the left parasternal windows. The parasternal long-axis view is most often located on the left side of the sternum and provides long axis heart images with the indicator pointing toward the patient's right shoulder. The parasternal short-axis view is in the same position as the long-axis view, however the index arrow is pointing toward the left shoulder of the individual being scanned and depicts the heart in an axial plane. The apical window is usually found under the left pectoralis major muscle. In the apical window, the index marker is first placed pointing to the resting surface of the individual being scanned, demonstrating the apical four-chamber view.[137] Various instrumentation settings on an ultrasound machine can be modified during image acquisition or after the image has been stored. These instrumentation settings ensure optimal imaging based on body habitus, anatomic structure, and blood flow.[137]

2.1.3 Echocardiography Modalities

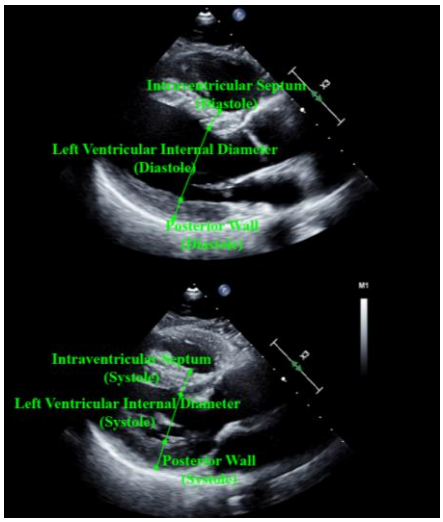
In 2D or B-mode echocardiography, the measuring distance of ultrasound is estimated using the critical value, which is the speed of the ultrasound waves in tissue (~1540 m/s). This critical value is used to calculate the distance traveled by a reflected ultrasound based on the time it takes for the returned signal to enter the probe.[141] The contrast resolution (i.e., the different shades of grey in the ultrasound signal) is determined by the compression or dynamic range, which occurs in the signal processor. Adding colour can enhance the visual assessment, as this is easier for the human eye to distinguish the different features of the structure (i.e., the heart).[142] Other pieces of important information, such as hemodynamics, use the Doppler effect. The

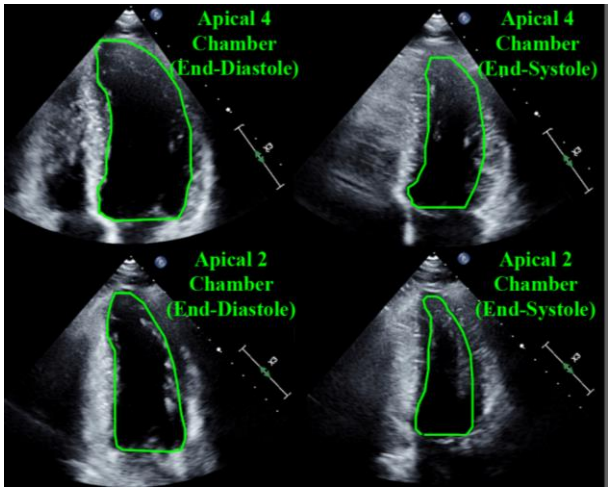
Doppler shift principle is used to assess the velocity and direction of motion relative to the ultrasound probe.[141] When ultrasound waves interact with the area of interest (i.e., blood or myocardium), the returning ultrasound waves have a different frequency from the originally transmitted waveform (i.e., a positive or negative Doppler shift).[141] Speckle tracking echocardiography is used for the analysis of myocardial deformation and LV mechanics. Using the acquired 2D images, spatial and temporal image processing algorithms in computers can detect acoustic markers (i.e., speckles) to track them frame-by-frame across the cardiac cycle.[140]

2.2 Left Ventricular Structural Indices

Measurement of the LV during systole and diastole reflect preload, afterload, and thickness of the myocardium.[143] CVD can appear with a thinner myocardium, leading to decreased LV dimensions and mass.[144] **Table 2-1** outlines how to measure the structural and volumetric indices of the LV.

Table 2-1. Measuring left ventricular structure

Image	Description of Measurement
	*Linear Measurements* – the LV wall thickness and dimension of the chamber are typically measured at end-diastole. The image should be along the centre axis to maximize the dimension and papillary muscles should not be visible. The measurement should be just beyond the mitral valve leaflet tips. At this level, the LV internal diameter (LVID) and the thickness of the interventricular septum and LV posterior wall should be determined and placed at the interface of the compacted myocardial system, which must remain perpendicular.



Volumetric Measurements – LV volume is measured using the biplane summation-of-disks method. Apical views are used with an appropriate sector size, displaying the LV, mitral valve, and some of the left atrium. Measures are carried out by tracing the LV cavity along the chamber wall's interface. Measuring the end-diastolic and end-systolic phases of the cardiac cycle is performed with the apical four- and two-chamber views (i.e., largest and smallest areas). Papillary muscles and trabeculae are not included, and a line across the mitral valve annulus is drawn to define this area.

2.2.1 Left Ventricular Structural Differences in Spinal Cord Injury

Individuals with chronic, traumatic SCI and no history of CVD risk factors show early signs of LV remodeling compared to non-injured individuals.[98] One study using echocardiography showed increased septal wall thickness and lower left ventricular internal diameter in diastole, even after correcting for age, weight, MAP, and physical fitness.[145] This may be because of the type of activities of daily living of individuals with SCI.[145] For example, the individuals in this study frequently performed isometric activities using only the upper part of the body (e.g., manual wheelchair propulsion and transfer tasks).[146,147] However, in another study, both sedentary and active individuals with SCI (i.e., both tetraplegia and paraplegia),[148] showed similar LV volumes and diameters relative to body weight.

2.3 Systolic Function

Systolic function indices are suggestive of the ability of the LV to pump blood into the systemic circulation.[143] Systolic dysfunction can be described from indices such as decreased ejection fraction, decreased velocity time integral, decreased SV, and increased ESV.[149] Global LV function is typically assessed in a clinical setting by measuring the difference between the end-diastolic and end-systolic value of a two-dimensional parameter divided by its end-diastolic value (i.e., fractional shortening or ejection fraction).[138] **Table 2-2** describes the indices used to quantify systolic function using 2D echocardiography.

Table 2-2. Indices of left ventricular systolic function

Measure	Description
Fractional Shortening	Derived from *Linear Measurements* previously described and may be useful in individuals with uncomplicated hypertension, obesity, or valvular diseases. However, the measure is inaccurate with regional myocardial wall motion abnormalities. This measure is expressed as a percentage.
Stroke Volume	Uses the recommended biplane method of disks for Volumetric Measurements (Table 2-1) and is calculated by subtracting the end-systolic volume from the end-diastolic volume. This measure is expressed as millilitres (mL) in humans.
Ejection Fraction	Calculated by dividing stroke volume by end-diastolic volume. This measure is expressed as a percentage.
Myocardial Contractile Velocity (S')	Measures longitudinal LV contraction. Early myocardial damage can be detected and has been shown to reveal long-axis impairment in various diseases, despite preserved ejection fraction. This measure is expressed in metres per second (m/s).

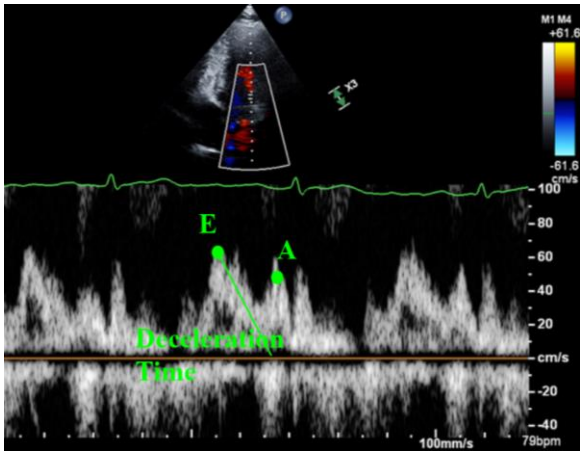
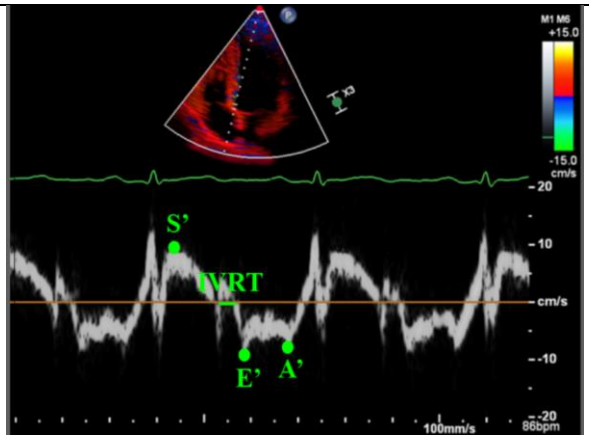
2.3.1 Left Ventricular Systolic Function Differences in Spinal Cord Injury

Systolic myocardial contraction velocity was higher in participants with SCI,[145] though this was not the case in one study where ~68% of participants did physical activity and had a shorter time since injury.[150] Participants with SCI had lower Q and $Q_{indexed}$ (to body surface area). Individuals with tetraplegia did not have reduced global systolic activity, although there was a tendency toward diminished Q.[20] In comparing Paralympic athletes with paraplegia and tetraplegia, a study showed that SV and Q was reduced in the tetraplegic group.[151] In another study, no difference in systolic function between active and sedentary individuals with tetraplegia,[152] while active individuals with paraplegia had higher SV but no differences in ejection fraction.[152]

2.4 Diastolic Function

Diastolic function indices suggest LV elasticity by measuring filling pressure and volume.[143] Diastolic dysfunction is known to cause increased stiffening of the ventricles, that compromise passive filling and relaxation, ultimately increasing the risk for heart failure.[153] The pressure within the left ventricle slowly decreases (i.e., increased isovolumetric relaxation time), which may lead to incomplete relaxation and decreased diastolic filling.[154] Furthermore, the age-related stiffening of blood vessels increases afterload, and contributing to diastolic dysfunction.[155] **Table 2-3** describes the indices used to quantify diastolic function using 2D echocardiography.

Table 2-3. Indices of left ventricular diastolic function

Image	Description of Measurement
	*Transmitral Inflow* – Early diastolic filling (E) reflects the left atrial-left ventricular pressure gradient during early diastole, affected by the rate of relaxation. Late diastolic filling (A) reflects the left atrial-left ventricular pressure gradient during late diastole, affected by compliance. E/A Ratio is used to identify filling patterns such as impaired relaxation. Deceleration time is the time it takes for the LV to stop early filling and is influenced by left ventricular relaxation and stiffness.
	*Tissue Doppler Velocity* – Early myocardial relaxation velocity (E') reflects left ventricular relaxation and filling pressure. E/E' Ratio can be used to predict filling pressure. Isovolumetric relaxation time (IVRT) is prolonged in individuals with impaired relaxation but normal filling pressures.

2.4.1 Left Ventricular Diastolic Function Differences in Spinal Cord Injury

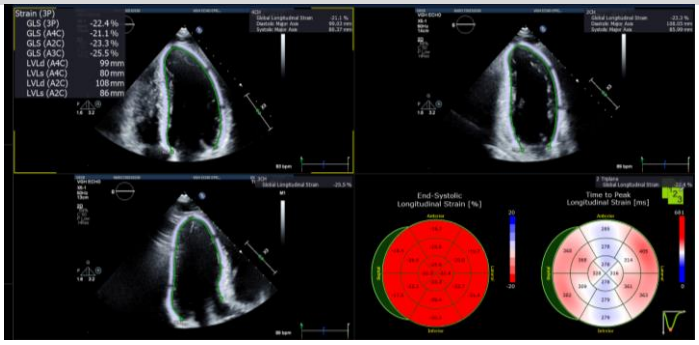
Studies have reported inconsistencies with diastolic function following SCI. Decreased early transmitral filling velocity (E),[145] decreased early relaxing tissue velocity (E'),[152] decreased ratio of early to late filling velocity (E/A),[145] and an increased ratio of early transmitral to myocardial tissue velocities (E/E'),[152] have all been reported, though isovolumetric relaxation time and mitral deceleration time were within normal limits.[145,150] Furthermore, a study using

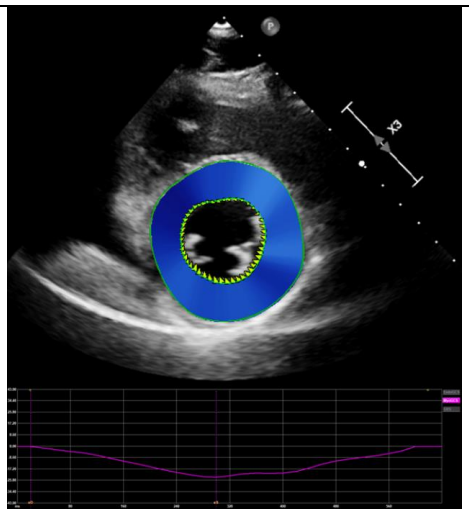
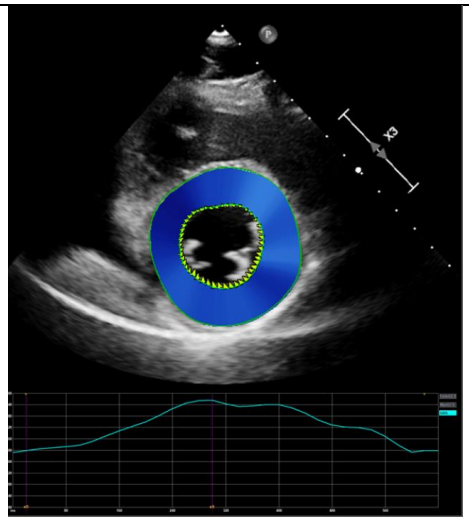
rapid saline infusion showed no differences between individuals with high-level SCI and non-injured individuals,[156] suggesting LV diastolic function is preserved in SCI despite a lower preload. Another study showed that individuals with SCI had indices of diastolic function within the recommended range and did not worsen with duration, level or severity of injury, though the increases in E/E' ratio should be noted.[143]

2.5 Mechanical Indices and Strain Imaging

The use of strain imaging in the general population has demonstrated that decreases in LV strain and torsion frequently predict systolic instability and can be observed until dramatic decreases in cardiac activity are apparent.[143] **Table 2-4** describes the different planes in which strain is measured.

Table 2-4. Measures of left ventricular strain

Image	Description of Measurement
	*Longitudinal Strain* – occurs from the base to the apex, denoted by negative strain as systolic contraction is occurring towards the transducer, located at the apex when imaging in the apical 4-chamber view.

	*Circumferential Strain* – is the counterclockwise motion of the myocardial fibres from base to apex and the opposite clockwise direction from apex to base, reducing the left ventricular cavity size and resulting in negative strain from the short axis view.
	*Radial Strain* – is the contraction or thickening of the left ventricular wall towards the center, that results in a positive strain value seen from the short axis view.

2.5.1 Left Ventricular Myocardial Framework

Myocytes are long, thin, mononucleated cells, joined together by intercalated disks. The endomysial layer supports individual myocytes and bundles these cells, forming the myocardial fibres in the perimysium.[157] Within the perimysium, collagen binds these adjacent myocardial fibres into laminar layers. These laminar sheets of myocardium slide alongside one another throughout the cardiac cycle.[158] This arrangement provides the framework for LV deformation (i.e., mechanics) throughout the cardiac cycle.[159] The LV myocardium consists of a

counterclockwise helical oriented endocardium to a clockwise helical oriented epicardium.[159] This formation leads to wall thickening and circumferential or longitudinal shortening.[159] The twisting motion of the LV allows for a uniform distribution of LV pressure during systole.[160] Diastolic suction in the form of potential energy is stored in the LV myocardial matrix during systole and is released during diastole, generating the pressure gradients in the early passive filling phase.[160]

2.5.2 Left Ventricular Mechanics

Strain can be measured in the longitudinal, circumferential, and radial planes, representing the lengthening and shortening of oblique, longitudinal, and circumferential fibres.[159] Circumferential fibres form the outer shell of the heart and compress the oblique fibres. During systolic ejection, circumferential fibres shorten and contract with the oblique fibres of the endocardial and epicardial fibres, and during isovolumetric relaxation, the LV increases its radius as circumferential fibres have stopped contracting.[161] Strain is defined by the Lagrangian formula: $\varepsilon(t) = L(t)\text{-}L(to)/L(to)$ and is positive or negative depending on if the segment length exceeds or is less than its original length, respectively. Rotation is expressed as rotations occurring in positive (counter clockwise) and negative (clockwise) degrees.[158] During systole, rotation at the base is primarily clockwise, and rotation at the apex is primarily counter clockwise, with the apex rotation being of higher magnitude.[158] LV twist describes the base-to-apex rotation along its longitudinal axis, characterizing LV systolic and diastolic function.[161,162] LV torsion is the twist for a given LV length, expressed as degrees per centimetre.[140]

2.5.3 Hemodynamic Influences on Left Ventricular Mechanics

Increases to twist and strain mechanics are likely due to passive stretch of the myocardium producing a greater active shortening of the different planes of myofibres (i.e., Frank-Starling mechanism).[163] Experiments demonstrating an increase in preload (i.e., infusion techniques) showed increases to LV volumes were accompanied by increases to LV apical rotation, twist and untwisting velocity, longitudinal strain, and circumferential strain with alterations during acute stress being more pronounced at the apex.[164] Reductions to both twist and strain mechanics are likely due to reduced active fibre shortening in the different planes of myofibres.[165] Experiments demonstrating an increase in afterload (i.e., hand grip exercise to increase total peripheral resistance) reduced EDV, SV, longitudinal strain, apical rotation, and LV twist. Dynamic exercise affects preload, afterload, and contractility, which ultimately contribute to changes in SV, and by association, LV twist.[166] Increasing LV twist during exercise is from the increased basal and apical rotations,[167] though the increased apical rotation is typically more pronounced.

2.5.4 Left Ventricular Mechanics in Spinal Cord Injury

Few studies have reported speckle tracking analysis in individuals with SCI. One study in athletes with SCI showed an elevation in the systolic mechanics in the tetraplegic group, which was thought to be attributed to reduced afterload, and decreased mechanics in the paraplegic group. For the paraplegic group, the lower mechanics was thought not to be suggestive of pathology, but rather resetting of LV mechanics in response to the high training volumes.[151]

2.6 Reliability of Echocardiographic Measurements

In Chapters 5, 7, and 8, a certified sonographer (S. Balthazaar) performed all of the measurements for the studies. **Table 2-5** shows the intraclass correlation for the remeasuring of ten randomly selected participants from Chapter 5. A Level III Echocardiographer (H. Girgis) performed additional re-analysis from 30 randomly selected participants in Chapters 5, 7, and 8, shown in **Table 2-6**.

Table 2-5. Intraobserver variability

	CYCLE 1	CYCLE 2	CYCLE 3	MEAN
E/A Ratio	0.944 (0.975-0.999)	0.991 (0.962-0.998)	0.984 (0.932-0.996)	0.993 (0.971-0.998)
Deceleration Time	0.867 (0.230-0.972)	0.833 (0.310-0.962)	0.933 (0.493-0.986)	0.928 (0.218-0.987)
E/E' Ratio	0.830 (0.291-0.961)	0.737 (-0.255-0.942)	0.824 (0.259-0.960)	0.918 (0.618-0.982)
SV	0.817 (0.260-0.955)	0.875 (0.522-0.969)	0.591 (-0.384-0.893)	0.932 (0.742-0.983)
LV Mass	0.992 (0.962-0.998)	0.991 (0.964-0.998)	0.992 (0.968-0.998)	0.961 (0.852-0.990)

Abbreviations: E/A, early diastolic filling to late diastolic filling; E/E', early diastolic filling to early myocardial relaxation; LV, left ventricle; SV, stroke volume
Data is presented as ICC (95% CI)

Table 2-6. Interobserver variability (Class III Echocardiographer)

	LOOP 1 (4Ch)	LOOP 2 (4Ch)	LOOP 3 (4Ch)	LOOP 1 (2Ch)	LOOP 2 (2Ch)	LOOP 3 (2Ch)	MEAN
EDV	0.855 (0.675-0.940)	0.844 (0.654-0.935)	0.909 (0.789-0.963)	0.889 (0.746-0.954)	0.807 (0.580-0.918)	0.868 (0.702-0.945)	0.978 (0.947-0.991)
ESV	0.720 (0.425-0.878)	0.844 (0.652-0.935)	0.902 (0.773-0.960)	0.793 (0.555-0.912)	0.772 (0.516-0.902)	0.476 (0.064-0.752)	0.490 (0.081-0.760)
SV	0.780 (0.530-0.906)	0.581 (0.206-0.809)	0.696 (0.384-0.867)	0.799 (0.565-0.915)	0.747 (0.471-0.891)	0.725 (0.433-0.880)	0.953 (0.887-0.981)
Q	0.868 (0.702-0.945)	0.726 (0.435-0.881)	0.872 (0.710-0.947)	0.858 (0.682-0.941)	0.773 (0.518-0.903)	0.781 (0.533-0.907)	0.974 (0.937-0.990)

Abbreviations: 2Ch, 2-chamber; 4Ch, 4-chamber; EDV, end diastolic volume; ESV, end systolic volume; Q, cardiac output; SV, stroke volume
Data is presented as ICC (95% CI)

CHAPTER 3. AIMS AND HYPOTHESES

This thesis aims to understand changes in cardiac structure and function within the first year following SCI and to investigate the impact of rehabilitation strategies on cardiac structure and function in individuals with chronic SCI.

AIM 1: To compare echocardiographic indices for individuals with sub-acute SCI (i.e., within the first year of injury) to individuals undergoing myocardial unloading conditions (i.e., bed rest or spaceflight) and to individuals who underwent cardiac denervation (i.e., heart transplant).

This was accomplished by systematically reviewing the published literature on echocardiographic indices in adults with SCI, after bed rest or spaceflight conditions, and post-heart transplant (Chapter 4).

Hypothesis 1.1: Individuals with SCI will have declining echocardiographic indices comparable to those undergoing myocardial unloading conditions. The echocardiographic indices in individuals who received heart transplants will not be comparable to those with SCI.

AIM 2: To compare cardiac structure and function between individuals with sub-acute SCI and chronic SCI and non-injured (control) individuals.

This was accomplished by a cross-sectional study that uses echocardiography to compare non-injured individuals, individuals with sub-acute cervical SCI, and individuals with chronic cervical SCI (Chapter 5).

Hypothesis 2.1: Individuals with chronic SCI will have worsened cardiac indices compared to individuals with sub-acute SCI. Individuals with sub-acute SCI will have worsened cardiac indices compared to non-injured individuals, but to a lesser extent.

AIM 3: To describe the prevalence of arrhythmias from the acute to sub-acute period following SCI based on level of neurological injury.

This was accomplished by using Holter monitoring on newly injured inpatients with traumatic SCI in a large tertiary care hospital (Chapter 6).

Hypothesis 3.1: A higher prevalence of arrhythmias will occur in the earlier phases of injury due to neurogenic shock following SCI.

Hypothesis 3.2: A high-level injury (i.e., cervical) will have a higher prevalence of arrhythmias compared to a low-level injury (i.e., thoracic).

AIM 4: To longitudinally assess the impact of neurological level of injury on cardiac structural and functional indices in the sub-acute period following SCI.

This was accomplished by using echocardiography to track the same individuals with cervical SCI and thoracolumbar SCI at three- and six-months post-injury (Chapter 7).

Hypothesis 4.1: Individuals with cervical SCI will have worsened cardiac indices compared to thoracolumbar SCI due to the diminished supraspinal sympathetic control of the heart.

AIM 5: To investigate the impact of rehabilitation strategies to reverse or mitigate decline in cardiac function in individuals with chronic SCI.

This was accomplished by comparing the effects of two different exercise interventions (i.e., passive body weight support treadmill training and active arm cycle ergometry) on cardiac indices before and after 72 sessions of training (Chapter 8).

Hypothesis 5.1: Cyclical passive movements of large muscles in the legs combined with the upright postural challenge to the cardiovascular system will provide a superior exercise modality with body weight supported treadmill training (BWSTT) compared to active arm cycle ergometry training (ACET).

The overall aim of this thesis was: 1) to understand cardiac measures in the months following SCI and 2) to investigate rehabilitation strategies for cardiac dysfunctions following chronic SCI. This was driven by the fact that this population is at a greater risk of developing CVD compared to the general population. In the next chapter (Chapter 4), I performed a scoping review of the literature to highlight what is known about cardiac structure and function, comparing the first year following SCI to microgravity and cardiac denervation conditions. Following this, I investigated of determining when these cardiac changes occur (Chapter 5-7). I then investigated strategies to improve cardiac function with exercise (Chapter 8).

CHAPTER 4. THE HEART AFTER SPINAL CORD INJURY – LOSING NERVES OR LOST IN SPACE? A SCOPING REVIEW

4.1 Introduction

Following SCI, individuals are likely to become less physically active[113] and undergo changes to their autonomic nervous system.[64] Findings of cardiac deconditioning are not uncommon in this unique population and contribute to CVD.[62] Consequently, CVD is the leading cause of morbidity and mortality in the SCI population, with at least threefold greater odds of heart disease compared to non-injured individuals.[6] As described in Chapter 1, studies have investigated the cardiac consequences following SCI in the chronic stage and compared to non-injured individuals.[98,123,168,169] The diminished supraspinal control to the heart following SCI may be comparable to the impact of absent autonomic influences on the heart, which can be seen within the first year of a heart transplant.[170] In addition to this, cardiac alterations have been shown following a period of bed rest (i.e., prolonged physical inactivity) and microgravity conditions (i.e., spaceflight) in previously healthy individuals who had no prior risk for CVD,[171] also potentially providing a comparative model to cardiac dysfunction after SCI.[172] Combined with the impact on LV indices that have been reported as early as two weeks following bed rest,[132] there is demand for further research to understand the timeline of cardiac consequences following SCI.

As described in Chapter 2, a method of assessing these cardiac consequences is to investigate structure and function of the LV. The LV can be altered in several diseases and has been found to correlate with numerous prognostic factors.[173–175] Quantification of cardiac mass, chamber size, and function are clinically important responsibilities of echocardiography.[138] Thus, this imaging modality is useful to compare the cardiac outcomes in individuals with SCI to heart

transplant recipients and non-injured myocardial unloading (NIMU; i.e., bed rest or spaceflight) individuals.

A summary of the literature with respect to the alterations of LV indices following SCI, NIMU, and heart transplant, may provide knowledge of the gaps and future directions for exploring how cardiac structure and function change over time. The purpose of this scoping review (AIM 1 of this thesis) was, therefore, to understand the literature on LV indices following SCI, using NIMU and heart transplant to better understand the disease process, specifically in the first year of the cardiac deconditioning process.

4.2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[176] were followed throughout the literature search, reporting of the data, and discussion of this review. The protocol was prospectively registered in the PROSPERO database (CRD42018091004). The primary scoping review question was "What do we know about cardiac indices in the first year of SCI compared to microgravity or cardiac denervation?". Characteristics could include cardiac structure, systolic function, diastolic function, and mechanical indices. Secondary review questions will explore how SCI compares to NIMU and heart transplant.

4.2.1 Literature Search

A systematic literature search was conducted using Medline, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. The search strategy was based on the PICOS

process.[177] When possible, Medical Subject Headings (MeSH)[178] were used as search terms. This search was last updated on March 10, 2021.

4.2.2 Study Selection

We included original articles reporting LV indices and excluded literature on non-human participants, non-English language literature, cross-sectional studies that did not compare the deconditioned participants to generally healthy individuals in the population, as well as case reports, conference abstracts, editorials, other systematic reviews, and studies with individuals under the age of 18 and/or older than the age of 60. All titles and abstracts of the articles were screened. If the abstracts were relevant to the topic, the corresponding articles were then screened by full-text.

4.2.3 Data Extraction

Mr. Nathan Hitchman and I extracted data independently and discrepancies were discussed with Dr. Tom Nightingale. Data extracted included the study author, date, location, number of participants, age of the participants, type of cardiac deconditioning (i.e., SCI, NIMU, or heart transplant), echocardiography acquisition, and type of study (i.e., cross-sectional or longitudinal). Articles relevant to the topic were found on the databases using the search terms developed by me in conjunction with Mr. Dean Giustini (librarian) and in consultation with co-authors. Examples of search terms used included: patient*, participant*, denerv*, decondition*, microgravity*, weightless*, bed rest*, echocardiograph*. For any references that used another method to describe their population other than mean ± standard deviation, the correct equation was applied for the conversion.[177]

4.2.4 Quality Assessment

The quality of the studies included in this literature review were assessed using a combination of the Newcastle-Ottawa Scale (NOS) for cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) and an effective score for evaluating echocardiography studies[98] with quantitative LV outcome measures for a total maximum score of 11. Therefore, we assigned a score of 0-4 to be low quality, 5-8 to be medium quality, and 9-11 to be high quality.

4.3 Results

4.3.1 Articles Included

The literature search and included articles are outlined in **Figure 4-1**.[179] A total of 23,769 citations were independently retrieved (4,333 from MEDLINE; 13,039 from EMBASE; 355 from Cochrane; 6,042 from Web of Science). Automatic tools were not used for screening. Of those, 5,674 duplicate citations were removed, and 18,095 unique citations remained. After screening of titles and abstracts, 17,933 citations were excluded, and 162 full-text articles were retrieved. An additional 125 articles were excluded that did not satisfy: 1) age criteria, 2) providing sufficient information regarding demographic information or outcome data, 3) comparing deconditioned individuals to healthy controls if cross-sectionally designed and/or 3) presented data during or after an intervention. In total, 37 articles were included in the review. Included studies enrolled a total of 981 participants. Of these, 386 were SCI participants (**Table 4-1**).

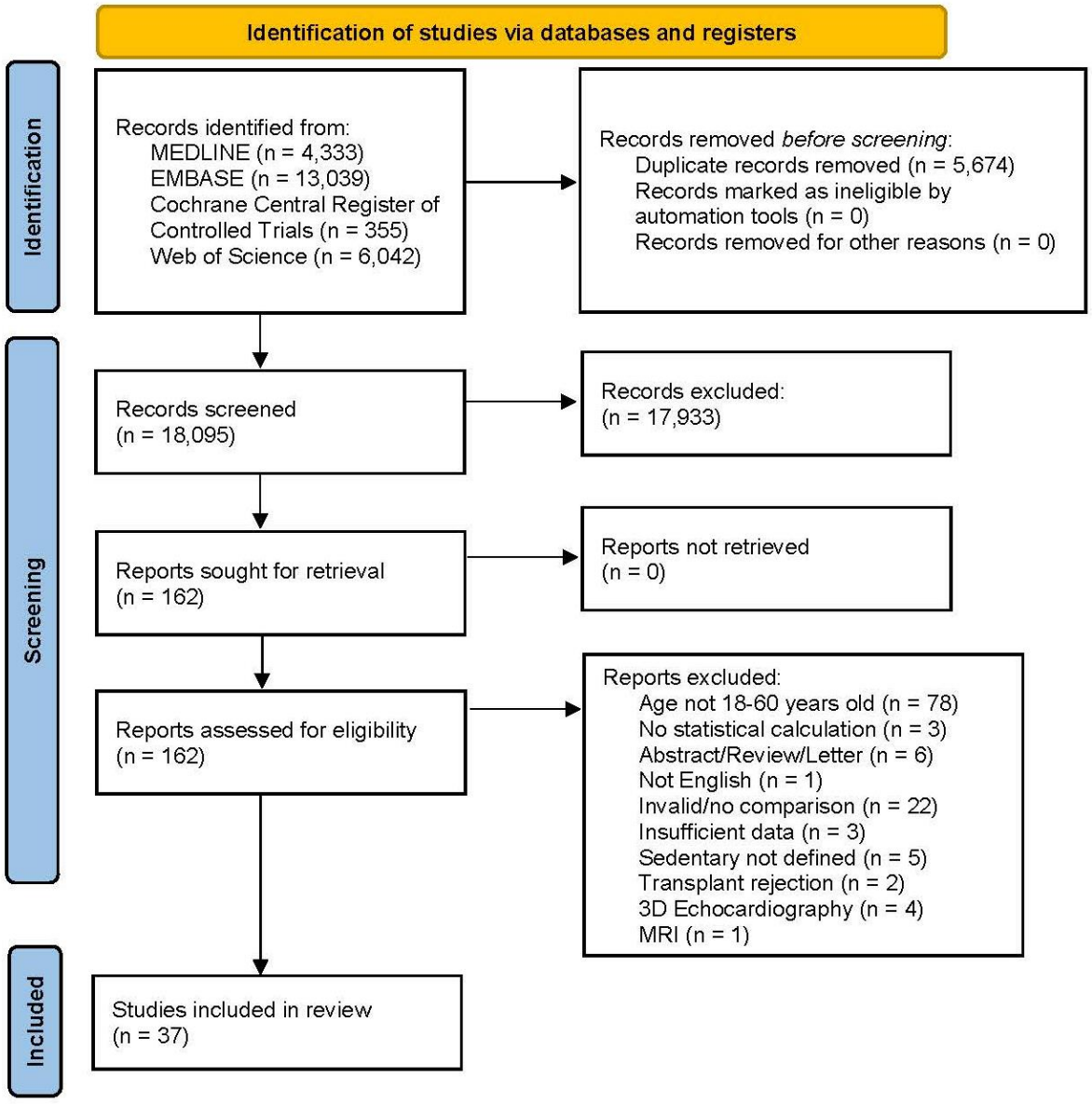


Figure 4-1. Flowchart of study selection

The SCI groups in these studies were comprised of participants with injury levels from C1-S5, American Spinal Injury Association (ASIA) Impairment Scale (AIS) grading A to D.[26] All studies were cross-sectional by design (**Table 4-1**).[20,100,130,133,145,150,152,156,180–188] Five studies

enrolled tetraplegic (i.e., cervical SCI) participants only,[20,130,182–184] three studies enrolled paraplegic (i.e., thoracolumbar SCI) participants only,[180,185,188] and nine studies enrolled both, with one study separating the tetraplegic and paraplegic participants.[133] Studies that enrolled paraplegic participants did not dichotomize into high-thoracic and low-thoracic levels (i.e., above and below T6, respectively).[133,180,181,185,187,188] However, two studies selected participants with injuries only at or above T6.[156,186] Autonomic completeness was not tested in these studies.[189]

Eight studies investigated NIMU participants;[95,190–196] all were longitudinal in design. Four studies were exclusively bed rest studies,[95,193,194,196] three studies were exclusively space flight,[190–192] and one study had bed rest and spaceflight participants.[195] Twelve studies investigated heart transplant participants.[197–208] Six of these studies were cross-sectional[199,201–203,205,206] and six were longitudinally designed.[197,198,200,204,207,208]

4.3.2 Participant Characteristics

The majority of studies had a greater number of male participants. The age of the participants ranged from a mean of 23 years to 53 years (**Table 4-1**). The participants in the heart transplant studies had various risk factors for CVD, while the participants in the SCI and NIMU studies had no known pre-existing cardiac conditions.

Table 4-1. Characteristics of articles included for review

Author, Year	Study Size (n)	Methods	Age (Years)	Type of Cardiac Deconditioning
Kessler *et al.*, 1986[133]	14	SCI: 7 paraplegics & 7 quadriplegics TSI: 1 year Echo: Participants seated; M-mode and 2D Study Type: Cross-Sectional	26 ± 8	SCI
Washburn *et al.*, 1986[187]	50	SCI: 22 paraplegics & 28 quadriplegics TSI: 38 ± 39 months since injury Echo: M-mode measurements Study Type: Cross-Sectional	28 ± 6	SCI
De Groot *et al.*, 2006[20]	7	SCI: AIS A C5-6 TSI: 17.7 ± 9.6 years Echo: M-mode, 2D and Doppler; averaged over 3 beats Study Type: Cross-Sectional	38 ± 8	SCI
Vriz *et al.*, 2018[188]	57	SCI: < C8 TSI: 22 ± 14 years Echo: M-mode and doppler; averaged over 5 beats Study Type: Cross-Sectional	43 ± 13	SCI
West *et al.*, 2012[184]	12	SCI: C5-C7, AIS A/B TSI: 9 ± 4 years since injury Echo: 2D, Doppler; averaged over 5 beats Study Type: Cross-Sectional	30 ± 5	SCI
Maggioni *et al.*, 2012[180]	17	SCI: T1-L3, AIS A Echo: not specified, but according to ASE guidelines Study Type: Cross-Sectional	36 ± 10	SCI

Gibbons *et al.*, 2016[181]	9	SCI: 9 AIS A/B ≤C4 TSI: 12 ± 10 year for females & 11 ± 4 year for males. Echo: Body 45° above horizontal; M-mode, 2D, Doppler; averaged over 5 beats Study Type: Cross-Sectional	26 – 56	SCI
Currie *et al.*, 2017[182]	9	SCI: C4-C7 AIS A/B TSI: 24 ± 12 years Echo: left-lateral decubitis, 2D, Doppler Study Type: Cross-Sectional	40 ± 10	SCI
Phillips *et al.*, 1988[183]	6	SCI: C5-C7, AIS not determined TSI: not mentioned Echo: supine, M-Mode imaging Study Type: Cross-Sectional	21 – 35	SCI
West *et al.*, 2012[130]	11	SCI: C5-C7 complete & incomplete TSI: 10 ± 4 years Echo: seated position, M-Mode, Doppler Study Type: Cross-Sectional	32 ± 8	SCI
Huonker *et al.*, 1998[185]	20	SCI: T1-S4, AIS not determined TSI: > 2 years Echo: 2D Study Type: Cross-Sectional	34 ± 10	SCI
DeRossi *et al.*, 2014[152]	29	SCI: All levels, AIS A/B TSI: 7.5 ± 0.9 years Echo: Seated, M-Mode, Doppler Study Type: Cross-Sectional	32 ± 1	SCI
Driussi *et al.*, 2014[145]	47	SCI: < C6, AIS A TSI: 22.12 ± 14.5 years Echo: 2D, M-Mode, Doppler Study Type: Cross-Sectional	44 ± 12	SCI
Matos-Souza *et al.*, 2011[150]	34	SCI: C4-T12, AIS A/B TSI: 6.7 ± 0.4 years	32 ± 1	SCI

		Echo: Seated, M-Mode, Doppler Study Type: Cross-Sectional		
Schreiber *et al.*, 2017[186]	22	SCI: < T6 AIS A/B TSI: > 1 year Echo: Sitting position, 2D, Doppler Study Type: Cross-Sectional	31 ± 7	SCI
Sharif *et al.*, 2017[156]	13	SCI: ≤ T6 AIS A-D TSI: 17 ± 10 years Echo: Left lateral decubitis, 2D, M-Mode, Doppler Study Type: Cross-Sectional	41 ± 8	SCI
Ely *et al.*, 2021[100]	29	SCI: C1-T10 AIS A-C TSI: 11 ± 5 Echo: Left lateral decubitis, 2D, Doppler Study type: Cross-Sectional	29 ± 5	SCI
Bungo *et al.*, 1987[190]	17	Spaceflight: 5-8 days Echo: Postflight + 0 days (n=7); 7-14 days postflight (n=17) Study Type: Longitudinal	44 ± 5	NIMU
Arbeille *et al.*, 2001[195]	2 – 10	Spaceflight: 7 days-6 months Bed rest: 10 hours-42 days Echo: B-mode and M-mode; averaged 10 cycles Study Type: Longitudinal	Not reported	NIMU
Summers *et al.*, 2005[191]	38	Spaceflight: 9-16 days Echo: Postflight +2-3hr and +3days; M-mode and 2D; averaged 3-4 beats Study Type: Longitudinal	42 ± 6	NIMU
Hung *et al.*, 1983[193]	12	Bed rest: 10 days with no decline angle Echo: post-intervention; M-mode Study Type: Longitudinal	50 ± 4	NIMU
Levine *et al.*,	12	Bed rest: 2 weeks, 6° head down tilt	24 ± 5	NIMU

1997[95]		Echo: post-intervention; 2D (B-mode); averaged 2-3 beats Study Type: Longitudinal		
Kozakova *et al.*, 2011[194]	10	Bed rest: 5 weeks, 6° head down tilt Echo: 24 hours after 5-week period; M-mode, 2D, and doppler; averaged over 5 beats Study Type: Longitudinal	23 ± 2	NIMU
Hamilton *et al.*, 2011[192]	6	Spaceflight: 34-190 days Echo: 55-167 days preflight, during, 5-16 days post; B-mode and M-mode Study Type: Longitudinal	Not reported	NIMU
Hoffmann *et al.*, 2021[196]	24	Bed rest: 60 days, 6° head down tilt Echo: 6 days before bed rest, 1 day before recovery; supine Study type: Longitudinal	Not reported	NIMU
Qin *et al.*, 2013[197]	34	Transplant: 3 groups; A, 3 months post-op, n=25; B, 6 months post-op, n=26; C, 12 months post-op; n=24 Echo: Modality not noted; number of beats averaged not noted Study Type: Cross-Sectional	40 ± 14	Transplant
Gehring *et al.*, 1988[202]	10	Transplant: average of 71 ± 21 days after surgery Echo: M-mode echo; averaged over 3 beats Study Type: Cross-Sectional	34 ± 9	Transplant
Gorcsan *et al.*, 1992[201]	34	Transplant: 1 year after surgery Echo: M-mode, 2D, Doppler; averaged over at least 3 beats Study Type: Cross-Sectional	46 ± 9	Transplant
Bech-Hanssen *et al.*, 2016[205]	43	Transplant: Median time from surgery to echo was 185 days Echo: 2D and Doppler; averaged over 3 beats	35 ± 14	Transplant

		Study Type: Cross-Sectional		
Borow *et al.*, 1985[203]	10	Transplant: Mean time from surgery to echo 14 ± 9 months Echo: M-mode; averaged over 5 beats Study Type: Cross-Sectional	25 ± 6	Transplant
Clemmensen *et al.*, 2016[198]	36	Transplant: Echo within 2 weeks of transplant, 1 month, 3 months, 6 months, and 12 months after transplant Echo: M-mode, 2D, Doppler; number of beats averaged not noted Study Type: Longitudinal	45	Transplant
Podrouzkova *et al.*, 2015[206]	43	Transplant: Assessed at two timepoints, T1 (88 ± 22 days) and T2 (253 ± 54 days) Echo: 2D, Doppler; number of beats averaged not noted Study Type: Longitudinal	49 ± 3	Transplant
Meluzin *et al.*, 2013[199]	50	Transplant: 51 ± 11 months since transplant Echo: 2D, Doppler; 3-5 consecutive cycles Study Type: Cross-Sectional	53 ± 2	Transplant
Raichlin *et al.*, 2009[207]	134	Transplant: One week, one year, and 3-5 years following surgery Echo: 2D, Doppler; number of cycles not noted Study Type: Cross-Sectional	49 ± 11	Transplant
Sade *et al.*, 2006[204]	7	Transplant: Echo weekly, bi-weekly, 3 weeks, 6 weeks, or 3 months one year after surgery Echo: 2D; number of cycles not noted Study Type: Longitudinal	31 ± 11	Transplant
Leenen *et al.*, 1991[208]	13	Transplant: 1-month, 3-months, 6-months, 9-months, 12-months after surgery	48 ± 11	Transplant

		Echo: 2D, M-mode; number of cycles not noted Study Type: Longitudinal		
Bittencourt *et al.*, 2021[200]	60	Transplant: 6 months following transplant Echo: 2D, Doppler; 3 consecutive cycles Study Type: Cross-Sectional	44 ± 11	Transplant

Abbreviations: 2D, two-dimensional; AIS, American Spinal Injury Association Impairment Scale; EDV, end diastolic volume; LV, left ventricle; NIMU, non-injured myocardial unloading; SV, stroke volume; TSI, time since injury

4.3.3 Quality Assessment

We used a modified version of the NOS combined with a previously published tool for assessing the quality of echocardiography. The latter accounts for changes in echocardiography techniques and technology over the period encompassing studies included in this review (**Table 4-2**).[98] All studies had an ascertainment of exposure and provided assessment of the outcomes. None of the studies received points for the comparability of the study groups. Only NIMU studies demonstrated that the outcome of interest (i.e., reduced echocardiographic indices) was not present at the start of the study, and therefore SCI and heart transplant studies did not receive points. Ten studies[95,100,150,152,156,186,192,197,199,202] had an experienced or trained sonographer acquiring the images. The quality of the studies varied, but were generally medium quality, with only five studies determined as low quality.[180,188,202–204] (**Table 4-2**).

4.3.4 Left Ventricular Indices following Cardiac Deconditioning

Measures (i.e., common clinical LV indices) were mapped onto a table to compare the changes or differences following SCI, NIMU, and heart transplant from each study (**Table 4-3**). The most commonly investigated LV measure was EF (30 studies). There were only 19 articles that measured any of the indices for diastolic function. Six articles measured global longitudinal strain. The following subsections discuss the type of cardiac deconditioning based on the mechanism (**Figure 4-2**).

Table 4-2. Quality assessment using the New Castle-Ottawa Scale and echocardiography-specific criteria for cohort studies

	Selection					Outcome			Echo-Specific			
Author, Year	Representativeness of Exposed Population	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest was not Present in Study	Comparability	Assessment of Outcome	Follow Up Long Enough for Outcomes to Occur	Adequacy of Follow Up Cohorts	Supine?	Modified Simpsons	Sonographer Highly Trained or Experienced?	Total Score
Kessler *et al.*, 1986[133]	*		*			*	*	*				**5**
Washburn *et al.*, 1986[187]	*		*			*		*	Y			**5**
De Groot *et al.*, 2006[20]	*	*	*			*	*	*	Y			**7**
Vriz *et al.*, 2018[188]	*		*			*	*					**4**
West *et al.*, 2012[184]			*			*	*	*	Y			**5**
Maggioni *et al.*, 2012[180]			*			*	*	*				**4**
Gibbons *et al.*, 2016[181]	*		*			*	*	*		Y		**6**
Currie *et al.*, 2017[182]	*	*	*			*	*	*	Y			**7**
Phillips *et al.*, 1988[183]		*	*			*	*	*				**5**
West *et al.*, 2012[130]	*	*	*			*	*	*				**6**
Huonker *et al.*, 1998[185]	*	*	*			*	*	*				**6**
DeRossi *et al.*, 2014[152]	*	*	*			*	*	*			Y	**7**
Driussi *et al.*, 2014[145]	*	*	*			*	*	*				**6**
Matos-Souza *et al.*, 2011[150]	*	*	*			*	*	*			Y	**7**
Schreiber *et al.*, 2017[186]		*	*			*	*	*			Y	**6**
Sharif *et al.*, 2017[156]	*	*	*			*	*	*	Y		Y	**8**
Ely *et al.*, 2021[100]	*		*			*	*		Y	Y	Y	**7**
Bungo *et al.*, 1987[190]	*		*	*		*		*	Y			**6**
Arbeille *et al.*, 2001[195]			*	*		*			Y			**5**
Summers *et al.*, 2005[191]	*		*	*		*		*				**5**
Hung *et al.*, 1983[193]			*	*		*		*	Y			**5**
Levine *et al.*, 1997[95]			*	*		*		*	Y	Y	Y	**7**
Kozakova *et al.*, 2011[194]			*	*		*		*	Y	Y		**6**
Hamilton *et al.*, 2011[192]	*		*	*		*		*	Y	Y	Y	**8**

Hoffmann *et al.*, 2021[196]	*	*	*	*		*		*		Y		**7**
Qin *et al.*, 2013[197]	*		*			*	*	*	Y	Y	Y	**8**
Gehring *et al.*, 1988[202]	*		*			*					Y	**4**
Gorcsan *et al.*, 1992[201]	*		*			*	*	*				**5**
Bech-Hanssen *et al.*, 2016[205]	*		*			*		*		Y		**5**
Borow *et al.*, 1985[203]	*		*			*		*				**4**
Clemmensen *et al.*, 2016[198]	*		*			*	*	*		Y		**6**
Podrouzkova *et al.*, 2015[206]	*		*			*		*		Y		**5**
Meluzin *et al.*, 2013[199]	*		*			*	*	*	Y	Y	Y	**8**
Raichlin *et al.*, 2009[207]	*		*			*	*	*				**5**
Sade *et al.*, 2006[204]	*		*			*				Y		**4**
Leenen *et al.*, 1991[208]	*		*			*	*		Y			**5**
Bittencourt *et al.*, 2021[200]	*	*	*			*		*		Y		**6**

Table 4-3. Comparison of cardiovascular indices between cardiac deconditioned groups

Author	Wall Thickness	LV Internal Diameter	LV Mass	End Diastolic Volume	End Systolic Volume	Stroke Volume	Ejection Fraction	Cardiac Output	Global Longitudinal Strain	Early Diastolic Filling (E)	Early Myocardial Relaxation	E/A Ratio	E/E' Ratio	Isovolumetric Relaxation Time	Blood Pressure	Heart Rate
Kessler *et al.*, 1986[133]	↔	↓	↓					↓							↓	↔
Washburn *et al.*, 1986[187]	↔	↓	↓												↓	
De Groot *et al.*, 2006[20]	↔	↓		↔			↔	↔				↔	↔	↔	↓	↔
Vriz *et al.*, 2018[188]							↔	↓				↓	↔		↓	↔
West *et al.*, 2012[184]	↔	↓	↓	↓	↔	↓	↓	↓				↔			↓	↔
Maggioni *et al.*, 2012[180]	↔	↓	↔	↓			↓					↔		↑		↔
Gibbons *et al.*, 2016[181]	↔	↔		↔											↔	↔
Currie *et al.*, 2017[182]	↔	↓	↔	↓	↔	↓	↓	↔		↔		↓		↑	↔	↑
Phillips *et al.*, 1988[183]			↔	↔	↔	↔	↑	↓							↓	↓
West *et al.*, 2012[130]				↓	↓	↓	↔	↓			↓				↓	↔
Huonker *et al.*, 1998[185]						↓	↔								↔	↑
DeRossi *et al.*, 2014[152]		↓	↔			↓	↔	↔			↓	↔	↑		↓	↔
Driussi *et al.*, 2014[145]	↑	↓	↔			↔	↔	↓		↓	↓	↓			↔	↔
Matos-Souza *et al.*, 2011[150]	↔	↔	↔				↔	↔			↓	↔	↑		↓	↔
Schreiber *et al.*, 2017[186]	↔	↓	↓				↔	↔		↔	↓	↔	↑		↓	↔
Sharif *et al.*, 2017[156]	↔	↓	↔	↓	↔	↓	↔	↓		↔	↔	↔	↔	↔		↔
Ely *et al.*, 2021[100]	↔	↔	↔	↔	↔	↔	↔	↔		↔	↔	↔			↔	↔
Bungo *et al.*, 1987[190]	↔					↓	↔								↑	↑

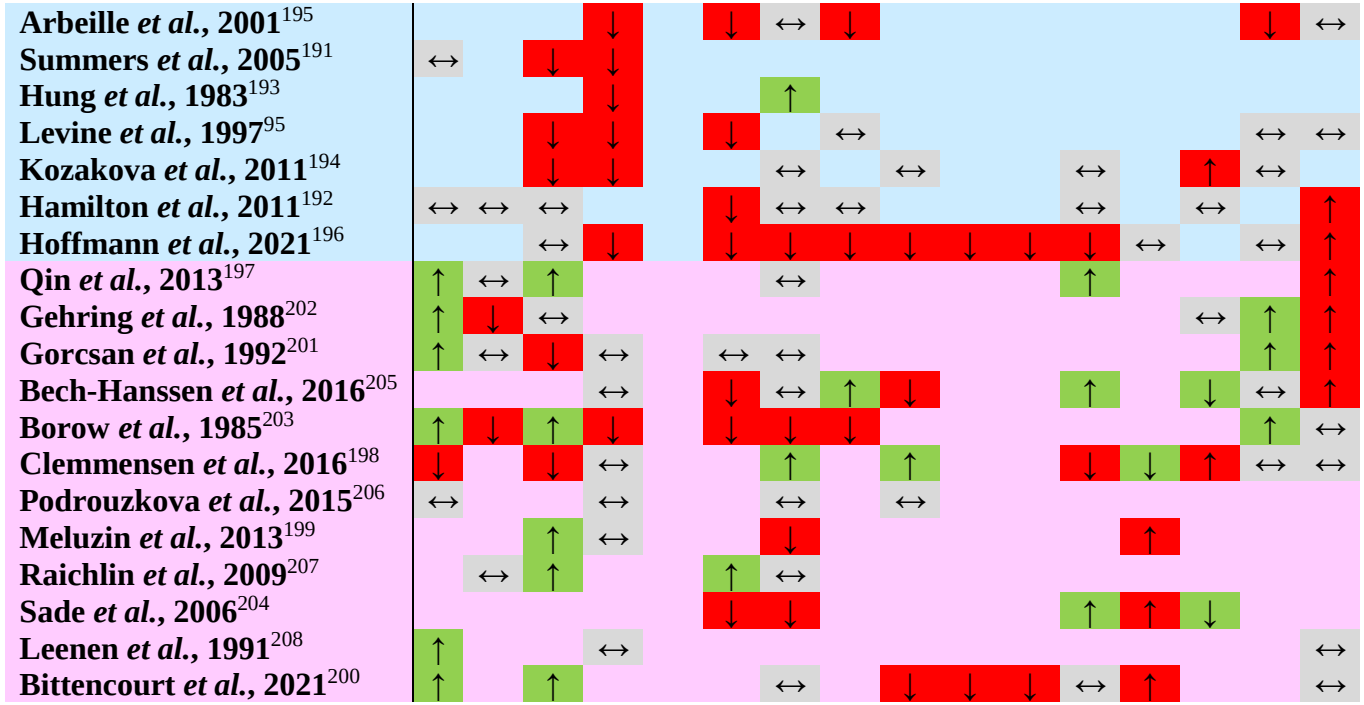
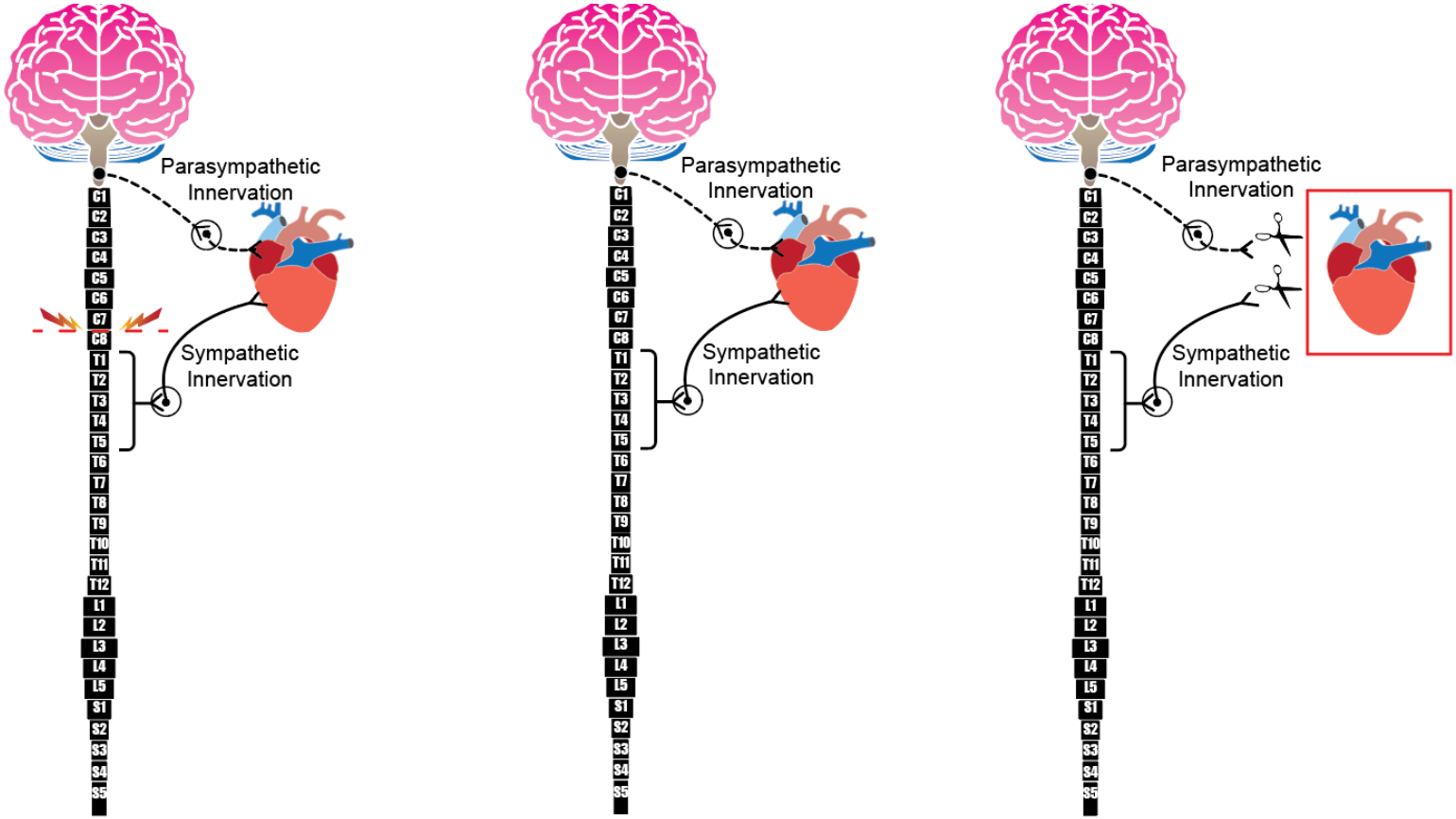

Arbeille et al., 2001[195]
Summers et al., 2005[191]
Hung et al., 1983[193]
Levine et al., 1997[95]
Kozakova et al., 2011[194]
Hamilton et al., 2011[192]
Hoffmann et al., 2021[196]
Qin et al., 2013[197]
Gehring et al., 1988[202]
Gorcsan et al., 1992[201]
Bech-Hanssen et al., 2016[205]
Borow et al., 1985[203]
Clemmensen et al., 2016[198]
Podrouzkova et al., 2015[206]
Meluzin et al., 2013[199]
Raichlin et al., 2009[207]
Sade et al., 2006[204]
Leenen et al., 1991[208]
Bittencourt et al., 2021[200]

Figure 4-2. Schematic overview of the cardiac deconditioning groups



Impaired Sympathetic Cardiac Control (i.e., high level spinal cord injury)

Non-Injured Myocardial Unloading (i.e., bed rest or spaceflight)

Cardiac Denervation (i.e., heart transplant)

4.3.5 Spinal Cord Injury

All SCI studies compared chronic SCI (i.e., > 12 months post-injury) to non-injured individuals using a cross-sectional design. Only one study assessed LV indices within the first year following SCI.[100] More than 50% of the studies in this review that investigated LVIDd, EDV, SV, Q, and E' reported a lower measure for the SCI group compared to the non-injured individuals. At least 50% of studies in this review reported no differences in wall thickness (i.e., septal and posterior wall), LV mass, ESV, EF, E, E/A ratio, and E/E' ratio between SCI and non-injured control groups.

4.3.6 Non-Injured Myocardial Unloading

All NIMU studies were longitudinal in design with the experiments lasting under one year. Participants in these studies had no history of CVD. Six of the eight studies reported on EDV and all found a decrease following NIMU.[95,191,193–196] Five of the eight studies reported on SV and all found a decrease following NIMU.[95,190,192,195,196] Three studies reported on any diastolic indices, with E/A ratio being the only measure in these studies.[192,194,196] EF, Q, and wall thickness were unchanged in at least 50% of the studies that obtained these measures.

4.3.7 Heart Transplant

Given that heart transplant is meant to extend the duration of life in individuals that undergo surgery,[209] it is not surprising that all twelve studies reported improvement or no differences with control groups. Seven studies looked at the first year following transplant:[197,198,200,202,204,207,208] One study showed a decrease in SV and EF within the first year

of transplant[204] and one study showed worsened diastolic indices and global longitudinal strain in individuals with transplant compared to the control group.[200]

4.4 Discussion

This review identified 37 articles on cardiac deconditioning involving individuals with SCI, individuals who underwent NIMU, and received heart transplants. Over 50% of articles were published after 2010, highlighting the advancements in echocardiography, and more importantly, the investigation of cardiac deconditioning in various environments. This review charted literature on the various LV indices that can be measured using echocardiography. This scoping review aimed to understand what is known about cardiac function after SCI in comparison to NIMU (i.e., bed rest and microgravity conditions) and following heart transplant. While the review intended to capture information on cardiac function immediately following SCI, only one recent article looked at associations of LV indices within the first year following SCI,[100] with a relatively small sample size, while all other articles that discussed cardiac function were in the chronic stage of SCI. This is a surprising gap in knowledge as we found that both NIMU and heart transplant articles retrieved showed a decline in LV indices within the first months following intervention. While the SCI literature suggest a decline in LV indices in comparing non-injured controls to individuals with chronic SCI,[98] there is a paucity in the literature regarding sub-acute cardiac changes individuals living with SCI, therefore longitudinal studies are warranted to document the cause-and-effect relationships regarding cardiac function following SCI.

SCI impairs sympathetic-mediated vasoconstriction, which results in an inability to redirect blood to peripheral muscles and a subsequent reduction in venous return.[18] This

hemodynamic impairment is most significant when SCI occurs at the cervical level, as sympathetic control of the heart is also diminished, impairing normal compensatory cardiac responses to hypotension.[104,210] Furthermore, SCI above T6 can result in loss of supraspinal control of autonomic sympathetic pathways.[52] One study extracted in this review,[20] argued the LV dimensions decrease to maintain wall stress (i.e., a maladaptation) and would be the optimal response to decreased physical activity without diminishing cardiac function.[98,156]

SCI has been proposed as an accelerated model for aging.[211] A comparison of NIMU to the aging process and restoration of cardiac workload is evident in a long-term follow-up study[212] describing five healthy, 20-year-old male participants undergoing three weeks of bed rest, followed by eight weeks of endurance training. Q declined by 26% after bed rest, followed by a 40% increase with training, with no significant changes in arteriovenous oxygen difference or HR (i.e., changes attributable to SV). The same participants were followed-up forty years later (i.e., to compare the aging process). At baseline, the measures were comparable to the initial three weeks of bed rest. The study found that three weeks of bed rest in a healthy 20-year old was as detrimental as 40 years of aging.[212]

There have been consistent findings of decreased cardiac muscle mass when comparing SCI to microgravity conditions (i.e., space flight).[17] An investigation using magnetic resonance imaging, showed a decrease in LV mass by 15% during supine bed rest and by 12% after spaceflight in sedentary non-athletic men without CVD.[132] Cardiac atrophy in NIMU does not appear to affect systolic function as it does in SCI,[213] likely due to the preserved sympathetic drive. Interestingly, cardiac atrophy following spaceflight may affect diastolic function as invasive studies have shown a leftward shift in the diastolic pressure-volume curve after two

weeks of head-down-tilt bed rest, resulting in a smaller LV EDV for any given filling pressure.[95] However, reporting on diastolic dysfunction following SCI remains inconclusive to date.[98]

Heart transplant results in the denervation of both sympathetic and parasympathetic nerve fibres.[214] Similar to some individuals with SCI,[90] individuals with a denervated heart (i.e., post-transplant) are unable to experience angina with ischemia. Additionally, the bradycardia and hypotension that may be found with inferior wall infarction post-transplant,[215] are similar to the characteristics of neurogenic shock following SCI in cervical and high-thoracic SCI.[216] Transplanted hearts also rely on ventricular remodeling to maintain Q,[197] with the alterations in LV mass likely driven by increases in wall thickness[197,201–203,208] to maintain a target pressure. Following heart transplant, catecholamine stores are decreased in the cardiac muscle, and individuals may experience more arrhythmias due to dependence on circulating catecholamines.[214] A similar finding can be found in individuals with SCI with the autonomic imbalance that occurs post-injury, due to the preserved parasympathetic input and diminished sympathetic drive.[107]

Exercise capacity is also lower in SCI, NIMU, and heart transplant groups, due to different mechanisms of cardiac deconditioning. Early post-heart transplant recipients have diminished exercise capacity as the HR is slower to increase during exercise due to the reliance on non-cardiac circulating catecholamines,[214] similar to individuals with SCI lesions above T6.[129] For individuals who have undergone NIMU, it has been suggested that it is the orthostatically induced cardiac underfilling (i.e., decreased preload) that is the major cause of reduced exercise capacity.[193] Regardless of mechanism, EDV was generally found to be lower in all three deconditioned groups (i.e., SCI, NIMU, heart transplant).[95,130,156,180,182,184,191,193–196,203] The diminished sympathetic drive to the heart that occurs following high-level SCI is

compounded with the impaired peripheral vasoconstriction (reducing cardiac preload),[217] perhaps impacting exercise capacity to a greater extent. In all cases of cardiac deconditioning, exercise training may improve the exercise capacity of SCI, NIMU, and heart transplant individuals.[218–221]

The review identified several LV indices from the selected literature retrieved for SCI, NIMU, and heart transplant. This was expected, given CVD is a leading cause of death globally.[222] Given the reduced physical inactivity[223] and potentially diminished sympathetic control to the heart[13] following SCI, it is perhaps unsurprising that the cardiac deconditioning that occurs shares some overlap with NIMU and post-heart transplant conditions. Further quantitative assessment is needed to compare the cardiac deconditioning. The relatively new application of speckle tracking should be investigated with these studies. This review highlighted the lack of evidence to make a strong conclusion on the myocardial deformation of these conditions from any of the studies in this review. Only six of the 37 studies incorporated global longitudinal strain into their analysis,[194,196,200,205,206,224] though it is understood the clinical application of strain has become relevant just over the last decade. Therefore, further studies need to be performed before reporting any associations and making conclusions.

Considering comparisons in volume capacity, cardiac atrophy, ability to exercise, and cardiac function, it is worth exploring longitudinal changes in individuals with SCI, as there can be both effects of myocardial unloading and attenuated nervous system control in this population. Clinical implications should dedicate serial diagnostic echocardiography testing for individuals with SCI as there may be changes in cardiac structure and function as the injury progresses.

4.4.1 Strengths and Limitations

The strengths of this review include a rigorous and systematic search strategy advised by a biomedical librarian. This allowed for overview of the available research evidence to be synthesized and to identify a knowledge gap in the field of SCI. However, as the intent of this review was to compare cardiac function in SCI to myocardial unloading and cardiac denervation, establishing what is the primary cause of cardiac dysfunction following SCI remains to be answered. Furthermore, the population selected for the NIMU group were exposed to complete bed rest or microgravity, which does not completely capture the activity levels of the SCI as this population is not completely inactive. Other limitations include our search restriction of English-language which may have potentially introduced a publication bias, although formal assessment of such was considered in our risk of bias analysis. Therefore, this review should mainly be used as a guide for the direction of future studies.

4.5 Conclusion

In summary, this review identified studies that examined LV indices in individuals with SCI, who underwent NIMU, and who underwent heart transplant. Overall, these individuals have reduced LV indices compared to the control group or prior to their intervention, with heart transplant recipients improving one year after surgery. However, there is a paucity in the literature regarding cardiac function within the first year following SCI compared to individuals who underwent myocardial unloading conditions (i.e., bed rest or space flight) and individuals who underwent cardiac denervation (i.e., heart transplant). This knowledge may help in understanding if the cardiac alterations following SCI can be more attributed to physical inactivity or a compromised neuronal component. Such an understanding would inform

guidelines to monitor individuals with SCI and develop strategies to effectively mitigate or even prevent the decline of LV indices. Importantly, the evidence of decreasing LV indices immediately following NIMU and heart transplant, suggests that further investigation into cardiac function during the first year post-SCI is warranted. This will be discussed in Chapter 5.

CHAPTER 5. ALTERATIONS IN LEFT VENTRICULAR STRUCTURE, FUNCTION, AND MECHANICS COMPARING SUB-ACUTE AND CHRONIC SPINAL CORD INJURY TO NON-INJURED INDIVIDUALS[1]

5.1 Introduction

SCI immediately interrupts connections between supraspinal structures and multiple physiological systems that are controlled in the spinal cord.[225] These connections include sensorimotor and autonomic conditions that influence many bodily processes including cardiovascular function.[104] Sympathetic innervation to the heart originates from the upper-thoracic segments (T1-T5),[226] therefore any severe SCI >T1 is likely to cause sympathetic disruption to the heart. The disruption of these descending autonomic pathways, as is the case with cervical SCI (C-SCI), can cause abnormalities in cardiac function due to an intact parasympathetic (vagal) control and decreased sympathetic activity.[64] This sympathovagal imbalance may also play a role in the heightened risk for development of CVD,[6] which ultimately results in maladaptive cardiac remodeling.[20]

The diminished supraspinal control in combination with a loss of skeletal muscle pumping activity below the lesion level may lead to increased venous blood pooling in the lower

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[1] A version of Chapter 5 has been peer-reviewed and is undergoing revisions for publication. Fossey MPM*, **Balthazaar SJT***, Squair JW, Williams AW, Poormasjedi-Meibod MS, Nightingale TE, Erskine E, Hayes B, Ahmadian M, Currie KD, Walter M, Krassioukov AV[#], West CR[#]. Spinal cord injury impairs cardiac function due to impaired bulbo-spinal sympathetic control.

limbs and abdominal viscera.[11] The resulting myocardial unloading causes a reduction in LV filling and preload,[227] that is further amplified by a reduction in blood volume secondary to chronic physical inactivity.[19,156] These alterations in preload and blood volume cause a decline in SV and EDV.[130,182,185]

These SCI-induced alterations to cardio-autonomic function, in addition to other cardio-metabolic sequelae (e.g., alterations in physical activity,[228] metabolism,[229,230] hemodynamics,[71,83] and arterial stiffness[231]) contribute to the increase in the incidence of acute cardiac events.[101,232] As concluded in Chapter 4, echocardiography studies to date have investigated differences between non-injured individuals and those with chronic SCI,[98] however the cardiac consequences within the first year following SCI remains unclear. Therefore, the purpose of this chapter is to compare cardiac structure and function in individuals with sub-acute SCI (i.e., within the first year) and compare them to non-injured controls and individuals with chronic SCI (AIM 2 of this thesis). This may preclude researchers and clinicians from optimizing treatment strategies for patients with SCI.

5.2 Methods

5.2.1 Ethical Approval

Clinical protocols were approved by the University of British Columbia Clinical Research Ethics Board and conducted in accordance with the second Helsinki Declaration.[233] Individuals provided written informed consent prior to data collection.

5.2.2 Experimental Design

Eligible participants were between the ages of 18-60 years old, and had sustained a traumatic motor-complete (American Spinal Injury Association Impairment Scale A/B) SCI between C3-C8, as classified using the International Standards for Neurological Classification of SCI.[26] Individuals in the sub-acute group (S-A; ≤ 5 months TSI; n = 23) were recruited from the GF Strong Rehabilitation Centre, Vancouver, BC, Canada. Individuals in the chronic group (CHRON; ≥ 24 months TSI; *n* = 22) were recruited from the community via the Blusson Spinal Cord Centre (BSCC), Vancouver, BC, Canada. The non-injured controls (CON; n = 14) were recruited from the Vancouver community and were compared for age, sex, height, and weight to SCI individuals. Exclusion criteria comprised any history of CVD, which was confirmed with a verbal medical history, and any language or cognitive barrier that prevented the individual from following English instructions. Using a cross-sectional design, I assessed cardiac volumes, function and mechanics in individuals with sub-acute or chronic SCI, and in non-injured controls via transthoracic echocardiography (TTE).

5.2.3 Echocardiography

As an experienced sonographer, I performed TTE using a Vivid 7 / i ultrasound unit (GE Healthcare, Mississauga, ON). Individuals enrolled in the study were transferred to an echocardiography table and rested in the left lateral decubitus position for five minutes. HR was recorded simultaneously with echocardiographic images using a three-lead electrocardiogram. Three consecutive cardiac cycles were recorded at the end of a tidal expiration, and the mean value was recorded for each parameter. All measures were performed according to American Society of Echocardiography (ASE) guidelines.[138] Indices of LV mechanics were derived from

apical four-chamber and parasternal short-axis images at the level of the mitral valve (basal), papillary muscle (mid), and apex (apical). Images were analyzed using 2D speckle-tracking software in accordance with current guidelines.[140] To control for differences in HR, raw speckle-tracking traces were imported into customized post-processing software (2D Strain Analysis Tool, Stuttgart, Germany), which interpolates the data into 600 points in systole and 600 points in diastole using a standard cubic spline algorithm.

5.2.4 Statistical Analysis

Data are presented as median (first quartile to third quartile). Statistical analyses were performed using Statistical Package for Social Science software (SPSS Version 27, IBM, Chicago, IL, USA) with statistical significance set at ≤ 0.05. Graphical representations were made in Prism (version 6.0e, GraphPad Software, San Diego, CA, USA) and Adobe Illustrator (version 13.1.1, Adobe Inc., 2019, San Jose, CA, USA). Outliers were removed using the ± 2 SD method. Normality was tested with the Shapiro-Wilk test. Equality of variances were tested with either the Bartlett or Levene test, when appropriate. Group differences were analyzed with a non-parametric Kruskal Wallis with Mann-Whitney U post-hoc. Participant characteristics were analyzed using a non-parametric Kruskal Wallis with post-hoc test or a Mann-Whitney U t-test. Additionally, the categorical variables of sex and American Spinal Injury Association impairment scale were analyzed using a Fisher's exact test.

5.3 Results

5.3.1 Temporal Progression of Cardiac changes Post-SCI

To assess the temporal changes in cardiac structure and function following high-level SCI we prospectively recruited a large cohort of individuals (n = 59) with sub-acute (≤ 5 months post-SCI) and chronic cervical SCI (≥ 24 months post-SCI), as well as non-injured controls, and used TTE to measure LV structure, function and mechanics (**Table 5-1**). We found that LV volumes and systolic velocity (S') were lower in individuals with chronic SCI compared to non-injured controls (**Figure 5-1.b-e**). We also found that E' was lower and E/E' ratio was higher in individuals with chronic SCI versus non-injured controls, implying altered diastolic function. With respect to LV mechanics, we found that individuals with chronic cervical SCI had significantly lower peak LV twist (**Figure 5-1.f,i; Table 5-2**) that predominantly resulted from lowered-peak apical rotation (**Figure 5-1.h,l**) compared to those with sub-acute SCI. Reduced peak LV twist was accompanied by slower peak systolic twist velocity (**Figure 5-1.g,j**) and slower untwisting rate (**Figure 5-1.g,k**) in individuals with chronic cervical SCI versus those with sub-acute C-SCI and non-injured controls. There were otherwise no differences between any groups for peak basal rotation, global circumferential strain, or longitudinal strain.

Table 5-1. Participant characteristics of non-injured, sub-acute, and chronic injured groups

	GROUP			
	NON-INJURED	**SUB-ACUTE**	**CHRONIC**	**P VALUE**
Age (years)	37 (26 to 51)	41 (32 to 55)	43 (34 to 50)	$P = 0.674$
Height (cm)	174 (170 to 181)	179 (167 to 183)	175 (167 to 184)	$P = 0.826$
Weight (kg)	81 (71 to 87)	82 (73 to 95)	75 (65 to 81)	$P = 0.130$
BSA (m^2)	1.99 (1.82 to 2.05)	2.02 (1.87 to 2.15)	1.87 (1.77 to 2.01)	$P = 0.141$
Male/Female (% Male)	10/4 (71%)	14/9 (61%)	15/7 (68%)	$P = 0.828$
AIS A/B (%A)	-	9/14 (39%)	14/8 (64%)	$P = 0.139$
TSI (days)	-	100 (84 to 109)	5463 (2678 to 9222)	$\mathbf{P < 0.001}$

Continuous values are median and quartiles (25% to 75%). Non-injured (n = 14); Sub-acute SCI (n = 23): C3 (n = 1), C4 (n = 8), C5 (n = 7), C6 (n = 4), C7 (n = 1), C8 (n = 2); Chronic SCI (n = 22): C4 (n = 5), C5 (n = 8), C6 (n = 7), C7 (n = 2). Outliers were not removed prior to analysis as individuals were matched. Continuous variables were analyzed using a non-parametric Kruskal Wallis or a Mann-Whitney U test. The categorical variables of sex and American Spinal Injury Association impairment scale (AIS) were analyzed using a Fisher's exact test. BSA, body surface area; TSI, time since injury.

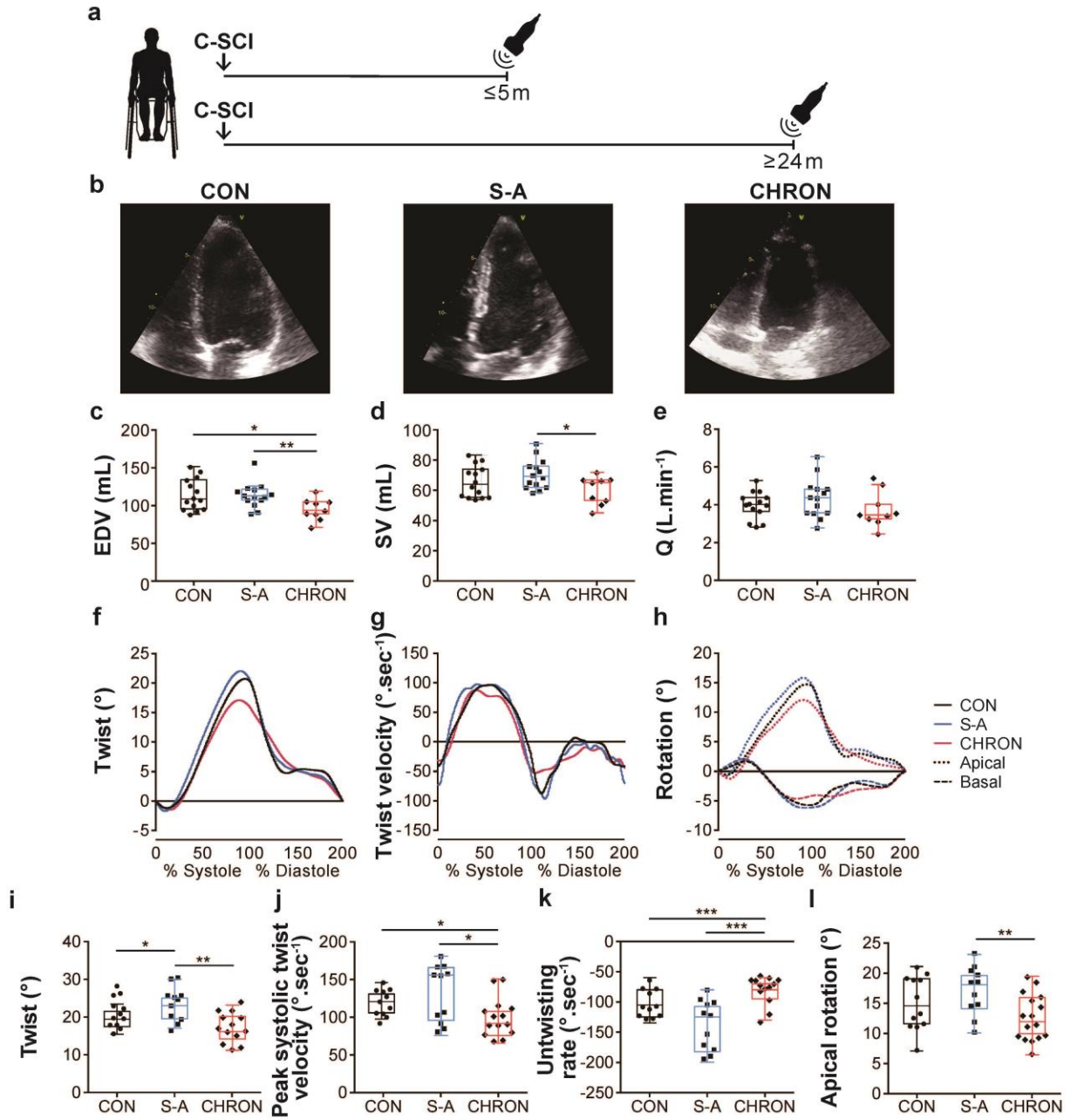

Figure 5-1. Temporal progression of echocardiography-derived left ventricular functional, volumetric, and mechanical indices

a Echocardiography was performed cross-sectionally on non-injured control individuals (CON), and on cervical SCI individuals at ≤ 5 months in the sub-acute period (S-A) and at ≥ 24 months in the chronic period post-SCI (CHRON). **b** Representative apical four-chamber images of previously described groups (scaled to each other). **c** End-diastolic volume (EDV) was reduced in CHRON *vs.* CON with similar trends for **d** stroke volume (SV) and **e c**ardiac output (Q). **f** Ensemble averaged twist, **g** twist velocity and **h** rotation curves during one cardiac cycle across all participants in each group. **i** Twist was lower in CHRON *vs.* S-A and tended to be lower in

CHRON *vs.* CON. **j** Peak systolic twist velocity was slower in CHRON *vs.* both CON and S-A. **k** Untwisting rate was slower in CHRON *vs*. both CON and S-A. **l** Apical rotation was lower in CHRON *vs*. S-A, while basal rotation was not. Data are presented as median with individuals represented as symbols (n = 9-22 per group) and were analyzed using a Kruskall Wallis test with Mann-Whitney U post-hoc: *P < 0.05, **P < 0.01 and ***P < 0.001.

Table 5-2. Echocardiographic measure differences between non-injured controls, sub-acute, and chronic injured groups

		GROUP		
	P VALUE	**NON-INJURED**	**SUB-ACUTE**	**CHRONIC**
LV volumetric, heart rate and systolic function measures				
EDV (mL)	***P* = 0.024**	108 (95 to 134)	112 (105 to 121)	93 (85 to 105) * ††
ESV (mL)	***P* = 0.005**	47 (41 to 58)	44 (38 to 46)	35 (29 to 38) * ††
SV (mL)	*P* = 0.096	64 (55 to 75)	69 (62 to 76)	64 (51 to 66) †
Q (L/min)	*P* = 0.310	4.01 (3.47 to 4.45)	4.36 (3.56 to 4.84)	3.45 (3.17 to 4.54)
HR (beats per minute)	*P* = 0.903	59 (54 to 65)	60 (56 to 67)	60 (52 to 72)
EF (%)	***P* < 0.001**	57 (56 to 60)	62 (59 to 65) ***	63 (61 to 64) ***
S' septal (m/s)	***P* = 0.001**	0.09 (0.08 to 0.11)	0.09 (0.08 to 0.12)	0.07 (0.06 to 0.08) *** ††
LV diastolic function measures				
E (m/s)	*P* = 0.856	0.72 (0.65 to 0.85)	0.74 (0.65 to 0.88)	0.79 (0.63 to 0.85)
Deceleration time (ms)	*P* = 0.529	222 (191 to 248)	216 (147 to 250)	189 (169 to 225)
A (m/s)	*P* = 0.364	0.46 (0.35 to 0.58)	0.51 (0.41 to 0.63)	0.50 (0.40 to 0.54)
E/A ratio	*P* = 0.387	1.74 (1.42 to 2.06)	1.42 (1.30 to 1.88)	1.57 (1.37 to 1.92)
IVRT (ms)	*P* = 0.228	68 (59 to 74)	70 (55 to 88)	74 (65 to 92)
E' septal (m/s)	***P* = 0.002**	0.13 (0.11 to 0.16)	0.12 (0.09 to 0.15)	0.09 (0.07 to 0.11) *** †
E/E' septal ratio	***P* = 0.012**	5.87 (4.83 to 6.80)	6.84 (5.75 to 8.11) .	7.40 (6.47 to 10.39) **
LV structural measures				
IVSd (cm)	*P* = 0.191	0.90 (0.88 to 1.00)	1.05 (0.90 to 1.20)	0.98 (0.80 to 1.20)
LVIDd (cm)	*P* = 0.443	4.54 (4.18 to 4.88)	4.50 (3.98 to 5.00)	4.30 (3.85 to 4.80)
PWd (cm)	*P* = 0.255	0.90 (0.88 to 1.00)	1.00 (0.90 to 1.10)	0.98 (0.80 to 1.10)
IVSs (cm)	*P* = 0.221	1.32 (1.19 to 1.48)	1.45 (1.20 to 1.70)	1.30 (1.20 to 1.60)
LVIDs (cm)	*P* = 0.894	3.00 (2.65 to 3.28)	2.95 (2.78 to 3.23)	2.90 (2.68 to 3.23)
PWs (cm)	*P* = 0.163	1.42 (1.23 to 1.58)	1.55 (1.40 to 1.70)	1.40 (1.28 to 1.60)
RWT	*P* = 0.466	0.41 (0.38 to 0.47)	0.44 (0.39 to 0.50)	0.46 (0.36 to 0.54)
Estimated LV mass (g)	*P* = 0.220	145 (107 to 172)	158 (129 to 203)	137 (103 to 167)

LV twist mechanical measures				
Twist (°)	***P* = 0.005**	19 (17 to 22)	23 (19 to 25) *	16 (14 to 21) ††
Peak twist velocity (°/sec)	***P* = 0.030**	120 (105 to 130)	155 (95 to 165)	91 (75 to 108) * †
Untwisting rate (°/sec)	***P* < 0.001**	-105 (-125 to -75)	-125 (-190 to 105)	-80 (-98 to -70) *** †††
Apical rotation (°)	***P* = 0.024**	15 (11 to 19)	18 (14 to 20)	12 (9 to 16) **.** ††
Basal rotation (°)	*P* = 0.412	-5 (-7 to -4)	-6 (-7 to -5)	-5 (-7 to -4)
Torsion (°)	***P* = 0.047**	2.10 (1.83 to 2.39)	2.47 (2.00 to 2.57) **.**	2.00 (1.86 to 2.40) †
LV strain measures				
Circumferential strain, apex (%)	*P* = 0.996	-26 (-28 to -22)	-26 (-27 to -23)	-26 (-27 to -25)
Circumferential strain, base (%)	*P* = 0.386	-20 (-21 to -19)	-18 (-19 to -17)	-19 (-25 to -19)
Longitudinal strain (%)	*P* = 0.561	-19 (-20 to -18)	-18 (-19 to -18)	-18 (-20 to -17)

Values are median and quartiles (25% to 75%). Volumetric, functional and structural measures: non-injured (*n* = 13-14); sub-acute (*n* = 14-23); chronic (*n* = 9-22). Mechanical and strain measures: non-injured (*n* = 11-14); sub-acute (*n* = 11-13); chronic (*n* = 9-18). Group differences non-parametric measures Kruskal Wallis with Mann-Whitney U post-hoc are shown with symbols. A, late transmitral filling velocity; d, end-diastolic; E, early transmitral filling velocity; E', early transmitral myocardial velocity; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; IVRT, isovolumetric relaxation time; IVS, intraventricular septum thickness; LV, left-ventricle; LVID, left-ventricular internal diameter; PW, posterior wall thickness; Q, cardiac output; RWT, relative wall thickness; s, end-systolic; S', myocardial contractile velocity; SV, stroke volume. Between-group comparison (*vs.* non-injured): **.***P* < 0.1, **P* < 0.05, ***P* < 0.01 and ****P* < 0.001; (*vs.* sub-acute): +*P* < 0.1, †*P* < 0.05, ††*P* < 0.01 and †††*P* < 0.001.

5.4 Discussion

In a large cohort of individuals with cervical SCI we demonstrate that chronic, but not sub-acute, SCI is associated with a reduction in LV volumes and mechanics. Individuals with C-SCI have reduced LV volumes and lower LV twist mechanics in the chronic phase (≥ 24 months post-SCI), but preserved cardiac function in the sub-acute phase of SCI (< 5 months). The reductions in LV volumes and mechanics following C-SCI take months to manifest in humans, potentially identifying a therapeutic window of opportunity for interventions in the sub-acute phase.

5.4.1 Potential Mechanisms

Decreased SV and Q leads to a reduction of heart chamber size, with LV atrophy being prominent.[20,98,135] However, compensatory myocardial fiber shortening is offset by a concomitant preserved EF. SCI may mediate decreased myocardial relaxation in individuals with higher lesion levels (i.e., C-SCI). Indeed, a cross-sectional study comparing individuals with chronic SCI to non-injured individuals has reported that individuals with SCI may have compromised diastolic function outcomes.[145] This is can be attributed to the volume unloading, or the incapacity to maintain sufficient venous return to the heart (i.e., reduced preload).[135]

5.4.2 Clinical Implications

C-SCI may disrupt autonomic cardiovascular homeostasis, which can lead to dynamic BP measures.[234] These prominent maladaptations in a clinical setting of extremely labile BP are characterized by episodes of low BP when in an upright position (i.e., OH), and episodes of high BP in response to afferent stimuli below the level of injury (i.e., AD).[2] These episodes of

abnormal BP may also play a role in the development of CVD following SCI.[12] Animal models have shown that repeatedly inducing AD results in reduced LV dimensions and altered cardiac volumes.[97]

For individuals living with C-SCI, clinicians should be attentive to cardiac structure, function, and mechanics throughout the time course of the injury; TTE may be useful to monitor these changes over time. Given values such as EDV, SV, and E' are common parameters collected with clinical echocardiography, the findings of this study may have wide use. Pre-clinical models have suggested that contractile dysfunction in high-level SCI results from the immediately diminished sympathetic input to the heart,[235] further suggesting the need for longitudinal monitoring of cardiac indices from the acute to chronic phase.

A potential strategy to reduce the burden of CVD in this group should focus on strategies to increase preload, as individuals with SCI have demonstrated improved diastolic responses to increased volume loading, suggesting some ventricular compliance.[156] Namely, regular exercise may increase heart size and is related to an increase in preload and venous compliance.[180] Other recommended strategies include compression bandages or support stockings to reduce the venous pooling in lower limbs,[75] increasing fluid and salt intake,[71] or pharmacological interventions such as the use of fludrocortisone to expand plasma volume[210] and midodrine to increase peripheral vasoconstriction.[236]

By defining the temporal events in cardiac structure and function, identification of future interventions should target the loss of sympathetic control with a view to offsetting the changes that occur in the heart. Recent empirical evidence supporting a cardio-beneficial effect on activation of sympathetic circuitry is the use of transcutaneous and epidural electrical stimulation of the spinal cord to increase cardiac function via the excitement of dorsal afferents, which

activates intraspinal circuitry to depolarize the sympathetic preganglionic neurons.[237,238] This research, therefore, implies that future cardio-therapeutic interventions should seek to either acutely target the preservation of the supraspinal sympathetic pathways or chronically target the spinal sympathetic pathways (i.e., neuromodulation) to offset reductions in cardiac function post-SCI.

5.4.3 Limitations

This is a cross-sectional study: longitudinal designs are preferable in determining the effects of SCI on cardiac structure, function, and mechanics. There is a wide range of TSI in which the echocardiograms were performed for the chronic group. Consequently, the outcomes may not be generalizable to all individuals in the chronic phase of C-SCI, but perhaps those living with C-SCI for at least a decade. Further, we cannot assume LV outcomes for this acute C-SCI population will be similar to this chronic C-SCI population as they are similar in age when TTE was performed. The chronic C-SCI group were taken from a convenience sample, and may not accurately represent all community-dwelling individuals living with SCI. Changes in hemodynamics can occur on a beat-to-beat basis, potentially affecting LV outcome measures. Autonomic completeness was not evaluated in this study, therefore assuming all individuals had the same diminished supraspinal sympathetic control to the heart. Lastly, we enrolled a relatively small number of participants; the small sample size can be a common occurrence when working with persons with physical disabilities due to challenges with participant identification and recruitment.[239] Larger studies adequately powered for clinical outcomes are warranted to confirm our results.

5.5 Conclusion

Individuals in the chronic stage of motor-complete traumatic C-SCI may be at risk for altered cardiac structure, function, and mechanics compared to individuals in the sub-acute stage and non-injured individuals. This finding may suggest that interventions can be applied during the acute/sub-acute setting before structural adaptations in the LV begin to occur. Better understanding of the pathophysiology and time-dependent changes of cardiac structure and function following SCI may enable us to mitigate the disease process resulting in compromised subclinical LV changes. Further longitudinal research following the same participants in the sub-acute stage of SCI is necessary to further our understanding of specific LV structure and function time course changes, as was assessed in Chapter 7.

CHAPTER 6. CARDIAC ARRHYTHMIAS SIX MONTHS FOLLOWING TRAUMATIC SPINAL CORD INJURY[2]

6.1 Introduction

Following a traumatic SCI, one of several challenges for any clinician is the management of cardiovascular events including arrhythmias.[53] The human heart is innervated by sympathetic and parasympathetic neurons, which can alter the HR given an autonomic response.[10] Following SCI, injury to the cervical level can disrupt sympathetic descending input to target organs below the lesion level.[12,97] Cervical SCI may result in either partial or total loss of supraspinal sympathetic control of the heart (T1-T5),[98] while the vagus nerve remains uncompromised, creating an unopposed parasympathetic dominance.[240] Though no structural or functional differences were found in Chapter 5, individuals with cervical SCI can present with compromised chronotropic, dromotropic, and inotropic responses.[241] In contrast, individuals with a low-thoracic SCI will have fully intact autonomic sympathetic and parasympathetic control of the heart and no impact on cardiac function.[64]

The use of a continuous 24-hour recording of a Holter monitor increases the chances of recording infrequent but recurrent arrhythmias compared to a brief clinical electrocardiogram

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[2] A version of Chapter 6 has been published. **Balthazaar SJT**, Sengeløv M, Bartholdy K, Malmqvist L, Ballegaard M, Hansen B, Svendsen JH, Kruse A, Welling KL, Krassioukov AV, Biering-Sørensen F, Biering-Sørensen T. Cardiac arrhythmias six months following traumatic spinal cord injury. The Journal of Spinal Cord Medicine (2021), In Press.

test.[242] The prospective observational study aims to investigate the incidence of arrhythmias at six months following traumatic SCI and to compare the prevalence of arrhythmias between participants with cervical and thoracic SCI (AIM 3 of this thesis). Participants with SCI at the cervical level have previously demonstrated impaired sympathetic innervation to the heart implying a greater risk of episodes of bradycardia, atrioventricular (AV) block, and cardiac arrest due to the unopposed parasympathetic activity.[107]

The acute period following high-level SCI can be commonly associated with profound cardiovascular autonomic dysfunctions[67] (i.e., hypotension, bradycardia), which are components of neurogenic shock.[243] Although arrhythmias following SCI have been documented previously, the occurrences and the nature of cardiac arrhythmias during early phases of recovery following SCI are not well documented. I hypothesized that the incidence of arrhythmias will decrease with time following the onset of SCI. Since consequences of autonomic dysfunction are injury-level dependent,[11] and further hypothesized that occurrence of arrhythmias will occur less frequently in individuals with thoracic SCI compared to individuals with cervical SCI.

6.2 Methods

6.2.1 Study Setting and Design

The Copenhagen University Hospital, Rigshospitalet, Denmark receives all patients with acute traumatic SCI. In brief, participants for this prospective study were admitted as traumatic SCI patients to the Department of Neurosurgery, the Spine Unit of Department of Orthopedic Surgery, or the Neurological Intensive Care Unit (ICU), and were screened for inclusion in the study.[107] Participants in the study had a Holter monitor applied in hospital. If the participants were discharged from hospital, they were equipped with the Holter monitor at their home, which

would then be sent back to the hospital following the monitoring period. The inclusion criteria for the study were traumatic SCI individuals with NLI from C1-T12 and age of 18 years or older, who signed informed consent forms. Exclusion criteria for the study were pregnancy, the use of cardiac pacemaker prior to SCI, and/or significant brain injury. The protocol was approved by the Scientific Ethics Committee of the Capital Region, Denmark.[107]

A clinician documented the NLI and severity using the International Standards for Neurological Classification of SCI (ISNCSCI) according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS).[244] Due to the limited number of participants with thoracic SCI, the participants were dichotomized into cervical (C1-C8; n = 44) and thoracic (T1-T12; n = 11) SCI groups as the main outcome of the study, however a sub-analysis was also performed to observe any differences within the thoracic group.

6.2.2 Materials

Holter (DelMar Reynolds, Lifecard CF, Lifecard: SE, Issaquah, WA) recordings were used to document HR and cardiac rhythm continuously for 24 hours. Holter monitors have been proven useful in diagnosing and observing cardiac arrhythmias.[242] I defined sinus bradycardia in two ways with the Holter analysis system (Sentinel, Spacelabs Healthcare, version 8.1, Sentinel: SE, Snoqualmie, WA),: as an episode of six beats or more with a HR <50 bpm (SB50) and as an episode of six beats or more with a HR <60 bpm (SB60).[107] The first Holter recording (Holter 1) was performed as close to admission as possible. Holters 2-5 recorded patient cardiac rhythms one to four weeks after SCI. The last Holter recording (Holter 6) was obtained six months after SCI.

6.2.3 Statistical Analysis

Data are presented as mean and one standard deviation (SD). A Shapiro-Wilk test was performed to assess normality of continuous variables, stratified by cervical and thoracic SCI groups. Statistical assessment of categorical variables was performed using the appropriate Chi-squared test or Fisher's exact test. Continuous variables were compared with Student's *t*-test or a Mann-Whitney U t-test (non-parametric). A repeated measure analysis of variance (ANOVA) was performed to investigate if there was any change in cardiac arrhythmias over time with Bonferroni's correction for multiple comparisons (or Kruskal Wallis with post-hoc test, if non-parametric). Analysis of covariance (ANCOVA) was used to adjust for age. To determine if there were any associations with severity of injury (i.e., AIS), point biserial correlation was used for continuous dependent variables and corrected Cramer's V was used for categorical dependent variables. *P* values < 0.05 were considered statistically significant. IBM SPSS for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) was used for analysis and graphical representations with editing in Adobe Illustrator version 25.2.3 (Adobe Inc., San Jose, CA).

6.3 Results

6.3.1 Participants

Fifty-five participants were included in the study. 44 participants had cervical SCI and 11 had thoracic SCI. A sub-analysis determined there were no differences in HR or arrhythmogenic occurrences between the six participants with a lower thoracic SCI (T6-T12) and five participants with an upper thoracic SCI (T1-T5), therefore we combined these individuals into one group for our main outcome. The participant characteristics are shown in **Table 6-1**. Participants with cervical and thoracic lesions were demographically similar except for age.

Using the International SCI Cardiovascular Function Basic Data Set,[245] 21 participants of the cervical group and two participants from the thoracic group were identified with a history of CVD; this was not relatively different to the participants of the thoracic group. Additionally, there were no differences between groups for participants on a respirator, that were operated on, or were in the ICU.

Table 6-1. Participant characteristics grouped by lesion

	CERVICAL SCI	THORACIC SCI	P VALUE
Number of Participants	44	11	0.88
Males	33 (75%)	8 (63%)	
Females	11 (25%)	3 (37%)	
Age (years)			
Mean ± SD	64 ± 14	45 ± 21	0.001
Range	36 to 91	22 to 77	
Injury Severity (ASIA Impairment Scale)			0.15
Grade A-C	29 (66%)	10 (91%)	
Grade D	15 (33%)	1 (9%)	
Mean Number of Days between Spinal Cord Injury and Holter 1 ± SD	4 ± 2	4 ± 3	0.15
Number of Participants with Previous Cardiovascular History	21 (48%)	2 (18%)	0.10
Number of Participants with Spinal Surgery Performed	32 (94%)	9 (100%)	0.67

Abbreviations: ASIA, American Spinal Injury Association; SD, standard deviation
The characteristics of the participants included in the study. Apart from age, these were comparable ($P \geq 0.10$) between the cervical and the thoracic groups using the appropriate tests for continuous or categorical variables.

6.3.2 Holter Monitoring

The number of days after SCI before the participants were equipped with Holter monitors varied mainly due to practical challenges including procuring informed consent, due to sedation, surgery, and other investigations. Holter 1 was performed 4 ± 2 days after injury, Holter 2 was performed 8 ± 3 days after injury, Holter 3 was performed 15 ± 2 days after injury, Holter 4 was

performed 21 ± 3 days after injury, Holter 5 was performed 29 ± 4 days after injury, and Holter 6 was performed 187 ± 28 days after injury. The results of the Holter recordings are shown in Table 2, comparing the groups, and Figure 1, comparing timepoints within groups. The closest timepoint to the Month 6 Holter showing significant changes in maximum HR, minimum HR, number of sinoatrial (SA) node arrests, number of atrioventricular (AV) blocks, and number of SVT arrhythmias are displayed in **Figure 6-1**.

6.3.3 Maximum Heart Rate

The mean maximum HR was different between cervical and thoracic SCI groups two weeks (97 ± 19 vs. 113 ± 10, $P = 0.017$), three weeks (97 ± 18 vs. 114 ± 13, $P = 0.009$), and four weeks (100 ± 18 vs. 119 ± 17, $P = 0.004$) post-injury between cervical and thoracic participants, as shown in **Table 6-2**. The mean maximum HR was lower in the cervical group compared with the thoracic group after adjusting for age ($P = 0.009$) at the four-week time point.

There was a significant increase in the mean maximum HR at six months compared to four weeks (Figure 1) for the cervical SCI group (114 ± 18 vs. 100 ± 18, $P = 0.001$). Mean maximum HR at six months compared to ~4 Days Post-SCI (123 ± 14 vs. 106 ± 12, $P = 0.011$) and Week 1 post-SCI (123 ± 14 vs. 106 ± 11, $P = 0.008$) significantly increased for the thoracic group, with an increasing trend from Week 4 to Month 6 (119 ± 17 vs. 123 ± 14, $P = 0.05$). There were associations with a small effect size between severity of injury (i.e., AIS) and mean maximum HR in Week 2 ($r_{pb} = 0.292$, n = 52, $P = 0.036$), Week 3 ($r_{pb} = 0.304$, n = 50, $P = 0.032$), and Month 6 ($r_{pb} = 0.321$, n = 45, $P = 0.032$), with a trend in Week 1 ($r_{pb} = 0.248$, n = 54, $P = 0.07$). For the cervical group only, there were associations with a medium effect size between injury severity and mean maximum HR in Week 2 ($r_{pb} = 0.521$, n = 42, $P < 0.001$),

Week 3 (r_{pb} = 0.631, n = 40, P < 0.001), Week 4 (r_{pb} = 0.574, n = 38, P < 0.001), and Month 6 (r_{pb} = 0.534, n = 36, P = 0.001). There were no associations found between the thoracic group and injury severity (P > 0.35).

6.3.4 Minimum Heart Rate

The mean minimum HR in the period shortly after SCI (corresponding to Holter 1) was significantly lower in the cervical group compared with the thoracic group even after adjustment for age (58 ± 11 vs. 69 ± 12 years, p = 0.022). There was no significant difference for mean maximum or mean minimum HR between groups six months post-SCI or associations found between severity of injury and mean minimum HR.

6.3.5 Arrhythmogenic Occurrences

There are more SA node events in both groups compared to AV node events. The occurrence of SA node arrests decreased significantly after the first week following injury in the cervical group (7 vs. 2, P = 0.025). Two participants with cervical SCI had events of 2° AV block (Mobitz I and II), but not 3° AV block. One participant with cervical SCI had two episodes of ventricular escape rhythm. There was a significant difference between the occurrences of SVTs in Week 1 and Week 2 between the two groups (P = 0.021 and P = 0.020, respectively); when adjusting for age, P = 0.18 between the groups for Holter 2 and P = 0.10 for Holter 3. There was an association between severity of injury and participants who experienced SVT at Week 4 (P = 0.033) for the cervical group compared to the thoracic group and a trend at Month 6 (P = 0.07); participants with less severe injuries experienced SVT events. The Holter monitor

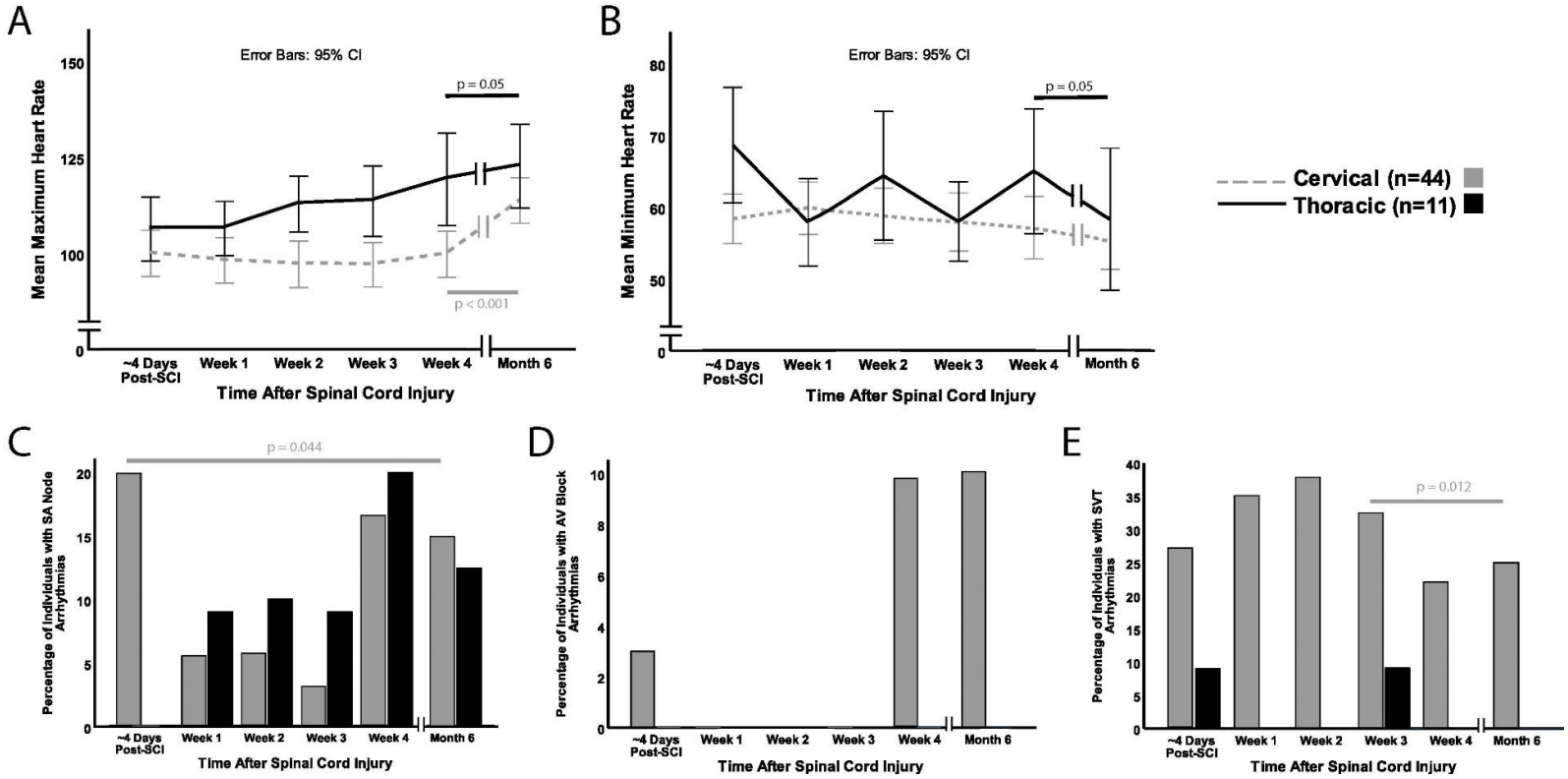

Figure 6-1. Holter monitoring changes six months following spinal cord injury

Temporal changes seen in a 24-hour Holter monitor shortly after spinal cord injury and up to six months. **A,** mean maximum HR measured in beats per minute shows a significant increase from the Week 4 timepoint to the Month 6 timepoint ($P < 0.001$) for the cervical group and an increasing trend for the thoracic group ($P = 0.05$). **B,** mean minimum HR shows a decreasing trend from the Week 4 timepoint to the Month 6 timepoint ($P = 0.05$) in the thoracic group, while the cervical group did not change. **C,** the percentage of individuals in the cervical group with SA node arrhythmias decreased significantly from approximately four days after injury to the Month 6 timepoint ($P = 0.044$). **D,** a graphical representation of the percentage of individuals that had any type of AV block over the 6-month period; there were AV blocks observed in the cervical group, but not the thoracic group. **E,** the percentage of SVT arrhythmias that occurred at the Month 6 timepoint decreased significantly from the Week 3 timepoint ($P = 0.012$) in the cervical group and showed no changes in the thoracic group.

Abbreviations: AV, atrioventricular; HR, heart rate; SA, sinoatrial; SCI, spinal cord injury; SVT, supraventricular tachycardia

Table 6-2. Occurrence of arrhythmias between participants with traumatic spinal cord injury

	HOLTER ~4 DAYS POST-SCI	HOLTER WEEK 1	HOLTER WEEK 2	HOLTER WEEK 3	HOLTER WEEK 4	HOLTER MONTH 6
Sinus Bradycardia (SB50)						
Cervical SCI	10 [a]	7 [a]	12 [b]	11 [c]	10 [d]	10 [e]
Thoracic SCI	0	3	2 [b]	2 [c]	0 [d]	3 [e]
Sinus Bradycardia (SB60)						
Cervical SCI	25 [a]	24 [a]	25 [b]	23 [c]	24 [d]	27 [e]
Thoracic SCI	4	7	3 [b]	6 [c]	4 [d]	6 [e]
Mean Maximum Heart Rate ± SD bpm						
Cervical SCI	100 ± 20 [a]	98 ± 19 [a]	**97 ± 19**** [b]	**97 ± 18**** [c]	**100 ± 18**** [d]	114 ± 18 [e]
Thoracic SCI	106 ± 12	106 ± 11	**113 ± 10**** [b]	**114 ± 13**** [c]	**119 ± 17**** [d]	123 ± 14 [e]
Mean Minimum Heart Rate ± SD bpm						
Cervical SCI	**58 ± 11*** [a]	60 ± 12 [a]	59 ± 12 [b]	58 ± 13 [c]	57 ± 13 [d]	55 ± 12 [e]
Thoracic SCI	**69 ± 12***	58 ± 9	64 ± 13 [b]	58 ± 8 [c]	65 ± 12 [d]	58 ± 13 [e]
Supraventricular Arrhythmias						
Cervical SCI	10 [f]	**13*** [g]	**14*** [h]	11 [i]	7 [j]	5 [k]
Thoracic SCI	1	**0***	**0***	1	0 [j]	0 [k]
Two or more Ventricular Ectopic Beats in Run						
Cervical SCI	**11*** [f]	7 [g]	4 [h]	6 [i]	3 [j]	3 [k]
Thoracic SCI	**0***	0	0	0	1 [j]	1 [k]
Escape Rhythms						
Cervical SCI	0 [f]	6 (0-5) [g]	0 [h]	0 [i]	3 (0-3) [j]	2 (0-2) [k]
Thoracic SCI	0	0	0	0	0 [j]	0 [k]

SB50: sinus bradycardia <50 beats per minute (bpm); SB60: sinus bradycardia <60 bpm; SCI: spinal cord injury; SD: standard deviation

P* < 0.05, ***P* < 0.01 and **bold; unpaired *t*-test to compare arrhythmia occurrences between cervical and thoracic groups

Cervical SCI, n = 44; Thoracic SCI, n = 11 unless otherwise indicated

[a]: Cervical SCI n = 43; [b]: Cervical SCI n = 42, Thoracic SCI n = 10; [c]: Cervical SCI n = 40, Thoracic SCI n = 10; [d]: Cervical SCI n = 38, Thoracic SCI n = 10; [e]: Cervical SCI n = 36, Thoracic SCI n = 9; [f]: Cervical SCI n = 35; [g]: Cervical SCI n = 36; [h]: Cervical SCI n = 35; [i]: Cervical SCI n = 34; [j]: Cervical SCI n = 34, Thoracic SCI n = 10; [k]: Cervical SCI n = 22, Thoracic SCI n = 8

Unless stated, values represent absolute numbers of participants (range of occurrences for each patient)

taken ~4 Days Post-SCI showed significantly more occurrences of two or more ventricular ectopic beats in a run (11 vs. 0, $P = 0.033$). There was no difference between the occurrences of SA node arrests, two ectopic beats in run or bradycardia (SB50 and SB60) at the six-month time point (**Table 6-2**).

6.4 Discussion

To our knowledge, this is the first study to assess the prevalence of cardiac arrhythmias up to six months after SCI. The participants have been expanded from our previous publication that observed arrhythmias only one month following SCI.[107] Our results demonstrate that arrhythmias occur in the first month post-injury predominantly in individuals with cervical SCI. By the sixth month post-injury, there are no differences in occurrences of arrhythmias between cervical and thoracic groups. This is of important clinical relevance as this may suggest that the most crucial time for cardiac rehabilitation strategies after SCI occur within the first six months and further investigation on cardiac function in this period is warranted.

6.4.1 Heart Rate

Bradycardia is the most common arrhythmia found after SCI.[246] Bradycardia and cardiac arrest are complications of acute cervical SCI,[247] however as some sympathetic activity may return, a gradual improvement in HR is seen approximately six months after injury.[13] This contrasts with our observations revealing persistent bradycardia after six months. Bradycardia occurred in 29% (SB50) and 77% (SB60) of the participants observed with cervical SCI six months post-injury. Similar results were found in the thoracic SCI group with 33% (SB50) and 66% (SB60), noting that the thoracic group was a smaller sample size.

Our results demonstrated no difference in the mean maximum HR between cervical and thoracic participants at six months post-injury. Maximum HR significantly increased for the cervical group and shows an increasing trend for the thoracic group between Week 4 and Month 6. Minimum HR shows a decreasing trend for the cervical group between Week 4 and Month 6. Studies have shown HR returning to normal at six weeks post-SCI.[13] This finding is perhaps in line with previous conclusions made about autonomic function recovery from HR variability analysis.[57] Increases in normal sinus beats likely reflect at least partial recovery of descending fibers providing supraspinal sympathetic control over the heart.[248] Furthermore, the small associations between injury severity and mean maximum HR, with a trend as early as one week post-injury may suggest the onset of cardiac recovery upon treatment of neurogenic shock.[243] Indeed, there were associations with medium effect sizes with increased maximum HR and injury severity in the cervical group beyond the Week 1 assessment.

6.4.2 Sinoatrial Node Arrest and Atrioventricular Block

SA node arrests were observed at every time point in the participants with cervical SCI. It is worthy to note that SA node arrests occurred in one individual in the thoracic group for all observation periods except Holter 1 and Holter 6. The level of injury for this 29-year-old, with no known history of CVD was T10 AIS A. This patient was not in intensive care, had no cardiac events to report, and the innervation to the heart due to injury would not be compromised due to the low level of injury.

A majority of the 2° AV block arrhythmias (both Mobitz I and II) occurred at the Week 4 and Month 6 time points in individuals with cervical SCI. The participant with 3° AV block at Week 4 after injury had a history of CVD with a C2 AIS A injury. Along with the 3° AV block,

several SA node blocks and escape rhythms were present at Week 4 but did not persist at Month 6.

One of the individuals with a C4 AIS C injury had eight episodes of AV block immediately after injury; the disruption of sympathetic innervation in the cervical SCI group is likely the cause of AV block as the stronger vagal stimulation has been shown to be associated with this arrhythmia.[249] Even though the severity by ISNCSCI was a grade C, this individual may have had more severe autonomic impairments, highlighting the need for increased clinical assessment of autonomic functions.[54]

The consequences of cervical SCI are a loss of sympathetic drive and low resting arterial BP caused by vasodilatation and a loss of cardiac inotropy.[107] This loss of sympathetic drive may predispose participants with cervical SCI might be predisposed to SA node arrests due to unopposed vagal activity.[225] The same stimulus reduces conduction in the AV node and the bundle of His resulting in episodes of AV blocks. However, it is not well understood why more SA node events occurred in both groups compared to AV block (**Figure 6-1**).

6.4.3 Supraventricular Tachycardia

SVT can be detrimental to the heart and over time, can lead to heart failure,[250] or cause other consequences, such as a systemic embolism.[251] The occurrences of SVT in this study, particularly in the cervical group, may be explained by the consequential spontaneous sympathetic hyperactivity due to the diminished sympathetic control of the heart.[92] There were higher number of participants with SVT in Week 1 and Week 2 for the cervical group compared to the thoracic group (**Table 6-2**). At Month 6, twelve episodes of SVT were recorded on participants with cervical injury by the Holter monitor, while there were no recordings of SVT in

the thoracic group. The association between severity of injury and SVT occurrences suggest that lower severity of SCI may spare some sympathetic control to the heart, since associations (both significant and trending) were seen at Week 4 and Month 6.

Supraventricular premature beats, including atrial premature beats, are common during 24-hour ambulatory monitoring in individuals older than 60 years of age.[252] Though age is an important confounding variable in this study, the number of SVT episodes that occurred at Month 6 was significantly lower when compared to immediately after injury (Holter 1, $P = 0.049$) and Week 2 after injury (Holter 3, $P = 0.019$) in the cervical group. Changes in SVT occurrences could be an indicator of cardiac changes (due to secondary myocardial injury), as previously suggested in an experimental study.[253] Therefore, tracking changes in cardiac structure and function in the months following injury may be of further interest, as explored in Chapter 7.

6.4.4 Limitations

The main limitation of the study is the small number of participants in the thoracic group reduces the statistical power for comparison. Furthermore, splanchnic outflow arises from the upper thoracic and cervical levels; though statistical testing did not suggest any differences within the thoracic group for this study, future testing with a larger sample size in upper and lower thoracic groups may need to differentiate upper and lower thoracic injuries. Therefore, the validity of these statistics between the cervical and the thoracic SCI groups must be interpreted with caution. The large difference in age is a limitation, however, all associations were also assessed using models adjusting for age. There is the possibility that we may have missed significant events between the end of the first month and six months, which could provide more

information on the temporal adaptations to the absence of sympathetic control following SCI. Similarly, continuous Holter monitoring could be applied over a longer time period (i.e., 48 hours) in future studies to capture more information, specifically in the acute phase of injury. Finally, reporting on the symptoms of participants during the Holter monitoring period may help develop the next steps for clinical management. The number of days after SCI before the participants were equipped with Holter monitors varied mainly due to practical challenges including obtaining informed consent, sedation, surgery, other investigations, transfer to other departments/hospitals, etc.

6.5 Conclusion

It is important for clinicians and allied health professionals to note that many individuals with cervical SCI experience arrhythmias such as bradycardia, SA node arrest, SVT, and more rarely cardiac arrest, within the first month after SCI. As previously observed, no arrhythmias were seen in participants with thoracic SCI, with the exception of SA node arrests and limited bradycardia. However, it is worth noting that by Month 6, there were no significant differences in the arrhythmogenic occurrences that were initially revealed in the first month after SCI. A larger and more in-depth study may provide insight about how the heart adapts to diminished sympathetic innervation and the characteristics of cardiovascular instability for each injury level resulting from an acute traumatic SCI.

CHAPTER 7. TEMPORAL CHANGES OF CARDIAC STRUCTURE, FUNCTION, AND MECHANICS DURING SUB-ACUTE CERVICAL AND THORACOLUMBAR SPINAL CORD INJURY IN HUMANS[3]

7.1 Introduction

LV atrophy and decreased volumes are well documented in chronic SCI.[98] Decreased functional outcomes can result from impaired supraspinal sympathetic control over the cardiovascular system, such that cardiac responses to stress or exercise are diminished in individuals with high-level SCI compared with non-injured controls.[63] Compounded with the higher prevalence of physical inactivity in the SCI population,[113] it is perhaps unsurprising that CVD is the leading cause of mortality.[254] These aforementioned factors have more substantial effects for individuals with cervical SCI compared to thoracolumbar SCI due to the combination of impaired sympathetic control to the heart,[53] lack of skeletal muscle pump (i.e., decrease in preload),[210] and greater functional impairments limiting physical activity.[120]

Previous research has demonstrated reduced echocardiographic indices of LV systolic function in individuals with cervical SCI compared to those with thoracolumbar SCI at the chronic stage of injury, owing to the sympathetic input to the heart originating from T1-T5.[11] Therefore, cardiac changes in the sub-acute period (i.e., within the first year) following

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[3] A version of Chapter 7 is currently under peer-review. **Balthazaar SJT***, Walter M*, Nightingale TE, Currie KD, West CR, Tsang TSM, Krassioukov AV. Temporal changes of cardiac structure, function, and mechanics during sub-acute cervical and thoracolumbar spinal cord injury in humans.

SCI could vary based on the NLI.[100] Furthermore, characterizing the time frame of cardiac alterations may provide insight into the increased risk of CVD in those with SCI and aid in the timing of cardiac rehabilitation interventions.

No study to date has examined the longitudinal changes in cardiac function post-SCI in the sub-acute setting, stratifying for NLI. Thus, the aim of this present exploratory study (AIM 4 of this thesis) was to detect potential changes in LV structure, function, and mechanics, in individuals with cervical and thoracolumbar SCI at three- and six-months post-SCI using TTE.

7.2 Methods

7.2.1 Ethical Approval

Clinical protocols were approved by the University of British Columbia Clinical Research Ethics Board and conducted in accordance with the second Helsinki Declaration.[233] Individuals provided written informed consent prior to data collection.

7.2.2 Participants

The NLI and the severity of SCI were classified according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) by a trained physician (i.e., providing an American Spinal Injury Association Impairment Scale (AIS) grade).[26] Participants were asked the volume of leisure time physical activity (LTPA) and rated the intensity of each activity as moderate (some physical effort), or heavy (maximum physical effort) over the previous seven days as per the SCI-specific intensity classification chart.[255] Exclusion criteria for

all participants included any history of CVD and any language or cognitive barrier that prevented the participant from following English instructions.

7.2.3 Echocardiography

TTE was performed on a commercially available ultrasound (Vivid 7/i; GE Medical, Horton, Norway) and stored for offline analysis using specialized computer software (EchoPAC; GE Healthcare, Horton, Norway) according to the recommendations of the American Society for Echocardiography[138], by a single analyzer, blinded to time point and group.

The average of three cardiac cycles was used to determine LV structure and functional indices. Measures of LV structure at end-diastole and end-systole were reported from the parasternal long-axis views, and derived the calculation for relative wall thickness.[256] Volumetric measurements and systolic functions were derived from the apical four- and two-chamber views using the modified Simpson's biplane method. Q was calculated as the product of SV and HR. LV diastolic indices were calculated using early septal relaxation velocity (E'), early (E) and late (A) transmitral flow, and early-to-late transmitral filling velocity (E/A) ratio derived from pulsed-wave Doppler. The E/E' ratio was calculated to estimate LV filling pressure. Deceleration time and isovolumetric relaxation time were also determined on the spectral Doppler trace. LV mass index was calculated with the Devereux method and indexed to body surface area using the DuBois method.[257,258]

Indices of LV mechanics were derived from apical four-chamber and parasternal short-axis images at the level of the mitral valve (basal), papillary muscle (mid), and apex (apical). Images were analyzed using 2D speckle-tracking software in accordance with recommended guidelines.[140] Raw speckle-tracking traces were imported into customized post-processing

software (2D Strain Analysis Tool, Stuttgart, Germany), and data was interpolated into 600 points in systole and 600 points in diastole using a cubic spline algorithm. Peak strain and strain rate in systole and diastole were determined for each parasternal short-axis view (radial, circumferential) and the apical four-chamber view (longitudinal). Basal and apical peak rotation and rotation rate in systole and diastole were determined. Twist was determined as the maximum value obtained when subtracting the frame-by-frame basal rotation from the frame-by-frame apical rotation. Torsion, a measure of twist normalized to LV chamber size, was calculated by dividing peak twist by the LV end-diastolic length.

7.2.4 Statistical Analysis

Data are presented as median (first quartile to third quartile). Statistical analyses were performed using Statistical Package for Social Science software (SPSS Version 27, IBM, Chicago, IL, USA) with statistical significance set at ≤ 0.05. Wilcoxon Signed Rank test was used to analyze outcomes between timepoints within groups. Group differences were analyzed using the Mann Whitney U test. Results are displayed as raw data or median with interquartile range. Graphical representations were made in Prism (Version 9.1.1, GraphPad Software, San Diego, CA), SPSS, and Adobe Illustrator (Version 25.2.3, Adobe Inc., San Jose, CA).

7.3 Results

7.3.1 Participant characteristics

A total of 10 male participants with motor-complete (AIS A/B) cervical (n = 5) or thoracolumbar SCI (n = 5) were included. TTE was conducted 79 (65 to 108) and 204 (191 to

218) days post-SCI. Demographics are highlighted in **Table 7-1**, with no significant differences observed between groups.

7.3.2 Changes in Cardiac Structure, Function and Mechanics

At three months post-SCI vs. six months post-SCI, TTE revealed a significant decrease in LVIDd, EDV, ESV, SV, S', and E/E' ratio for individuals with cervical SCI. For LV systolic mechanics, longitudinal strain rate was lower in the cervical group at three compared to six months (**Figure 7-1**). Further indices for LV dimensions, systolic function, and diastolic function are highlighted in **Table 7-2**. There were no differences between the cervical and thoracolumbar groups for echocardiographic measures at three- or six-months post-SCI, except for EF ($P <$ 0.01), which was still within the normal range of 52-72% for males as per ASE guidelines. LV mechanics parameters can be found in **Table 7-3**. For LV systolic mechanics, apical rotation was higher in the thoracolumbar group at six months compared to three months, whereas radial strain rate at the mid-level was lower. For LV diastolic mechanics, longitudinal strain rate was lower in the cervical group at six months compared to three months.

Table 7-1. Demographics, injury characteristics, and perceived physical activity level of participants

Participant	NLI	AIS	Sex	Age (years)	Height (cm)	Weight (kg)	3 Months		6 Months	
							MH-LTPA (min/week)	UEMS (max. score 50)	MH-LTPA (min/week)	UEMS (max. score 50)
1	C6	A	M	28	188	82	80	24	360	24
2	C5	A	M	41	180	102	120	12	0	18
3	C5	A	M	35	183	80	840	24	360	24
4	C4	B	M	59	180	98	0	19	0	40
5	C5	A	M	32	186	78	39	7	160	11
Median (IQR)	-	-	-	35 (30 to 50)	183 (180 to 187)	82 (79 to 100)	80 (20 to 480)	19 (10 to 24)	160 (0 to 360)	24 (15 to 32)
6	T9	A	M	23	183	88	180	50	360	50
7	T7	A	M	50	170	72	450	50	0	50
8	T9	A	M	33	190	136	0	50	0	50
9	L1	A	M	59	179	56	0	50	0	50
10	L1	B	M	33	180	72	0	50	180	50
Median (IQR)	-	-	-	33 (28 to 55)	180 (175 to 187)	72 (67 to 112)	0 (0 to 315)	50	0 (0 to 270)	50

The cervical and thoracolumbar groups were not significantly different ($P > 0.21$) with respect to sex, age, height, weight, and TSI (at each measurement timepoint). The severity (AIS grade) and NLI as well as UEMS were assessed in accordance with the International Standards for Neurological Classification of SCI (ISNCSCI).

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; C, Cervical; IQR, Interquartile range; L, Lumbar; M, Male; MH-LTPA, Moderate-to-Heavy Leisure Time Physical Activity; NLI, Neurological Level of Injury; T, Thoracic; TSI, time since injury; UEMS, Upper Extremity Motor Score.

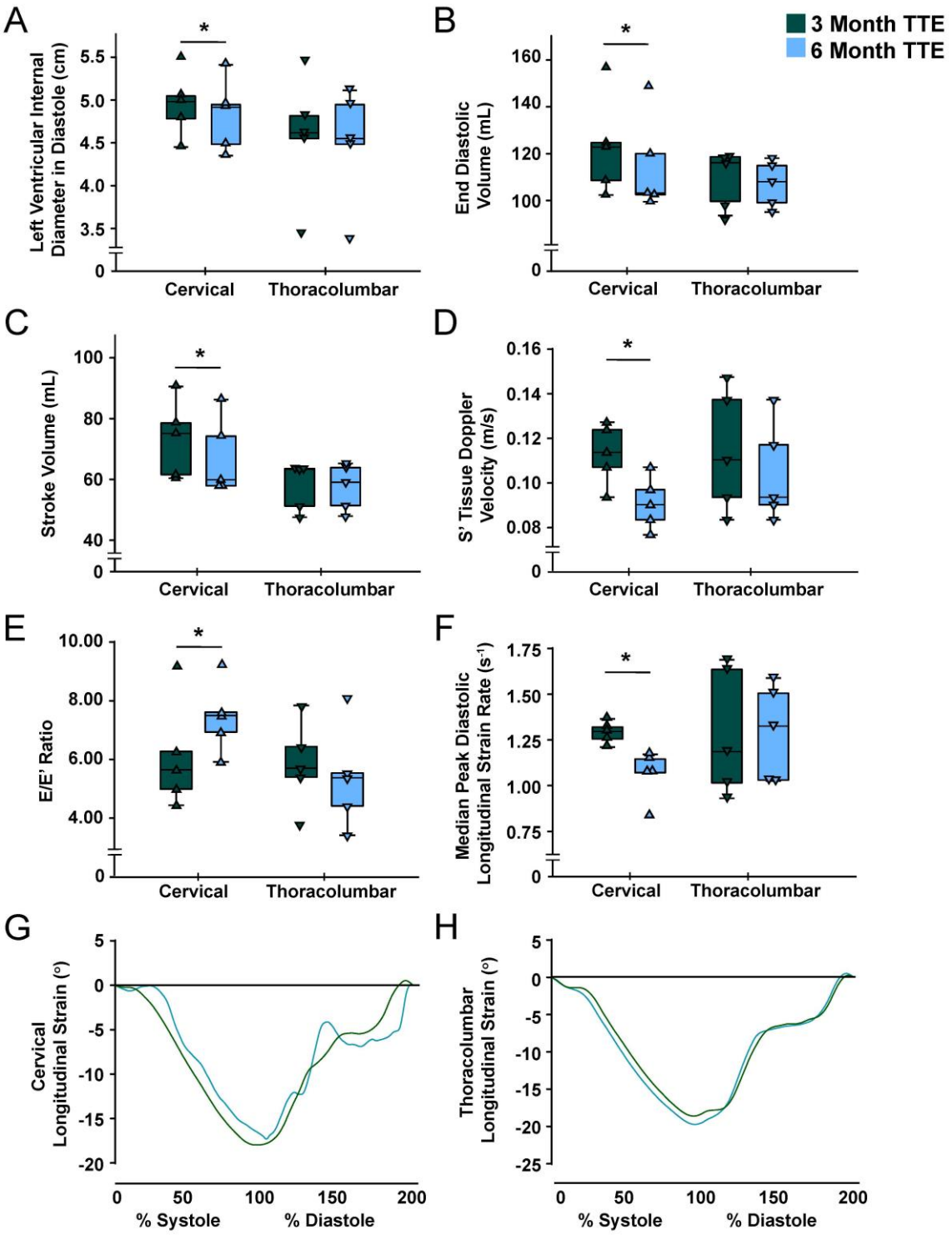

Figure 7-1. Progression of echocardiography-derived left ventricular functional, volumetric, and mechanical indices during sub-acute spinal cord injury

A, left ventricular internal diameter in diastole was significantly reduced in the cervical group at six vs. three months [4.90 cm (4.40 to 5.17) vs. 4.97 (4.60 to 5.25), $P = 0.043$], yet not in the

thoracolumbar group [4.53 cm (3.92 to 5.02) vs. 4.60 (3.98 to 5.12), $P = 0.41$]. **B,** end diastolic volume was significantly reduced in the cervical group at six vs. three months [101.33 mL (99.17 to 133.18) vs. 120.83 (103.58 to 139.42), $P = 0.043$], yet not in the thoracolumbar group [107.67 mL (96.83 to 116.08) vs. 113.83 (94.50 to 116.67), $P = 0.89$]. **C,** stroke volume was significantly reduced in the cervical group at six vs. three months [60.00 mL (58.00 to 80.33) vs. 75.17 (61.08 to 84.67) mL), $P = 0.042$], yet not in the thoracolumbar group [59.17 mL (49.75 to 64.67) vs. 63.33 (49.50 to 63.75), $P = 0.50$]. **D,** myocardial contractile velocity (S') was significantly reduced in the cervical group at six vs. three months [0.09 m/s (0.08 to 0.10) vs. 0.11 (0.10 to 0.13), $P = 0.043$], yet not in the thoracolumbar group [0.09 m/s (0.09 to 0.13) vs. 0.11 (0.09 to 0.14), $P = 0.10$]. **E,** early diastolic filling over early myocardial relaxation velocity (E/E') ratio was significantly increased in the cervical group at six vs. three months [7.48 (6.42 to 8.42) vs. 5.64 (4.71 to 7.72), $P = 0.043$], yet not in the thoracolumbar group [5.37 (3.92 to 6.81) vs. 5.69 (4.59 to 7.12), $P = 0.14$]. **F,** median peak diastolic longitudinal strain rate was significantly lower at six vs. three months in the cervical group [1.07 degrees/sec (0.95 to 1.15) vs. 1.29 (1.23 to 1.34), $P = 0.043$] yet not in the thoracolumbar group [1.32 degrees/sec (1.02 to 0.54) vs. 1.18 (0.97 to 1.66), $P = 0.69$]. **G and H,** global longitudinal strain standardized to cardiac cycle length for all participants at the three- and six- month timepoints for the cervical (**G**) and thoracolumbar (**H**) SCI groups; no differences were observed within groups.
Abbreviations: TTE, transthoracic echocardiography
* Cervical 6 months different from cervical 3 months ($P < 0.05$). Data are displayed individually (i.e., each triangle represents one individual) and grouped (i.e., box-and-whisker plots).

Table 7-2. Echocardiographic indices for left ventricular structure and function between cervical and thoracolumbar SCI groups and within three- and six-month time points

	GROUP	TIME SINCE INJURY AT 3 MONTHS	TIME SINCE INJURY AT 6 MONTHS
Heart rate measures			
HR (bpm)	All SCI	72 (58 to 79)	66 (63 to 78)
	Cervical	64 (51 to 74)	64 (50 to 74)
	Thoracolumbar	77 (65 to 91)	76 (66 to 82)
LV volumetric and systolic measures			
EDV (mL)	All SCI	115 (100 to 121)	**105 (99 to 118)** †
	Cervical	121 (104 to 139)	**101 (99 to 133)** †
	Thoracolumbar	114 (95 to 117)	108 (97 to 116)
ESV (mL)	All SCI	46 (44 to 53)	47 (43 to 51)
	Cervical	46 (41 to 56)	**43 (40 to 53)** †
	Thoracolumbar	50 (45 to 53)	49 (47 to 51)
SV (mL)	All SCI	64 (58 to 76)	60 (56 to 67)
	Cervical	75 (61 to 84)	**60 (58 to 80)** †
	Thoracolumbar	63 (50 to 64)	59 (50 to 65)
CO (L/min)	All SCI	4.5 (3.6 to 5.9)	4.4 (3.4 to 4.8)
	Cervical	5.0 (3.1 to 6.1)	4.8 (3.0 to 5.2)
	Thoracolumbar	4.0 (3.7 to 5.6)	4.3 (3.7 to 4.7)
EF (%)	All SCI	56 (54 to 62)	57 (54 to 59)
	Cervical	61 (57 to 63)	58 (57 to 62)
	Thoracolumbar	54 (52 to 55) **	55 (52 to 56) **
S' (m/s)	All SCI	0.11 (0.09 to 0.13)	**0.09 (0.08 to 0.11)** †
	Cervical	0.11 (0.10 to 0.13)	**0.09 (0.08 to 0.10)** †
	Thoracolumbar	0.11 (0.09 to 0.14)	0.09 (0.09 to 0.13)
LV diastolic measures			
E (cm/s)	All SCI	73 (59 to 80)	**59 (53 to 70)** †
	Cervical	75 (66 to 95)	58 (50 to 74)
	Thoracolumbar	62 (55 to 73)	60 (52 to 69)
Deceleration Time (ms)	All SCI	190 (141 to 228)	219 (185 to 269)
	Cervical	214 (130 to 238)	217 (208 to 248)
	Thoracolumbar	167 (146 to 243)	260 (141 to 304)
A (cm/s)	All SCI	51 (42 to 57)	47 (43 to 63)
	Cervical	46 (40 to 54)	45 (39 to 51)
	Thoracolumbar	53 (38 to 68)	62 (45 to 71)

E/A	All SCI	1.47 (1.23 to 2.08)	**1.29 (0.99 to 1.48) †**
	Cervical	1.58 (1.40 to 2.15)	1.31 (1.16 to 1.61)
	Thoracolumbar	1.37 (0.83 to 1.91)	1.13 (0.73 to 1.45)
IVRT (ms)	All SCI	58 (55 to 81)	64 (57 to 73)
	Cervical	76 (54 to 100)	62 (59 to 77)
	Thoracolumbar	57 (50 to 61)	66 (56 to 70)
E' Septal (m/s)	All SCI	0.14 (0.09 to 0.16)	0.10 (0.07 to 0.13)
	Cervical	0.16 (0.11 to 0.17)	0.09 (0.07 to 0.10)
	Thoracolumbar	0.11 (0.09 to 0.14)	0.13 (0.09 to 0.15)
E/E'	All SCI	5.67 (4.89 to 6.77)	6.42 (5.13 to 7.72)
	Cervical	5.64 (4.71 to 7.72)	**7.48 (6.42 to 8.42) †**
	Thoracolumbar	5.70 (4.59 to 7.12)	5.37 (3.92 to 6.81) *
LV dimensional measures			
IVSd (cm)	All SCI	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)
	Cervical	1.0 (0.9 to 1.2)	0.9 (0.9 to 1.0)
	Thoracolumbar	0.9 (0.9 to 1.0)	1.0 (0.9 to 1.1)
LVIDd (cm)	All SCI	4.8 (4.5 to 5.1)	4.7 (4.4 to 5.0)
	Cervical	4.9 (4.4 to 5.5)	**4.8 (4.3 to 5.4) †**
	Thoracolumbar	4.6 (3.9 to 5.1)	4.5 (3.9 to 5.0)
PWd (cm)	All SCI	0.9 (0.9 to 1.0)	1.0 (0.9 to 1.0)
	Cervical	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)
	Thoracolumbar	0.9 (0.9 to 1.0)	1.0 (0.9 to 1.0)
IVSs (cm)	All SCI	1.5 (1.2 to 1.7)	1.3 (1.3 to 1.4)
	Cervical	1.6 (1.3 to 1.7)	1.3 (1.2 to 1.4)
	Thoracolumbar	1.3 (1.2 to 1.7)	1.3 (1.2 to 1.4)
LVIDs (cm)	All SCI	3.3 (3.0 to 3.5)	3.5 (3.1 to 3.5)
	Cervical	3.2 (2.9 to 3.7)	3.5 (3.1 to 3.7)
	Thoracolumbar	3.3 (2.7 to 3.6)	3.4 (3.0 to 3.5)
PWs (cm)	All SCI	1.5 (1.3 to 1.7)	1.5 (1.4 to 1.6)
	Cervical	1.6 (1.3 to 1.9)	1.5 (1.4 to 1.7)
	Thoracolumbar	1.4 (1.3 to 1.2)	1.5 (1.3 to 1.6)
RWT	All SCI	0.39 (0.37 to 0.45)	0.44 (0.38 to 0.46)
	Cervical	0.40 (0.35 to 0.46)	0.43 (0.38 to 0.46)
	Thoracolumbar	0.38 (0.37 to 0.46)	0.45 (0.37 to 0.49)
Estimated LV mass (g)	All SCI	170 (130 to 198)	171 (143 to 185)
	Cervical	188 (157 to 216)	180 (141 to 187)
	Thoracolumbar	145 (107 to 180)	169 (116 to 181)

Estimated LV mass index (g/m^2)	All SCI	85 (57 to 97)	85 (65 to 90)
	Cervical	88 (72 to 107)	81 (68 to 91)
	Thoracolumbar	82 (48 to 91)	88 (55 to 90)

Values are median and quartiles (25% to 75%). Effects from Mann-Whitney U test performed for between-group comparisons. Between the three- and six-month time points for the SCI groups, a Wilcoxon signed-rank test for within-group comparisons. A, late diastolic mitral filling velocity; CO, cardiac output; d, diastolic; E, early diastolic mitral filling velocity; E', early myocardial relaxation tissue Doppler velocity; EDV, end-diastolic volume; ESV, end-systolic volume; IVS, interventricular septum; IVRT, isovolumetric relaxation time; LV, left-ventricle; LVID, left ventricular internal diameter; PW, posterior wall; RWT, relative wall thickness; s, systolic; S', systolic myocardial contractile tissue Doppler velocity; SV, stroke volume. Between-group comparison (i.e., thoracolumbar versus cervical): $*P < 0.05$, $**P < 0.01$. Within-group comparison between three- and six- months: †$p<0.05$. All significant values are bolded at the six-month timepoint.

Table 7-3. Echocardiographic indices for left ventricular mechanics between cervical and thoracolumbar SCI groups and within three- and six-month timepoints

	GROUP	TIME SINCE INJURY AT 3 MONTHS	TIME SINCE INJURY AT 6 MONTHS
Systolic Peak			
Basal Rotation (°)	All SCI	-7.5 (-9.2 to -6.3)	-7.4 (-9.4 to -6.4)
	Cervical	-8.0 (-9.4 to -6.4)	-8.4 (-10.2 to -6.9)
	Thoracolumbar	-7.0 (-10.7 to -6.2)	-7.1 (-9.9 to -6.2)
Apical Rotation (°)	All SCI	10.6 (9.4 to 11.5)	12.1 (9.2 to 13.9)
	Cervical	10.1 (6.8 to 10.6)	9.36 (7.47 to 11.40)
	Thoracolumbar	11.4 (10.4 to 14.3)	**13.3 (12.1 to 16.9) *†**
Twist (°)	All SCI	17.6 (16.3 to 21.5)	20.35 (17.49 to 24.1)
	Cervical	17.2 (15.6 to 18.2)	17.6 (14.9 to 21.2)
	Thoracolumbar	20.8 (16.8 to 23.7)	21.8 (20.4 to 24.3)
Torsion (°/cm)	All SCI	1.9 (1.7 to 2.5)	2.3 (1.8 to 2.5)
	Cervical	1.7 (1.6 to 1.9)	1.8 (1.4 to 2.3)
	Thoracolumbar	2.5 (1.7 to 2.5)	2.2 (2.3 to 2.6)
Longitudinal Strain (%)	All SCI	-18 (-19 to -17)	-18 (-19 to -17)
	Cervical	-17 (-19 to -16)	-17 (-18 to -16)
	Thoracolumbar	-18 (-21 to -17)	-19 (-19 to -18)
Global Radial Strain (%)	All SCI	41 (30 to 61)	43 (35 to 57)
	Cervical	37 (30 to 45)	43 (39 to 53)
	Thoracolumbar	61 (29 to 65)	35 (27 to 64)
Global Circumferential Strain (%)	All SCI	-23 (-30 to -21)	-22 (-25 to -20)
	Cervical	-25 (-36 to -23)	-22 (-25 to -19)
	Thoracolumbar	-21 (-26 to -18)	-21 (-28 to -21)
Basal Rotation Rate (°/s)	All SCI	-75.3 (-95 to -64)	-74 (-91 to -50)
	Cervical	-82 (-126 to -70)	-78 (-107 to -47)
	Thoracolumbar	-64 (-84 to -62)	-69 (-86 to -55)
Apical Rotation Rate (°/s)	All SCI	104 (83 to 136)	104 (86 to 120)
	Cervical	102 (74 to 125)	104 (58 to 107)
	Thoracolumbar	107 (92 to 137)	117 (95 to 149)
Longitudinal Strain Rate (s^{-1})	All SCI	-1.09 (-1.19 to -0.96)	-1.01 (-1.05 to -0.94)

	Cervical	-1.07 (-1.32 to -0.94)	-1.00 (-1.03 to -0.90)
	Thoracolumbar	-1.11 (-1.15 to -0.96)	-1.04 (-1.11 to -0.91)
Global Circumferential Strain Rate (s^{-1})	All SCI	-1.29 (-1.91 to -1.18)	-1.22 (-1.49 to -1.08)
	Cervical	-1.19 (-1.97 to -1.18)	-1.17 (-1.35 to -0.96)
	Thoracolumbar	-1.29 (-1.79 to -1.19)	-1.39 (-1.71 to -1.04)
Diastolic Peak			
Basal Rotation Rate (°/s)	All SCI	63 (57 to 82)	59 (45 to 81)
	Cervical	63 (60 to 74)	56 (46 to 83)
	Thoracolumbar	70 (41 to 111)	62 (44 to 83)
Apical Rotation Rate (°/s)	All SCI	-109 (-136 to -91)	-122 (-133 to -83)
	Cervical	-108 (-130 to -88)	-86 (-122 to -73)
	Thoracolumbar	-110 (-143 to -94)	-130 (-142 to -112)
Longitudinal Strain Rate (s^{-1})	All SCI	1.27 (1.14 to 1.43)	1.10 (1.02 to 1.37)
	Cervical	1.29 (1.23 to 1.34)	**1.07 (0.95 to 1.15) †**
	Thoracolumbar	1.18 (0.97 to 1.66)	1.32 (1.02 to 1.54)
Global Radial Strain Rate (s^{-1})	All SCI	-3.60 (-4.59 to -2.19)	-3.15 (-3.95 to -2.45)
	Cervical	-3.20 (-4.29 to -2.14)	-2.83 (-4.05 to -2.46)
	Thoracolumbar	-4.01 (-5.27 to -1.88)	-3.47 (-4.16 to -2.07)
Mid Circumferential Strain Rate (s^{-1})	All SCI	1.26 (1.04 to 1.59)	1.24 (1.13 to 1.69)
	Cervical	1.27 (0.99 to 1.91)	1.20 (0.88 to 1.70)
	Thoracolumbar	1.26 (0.92 to 1.49)	1.28 (1.13 to 1.85)

Values are median and quartiles (25% to 75%). Effects from Mann-Whitney U test performed for between-group comparisons. Between the three- and six-month time points for the SCI groups, a Wilcoxon signed-rank test for within-group comparisons. Between-group comparison (i.e., thoracolumbar versus cervical): $*P < 0.05$. Within-group comparison between three- and six- months: $†P < 0.05$. All significant values are bolded at the six-month timepoint.

7.4 Discussion

To our knowledge, this is the first study to specifically investigate the time-course of cardiac changes in humans with sub-acute SCI (i.e. serial echocardiography within the first-year post injury). While previous studies have implicated that structural and functional changes occur by the chronic phase following an SCI injury, these current findings suggest changes may occur more rapidly than perhaps originally thought.

Reductions in structural and functional cardiac indices were found for individuals with cervical SCI over the first six months post-SCI, whereas these changes were not apparent for individuals with thoracolumbar SCI. This is most likely explained by disrupted supraspinal regulation of sympathetic activity to the heart following cervical SCI,[64] as cardiac sympathetic control is innervated from the T1-T5 spinal segments (**Figure 7-2**). Conversely, cardiac sympathetic control is preserved in those with thoracolumbar SCI. It has been demonstrated in individuals with chronic SCI that a higher NLI is likely to result in more devastating consequences for cardiac function.[259] However, these cardiac adaptations, assessed using echocardiography, have never previously been captured in the first six months following human SCI.

Despite reductions in LV structure and global function in the cervical group, indices of LV systolic mechanics were similar over time. Perhaps this can be attributed to a mechanical compensation post-SCI to maintain systolic function in the cervical SCI group. The observation of preserved systolic mechanics and reduced SV has been previously reported,[151] and thought to be attributed to reduced afterload from the chronically hypotensive state of individuals with SCI, even with reductions in loading.

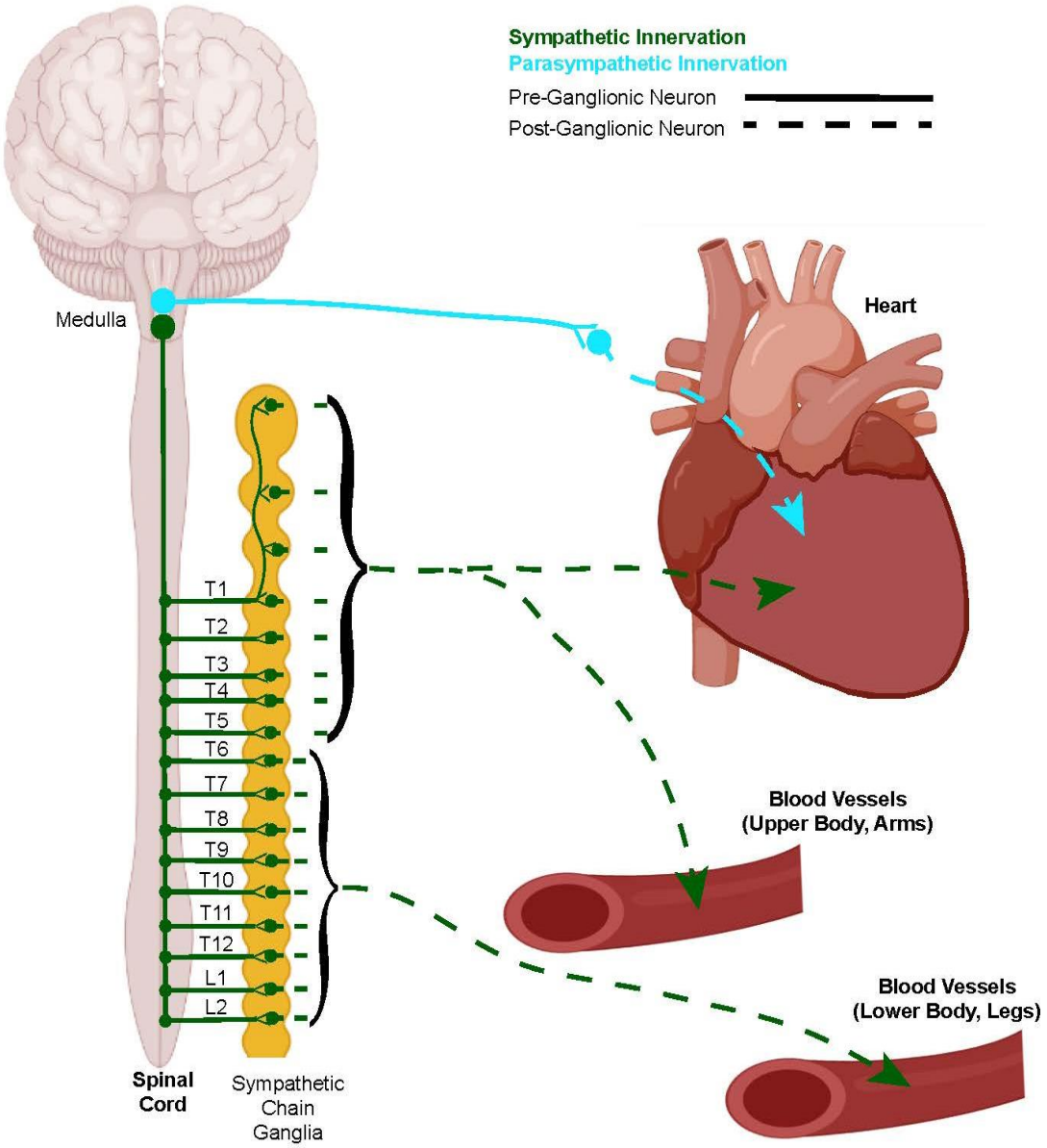

Figure 7-2. Schematic representation of autonomic innervation to the cardiovascular system

The medulla is a major site of origin to integrate autonomic outflow to the heart and blood vessels. The parasympathetic control to the heart exits the medulla via the vagal nerve (CN X). The preganglionic fibres (continuous lines) synapse with neurons within the cardiac ganglia, from which short postganglionic fibres (dashed lines) arise and synapse on the myocardium. The medulla also provides tonic sympathoexcitatory input to the sympathetic preganglionic neurons located within the thoracolumbar segments (from T1-L2). The sympathetic preganglionic fibres (continuous lines) exit the spinal cord and synapse on the ganglionic neurons within the paravertebral chain ganglia. Postganglionic fibres from these ganglionic neurons (dashed lines) synapse with the heart and blood vessels.[64] Cervical SCI may result in either partial or total loss of supraspinal sympathetic control of the heart (T1-T5),[98] while the vagus nerve remains

uncompromised.[240] In contrast, individuals with SCI below the T5 segment will have fully intact autonomic sympathetic and parasympathetic control of the heart and no impact on cardiac function.[64]

7.4.1 Alterations in Thoracolumbar SCI

Although individuals with thoracolumbar injuries do not reveal any structural or functional changes within six months, potentially due to the maintained sympathetic cardiac control, their long-term cardiac function should not be ignored. This is supported by the systolic changes in apical rotation and mid radial strain rate in the thoracolumbar group, as alterations in LV mechanics (i.e., strain imaging) precede structural and functional changes. Although further investigation is currently needed to define the usefulness of strain imaging clinically in this population, it offers physicians the opportunity to alter management before the onset of overt LV dysfunction.[260]

7.4.2 Leisure Time Physical Activity

Despite recommended exercise guidelines to improve cardiometabolic health following SCI,[113] 40% and 50% of the SCI participants at three- and six-months post-injury, respectively, self-reported zero minutes of moderate-to-heavy intensity LTPA per week. Previous literature suggests the cardiovascular deconditioning following SCI can be improved with exercise training.[63] The potentially disrupted sympathetic control to the heart and blood vessels after cervical SCI[64] can impair exercise performance and may diminish its beneficial effects on the cardiovascular system. Furthermore, given the reduced upper-extremity motor scores (range 11-40) individuals with cervical SCI struggle to perform volitional upper-body exercise of a sufficient intensity to offset CVD. Thus, individuals with cervical injuries may require alternative forms of exercise to prevent cardiac decline. Pre-clinical rodent models have shown

improvements in LVIDd, EDV, and SV following passive hind-limb exercise, suggesting passive lower limb manipulation may improve cardiac function.[135] Further research is required to promote exercise in humans with SCI in the sub-acute setting and investigate the efficacy of different exercise intensities and modalities to improve or maintain cardiac health.

7.4.3 Future Directions

Our novel findings, while preliminary and requiring verification with a larger cohort, reveal that significant cardiac changes occur in the sub-acute period following cervical SCI. However, it would be of interest to track these individuals into the chronic period of injury to observe any further decline. In addition to exercise, early pharmacological strategies may mitigate this cardiac decline, which potentially has implications for the risk of developing CVD. A recent pre-clinical study investigating the use of dobutamine in the acute setting to augment LV contractility, appears to preserve cardiac function in the chronic setting post-SCI.[261] Furthermore, novel neuromodulation strategies, such as the application of epidural stimulation to facilitate supraspinal control of the sympathetic nervous system could complement acute rehabilitation strategies.

7.4.4 Limitations

TTE recommendations to scan participants in the left-lateral supine position to avoid foreshortening[138] may present a limitation, as reductions to preload in an upright position[98] are common in individuals with SCI and should be considered for future studies. Furthermore, while NLI and severity of SCI was reported using validated methods, autonomic completeness of the injury was not measured, though associations between sensorimotor and sympathetic

impairments have previously been observed in non-athletic individuals with SCI.[55] Consequently, it is not possible to state with certainty that these findings are due to disrupted supraspinal cardiac control. MH-LTPA variations emphasize the potential limitations of self-reported questionnaires. Future research should incorporate validated, research-grade multi-sensor devices[262,263] to precisely quantify precise physical activity levels and to ascertain how the modification of certain physical activity dimensions might alter cardiac indices in the sub-acute setting.

7.5 Conclusion

Our data demonstrate a decline in several cardiac indices using TTE following cervical SCI, as early as six months post-SCI. These findings suggest that a lack of descending sympathetic control of the heart may be responsible for the rapid adaptive changes in cardiac indices. Worryingly, these changes begin in a relatively short time frame following cervical SCI, calling for the need to investigate effective therapeutic strategies to mitigate the decline of cardiovascular function in this population. In the next chapter, I assessed the cardiac indices following exercise training in individuals already in the chronic stage of SCI to test if these modalities were effective in improving this known cardiac decline.

CHAPTER 8. EFFECTS OF ACTIVE ARM-CYCLING VERSUS PASSIVE LEG EXERCISE INTERVENTIONS ON LEFT VENTRICULAR STRUCTURE, FUNCTION, AND MECHANICS OF INDIVIDUALS WITH CHRONIC MOTOR-COMPLETE SPINAL CORD INJURY: AN EXPLORATORY RANDOMIZED CLINICAL TRIAL

8.1 Introduction

SCI at or above the sixth thoracic segment can result in significant alterations of cardiovascular autonomic control, which is further compounded with physical deconditioning, leading to cardiac atrophy and reduced LV systolic function in this population.[98,135] For individuals living with chronic SCI, cardiovascular dysregulation has been associated with adverse clinical outcomes, including syncope, stroke, seizure, or death.[264] These individuals are generally less physically active,[265] and are at increased odds of developing CVD.[6,254] The onset of CVD has also been documented earlier in the lifespan of individuals with SCI compared with non-injured individuals,[43] and is the number one cause of morbidity and mortality in this population.[254]

The benefits of regular physical activity to reduce chronic disease risk factors commonly associated with SCI, including cardiovascular deconditioning, have been well documented.[126] Specifically with regards to cardiac function, 16 weeks of ACET for 20-40 minutes, three times per week, for individuals with paraplegia has been shown to improve SV when these participants were able to achieve a HR between 130 to 150 bpm.[121] However, the potentially disrupted sympathetic control to the heart and blood vessels after cervical or upper thoracic SCI[64] can impair exercise performance and may diminish the beneficial effects of physical activity on the cardiovascular system.[266] The combination of excessive venous pooling due to loss of vasoconstriction below the injury level is compounded with the loss of skeletal muscle pump,[104]

reducing the myocardial loading of the heart (i.e., preload) and leading to cardiac atrophy.[20] Thus, individuals with high-level SCI may require alternative forms of exercise to prevent cardiac decline. Individuals with chronic, motor-complete SCI performed four months of BWSTT, which increased femoral artery compliance, suggesting an improvement in vascular health.[122] In addition to this, pre-clinical rodent models have shown improvements in cardiac indices following passive hind-limb exercise[135] and electrically-stimulated cycling exercise has been shown to increase LV mass in humans via wall thickness and chamber size.[134]

The primary aim of this study (AIM 5 of this thesis) was to compare changes in LV indices using echocardiography following 72 sessions of ACET or BWSTT. It was hypothesized that the physical stimuli of BWSTT (i.e., the passive cyclical movements of the legs combined with the upright postural challenge to the cardiovascular system) will provide a notable exercise stimulus to improve LV indices in individuals with motor-complete SCI.

8.2 Methods

This study was conducted as part of a larger, multicenter, randomized clinical trial [The Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES)], aimed to evaluate the effectiveness of ACET and BWSTT in improving arterial stiffness in community-dwelling individuals living with SCI. A detailed study protocol for CHOICES has been previously published.[267] Echocardiography measurements were only collected at the International Collaboration On Repair Discoveries site in the Blusson Spinal Cord Centre at Vancouver General Hospital. The University of British Columbia Research Ethics Board approved all study procedures and all participants provided written informed consent (Clinical Trial Registration Number: NCT0178977).

8.2.1 Participants

Participants eligible for the study were between the ages of 18 and 60 years old, with motor-complete SCI of more than one year, between the fourth cervical and sixth thoracic neurological level (determined by the International Standards for Neurological Classification of SCI exam,[26] performed by a trained physician), and a carotid-femoral pulse wave velocity ≥ normal median volume of age-matched non-injured individuals.[268] A full list of exclusion criteria is published elsewhere[267] but included any active or history of CVD at enrollment, inability to understand English or provide informed consent, body mass in excess of 135 kg (absolute weight capacity of the body weight-supported treadmill), and other medical co-morbidities precluding safe participation in an exercise intervention. Eligible participants were randomly assigned into ACET or BWSTT using a central, web-based computer randomization service (Empower: http://www.empowerhealthresearch.ca/).

8.2.2 Training Intervention

The exercise interventions were implemented over a 72-session program, with a gradual progression to reach a target of 30 minutes for the participants in the ACET and 60 minutes for participants in the BWSTT arm. For safety reasons, stop criteria for exercise sessions were set at a systolic BP change ± 30mmHg from resting condition, a HR < 50 bpm or >150 bpm, symptoms of AD of OH (i.e., light-headedness, dizziness, changes in vision).

ACET: All training sessions were completed on a wall-mounted electrically-braked arm cycle ergometer (Lode BV, Groningen, The Netherlands). The intensity of ACET was prescribed to attain an rating of perceived exertion (RPE) 11-16 as a reflection of moderate-to-vigorous

intensity aerobic exercise.[269] Participants were asked to maintain a constant, self-selected cadence of >50 revolutions per minute (**Figure 8-1a**).

BWSTT: Guidelines for individuals with SCI using BWSTT have not been published, therefore previous studies were used as a foundation.[122,270] Currently there is no commonly accepted exercise intensity for BWSTT, especially as the leg movements are passive for the participant. Therefore we designed a 60 minute training session based on the previous literature.[122,271] The locomotor training protocol consisted of training individuals on a treadmill (Woodway, Weil am Rhein, Germany) using a body weight-support system (Andago, Hocoma AG, Volketswil, Switzerland). A minimum of two trainers assisted with BWSTT for the participant (**Figure 8-1b**).

8.2.3 Echocardiography

Echocardiography assessments were performed at baseline and after cessation of the exercise interventions. During rest, BP was measured using an automated device (Dinamap Carescape V1000; GE Healthcare, Buckinghamshire, UK). Echocardiography examinations were performed using a Vivid 7 ultrasound unit (GE Healthcare, Mississauga, ON), with images analyzed offline using dedicated software (EchoPAC; GE Healthcare, Horton, Norway) by a blinded assessor. Images were obtained in the parasternal long axis, parasternal short axis, and apical two-, three-, and four-chamber views according to the standards and recommendations of

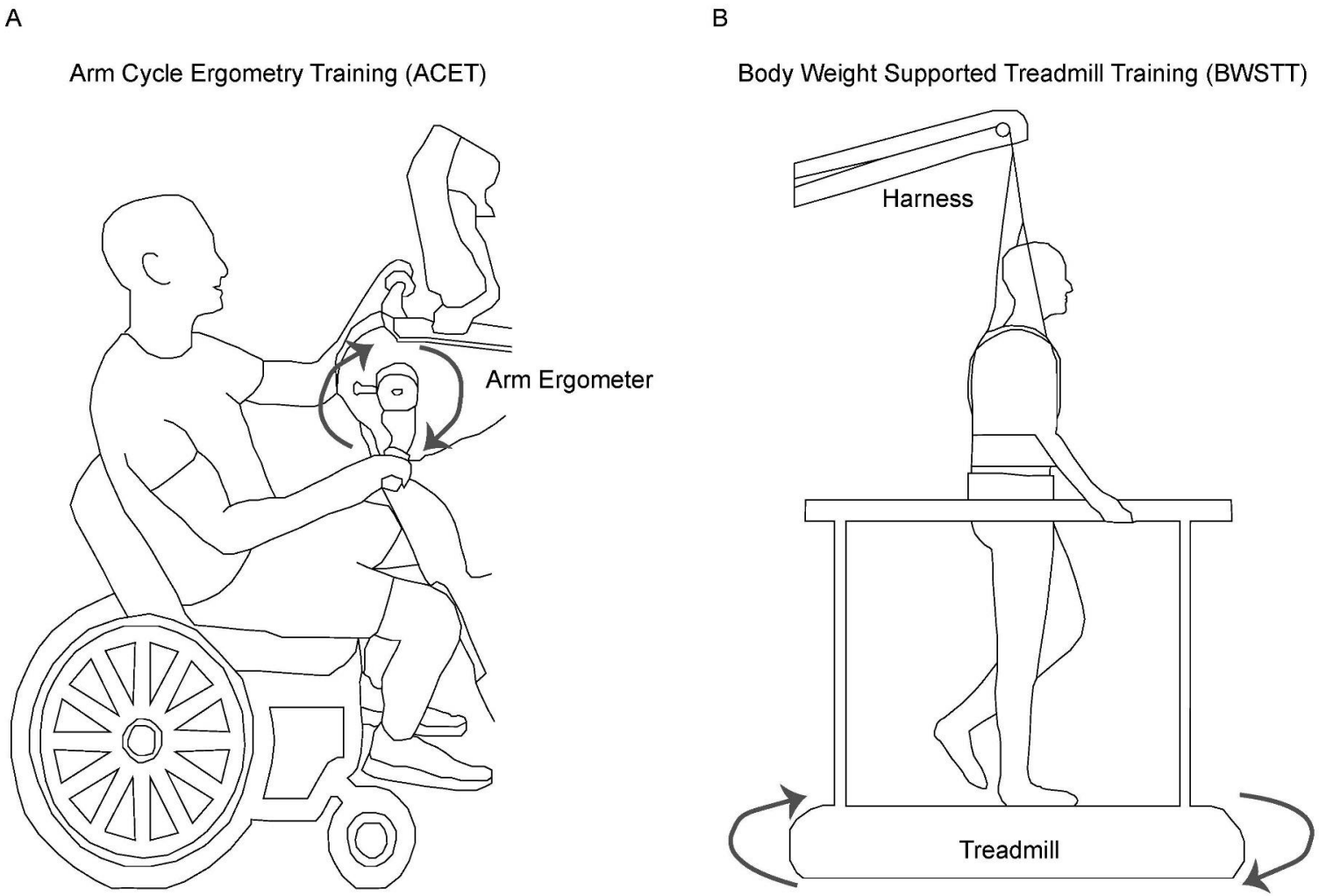

Figure 8-1. Schematic diagram of exercise modalities

the American Society of Echocardiography.[138,139] Mitral inflow velocities during early (E) and late (A) diastole were recorded from the mitral valve leaflet tips using pulsed-wave Doppler. The isovolumic relaxation time was measured as the time between aortic valve closure and mitral valve opening. The myocardial peak systolic (S′) and early diastolic (E′) contraction velocities were measured using tissue Doppler imaging (TDI). Three consecutive cardiac cycles were recorded for off-line analysis. End-systolic volume, end-diastolic volume, and ejection fraction were calculated using Simpson's biplane method of discs from the apical two- and four-chamber views and used to derive stroke volume and cardiac output. LV mass was estimated from the septal dimension, internal diastolic diameter, and posterior wall dimension using the recommended Devereux method.[272] Relative wall thickness of the LV is calculated as the ratio of twice the posterior wall dimension to the internal diastolic diameter.

Indices of LV mechanics were derived from apical four-chamber and parasternal short-axis images at the level of the mitral valve (basal), papillary muscle (mid), and apex (apical). Images were analyzed using 2D speckle-tracking software in accordance with recommended guidelines.[138] Raw speckle-tracking traces were imported into customized post-processing software (2D Strain Analysis Tool, Stuttgart, Germany), which interpolates the data into 600 points in systole and 600 points in diastole using a standard cubic spline algorithm. Peak strain and strain rate in systole and diastole were determined for each parasternal short-axis view (radial, circumferential) and the apical four-chamber view (longitudinal). Basal and apical peak rotation and rotation rate in systole and diastole were determined. Twist was determined as the maximum value obtained when subtracting the frame-by-frame basal rotation from the frame-by-frame apical rotation. Peak torsion, a measure of twist normalized to LV chamber size, was calculated by dividing peak twist by the LV end-diastolic length.

8.2.4 Statistical Analysis

Serial measurements of echocardiography indices at pre- and post-training were converted into simple summary statistics. Wilcoxon Signed-Rank statistical tests were used to compare the observed results pre- and post-exercise (intragroup) while Mann-Whitney U tests were used to compare the observed results between ACET and BWSTT groups at each timepoint (intergroup). Statistical analyses were performed using SPSS version 27.0 (IBM, Armonk, NY), with statistical significance accepted at *a priori* of $P < 0.05$. Graphical representations were made in Prism version 9.1.1 (GraphPad Software, San Diego, CA), SPSS, and Adobe Illustrator version 25.2.3 (Adobe Inc., San Jose, CA).

8.3 Results

8.3.1 Pre-training Characteristics

Of the 28 participants who were randomized to either the ACET ($n = 14$) or BWSTT ($n = 14$), 11 participants (6 ACET, 5 BWSTT) were retained for data analysis (**Table 8-1**). The reasons for exclusion included medical issues (n = 2), lack of adherence to the training sessions (n = 4), and poor image quality from either pre- or post-training TTE (n = 7). The CONSORT flow diagram is detailed in **Figure 8-2**.

8.3.2 Post-training Outcomes

During the 72 training sessions, mean RPE across all exercise sessions was 13 (12 to 14) (6: very, very light; 20 maximum exertion) for ACET and 11 (9 to 12) for BWSTT, $P = 0.021$. The post-training follow-up echocardiography took place 2 (2 to 12) and 5 (0 to 10) days from

Table 8-1. Baseline participant characteristics

PARAMETER	ACET (n = 6)	BWSTT (n = 5)
Age, years	36 (31 to 51)	35 (28 to 48)
Sex		
Male	5 (83%)	4 (80%)
Female	1 (17%)	1 (20%)
TSI, days	1095 (450 to 4816)	1754 (457 to 6285)
Lesion level		
Tetraplegia	3	2
Paraplegia	3	3
AIS grade		
A	5	3
B	1	2
RPE (first week of training)	10 (9 to 12)	10 (8 to 11)
Blood pressure (mmHg)		
SBP	109 (96 to 121)	115 (113 to 133)
DBP	61 (57 to 75)	65 (62 to 76)
MAP	77 (69 to 90)	83 (80 to 95)

Abbreviations: ACET, arm cycle ergometry training; AIS, American Spinal Injury Association Impairment Scale; BWSTT, body weight supported treadmill training; DBP, diastolic blood pressure; MAP, mean arterial pressure; RPE, rate of perceived exertion; SBP, systolic blood pressure; SSR, sympathetic skin response; TSI, time since injury

the last training session for the ACET and BWSTT groups ($P = 0.71$), respectively. There was a significant increase in E from baseline to post-training for ACET ($P = 0.027$) but not BWSTT ($P = 0.20$). Global systolic circumferential strain rate significantly increased following ACET ($P = 0.028$) but not BWSTT ($P = 0.72$). Global diastolic circumferential strain rate increased following ACET ($P = 0.043$) but not BWSTT ($P = 0.07$). LV twist significantly increased following ACET ($P = 0.043$) but not BWSTT ($P = 0.66$) (**Figure 8-3**). Following the training interventions, there was a significant difference between groups for deceleration time ($P = 0.045$), E/A ratio ($P = 0.018$), circumferential strain ($P = 0.037$), and global systolic circumferential strain rate ($P = 0.001$). All measures are shown in **Table 8-2** and **Table 8-3**.

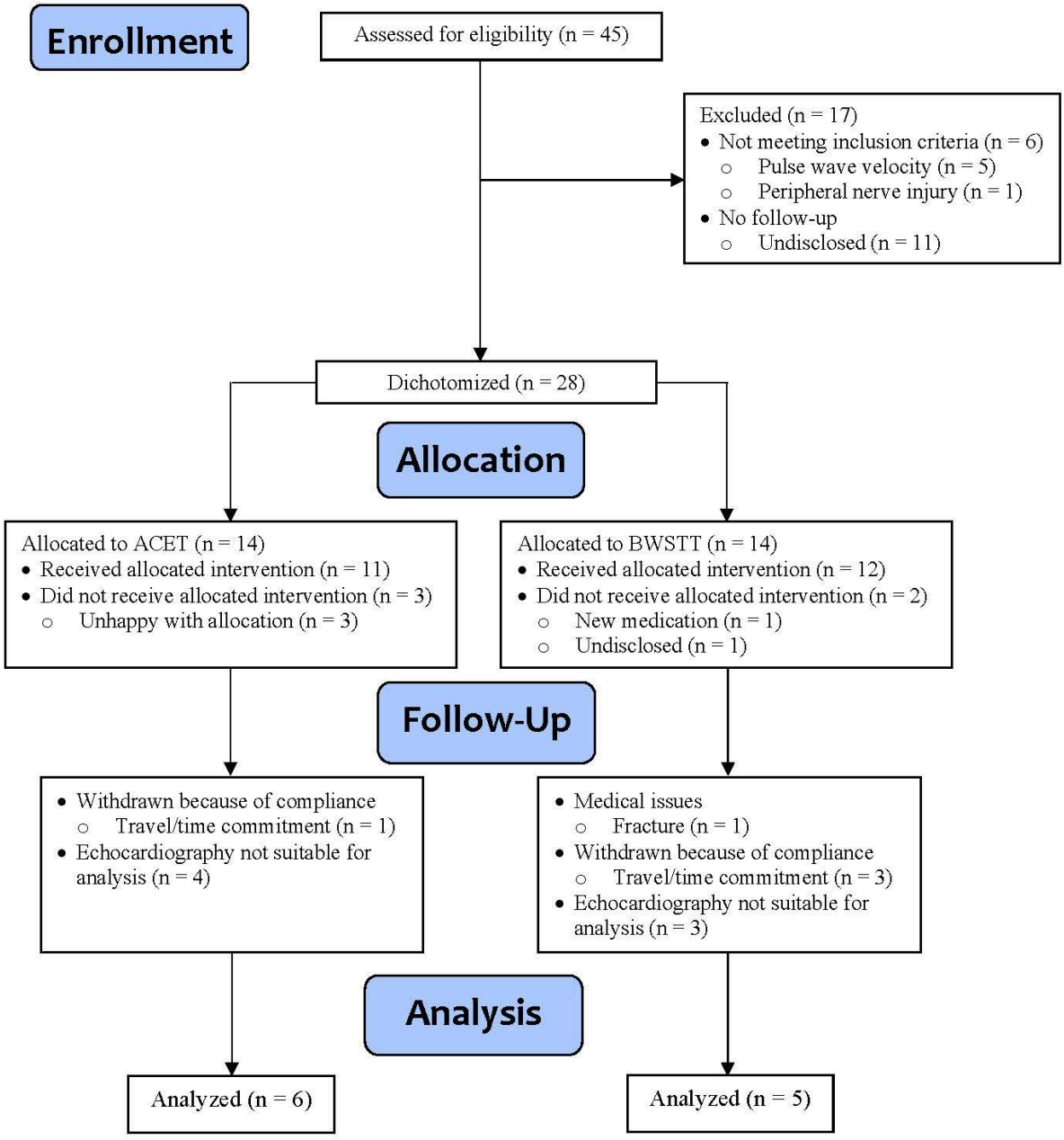

Figure 8-2. Study flow diagram

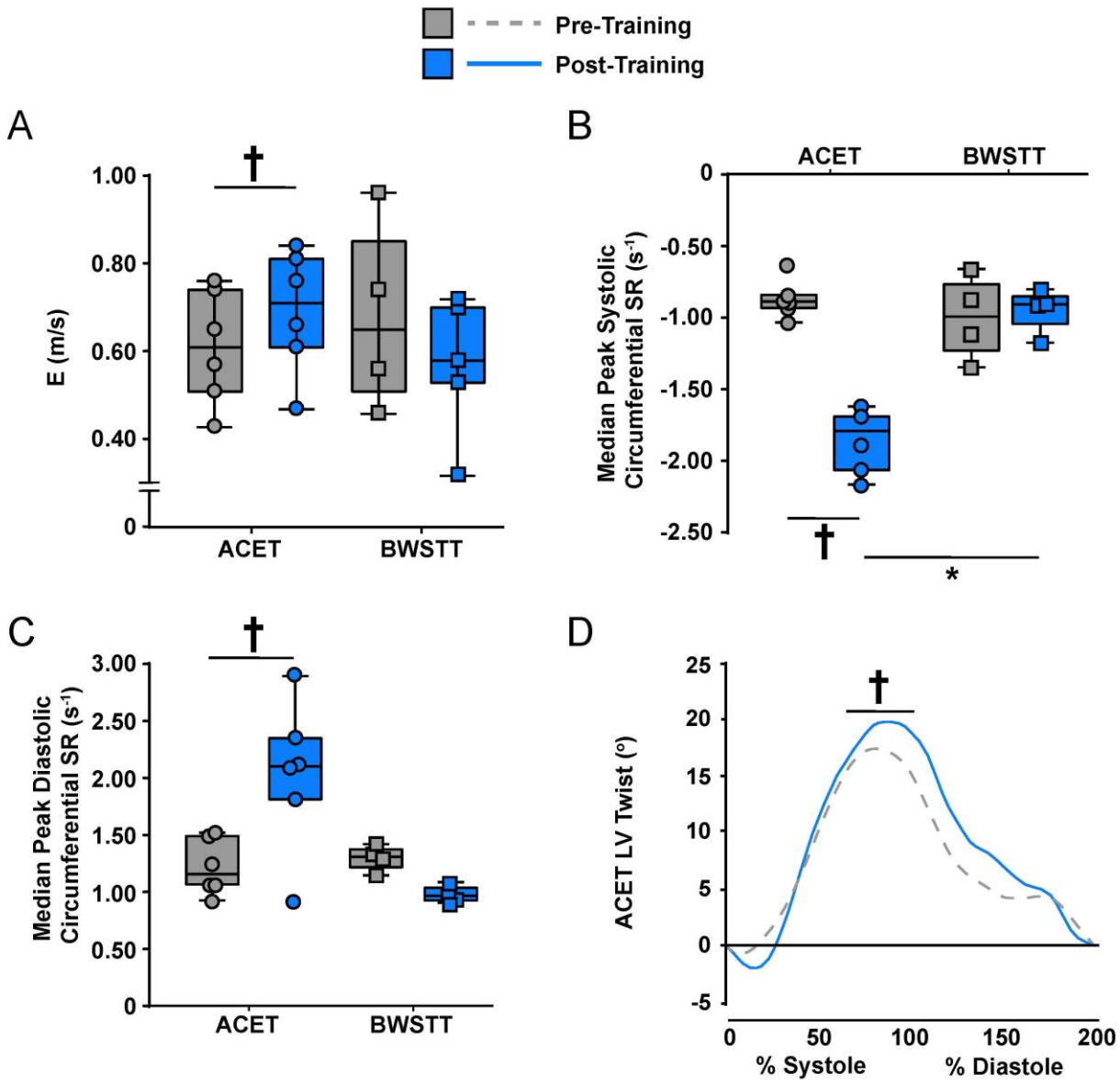

Figure 8-3. Echocardiographic changes with training

Changes from pre-training to post-training for arm cycle ergometry training (ACET) and body weight supported treadmill training (BWSTT). **A,** early diastolic filling velocities (E); **B,** global systolic circumferential strain rate (SR); **C,** global diastolic circumferential SR. Data are displayed individually (i.e., each triangle represents one individual) and grouped (i.e., box-and-whisker plots). **D,** left ventricular (LV) twist standardized to cardiac cycle length for participants in the ACET group. *Indicates significant difference between groups and † represents changes within groups, both at $P < 0.05$.

Abbreviations: ACET, arm cycle ergometry training; BWSTT, body weight supported treadmill training; LV, left ventricle; SR, strain rate

Table 8-2. Echocardiographic indices for left ventricular structure and function pre- and post-training between exercise groups

	GROUP	PRE-TRAINING	POST-TRAINING
Heart rate measures			
HR (bpm)	ACET	58 (51 to 66)	62 (56 to 68)
	BWSTT	54 (48 to 101)	64 (57 to 80)
LV volumetric and systolic measures			
EDV (mL)	ACET	92 (65 to 101)	100 (77 to 105)
	BWSTT	88 (79 to 107)	86 (81 to 94)
ESV (mL)	ACET	39 (29 to 45)	46 (35 to 47)
	BWSTT	39 (32 to 43)	37 (32 to 42)
SV (mL)	ACET	51 (37 to 60)	54 (42 to 58)
	BWSTT	50 (47 to 64)	49 (47 to 55)
Q (L/min)	ACET	2.80 (2.23 to 3.27)	3.07 (2.52 to 3.65)
	BWSTT	3.03 (2.41 to 5.62)	3.17 (2.63 to 4.30)
EF (%)	ACET	56 (52 to 59)	55 (53 to 56)
	BWSTT	59 (57 to 61)	57 (55 to 60)*
S' (m/s)	ACET	0.09 (0.08 to 0.09)	0.07 (0.07 to 0.11)
	BWSTT	0.09 (0.08 to 0.10)	0.08 (0.08 to 0.12)
LV diastolic measures			
E (cm/s)	ACET	0.61 (0.49 to 0.75)	0.71 (0.58 to 0.82) †
	BWSTT	0.65 (0.49 to 0.91)	0.58 (0.43 to 0.71)
Deceleration Time (ms)	ACET	236 (203 to 245)	204 (184 to 282)
	BWSTT	169 (131 to 341)	168 (122 to 210)*
A (cm/s)	ACET	0.46 (0.24 to 0.65)	0.45 (0.30 to 0.55)
	BWSTT	0.56 (0.39 to 0.76)	0.63 (0.46 to 0.66)
E/A	ACET	1.68 (0.86 to 2.10)	1.67 (1.32 to 2.13)
	BWSTT	1.20 (0.89 to 1.71)	0.88 (0.84 to 1.20)*
IVRT (ms)	ACET	64 (54 to 72)	55 (53 to 64)
	BWSTT	61 (54 to 69)	58 (49 to 65)
E' Septal (m/s)	ACET	0.09 (0.07 to 0.15)	0.12 (0.09 to 0.14)
	BWSTT	0.10 (0.10 to 0.11)	0.10 (0.08 to 0.13)
E/E'	ACET	6.10 (4.85 to 7.86)	7.58 (5.92 to 8.01)
	BWSTT	6.17 (5.41 to 8.88)	5.83 (3.90 to 7.23)
LV dimensional measures			
IVSd (cm)	ACET	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)
	BWSTT	0.9 (0.9 to 1.0)	1.0 (0.9 to 1.1)
LVIDd (cm)	ACET	4.3 (3.9 to 5.3)	4.3 (4.2 to 4.8)

	BWSTT	4.6 (3.6 to 5.0)	4.2 (4.0 to 4.6)
PWd (cm)	ACET	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)
	BWSTT	0.9 (0.9 to 1.0)	1.0 (0.9 to 1.1)
IVSs (cm)	ACET	1.3 (1.2 to 1.6)	1.4 (1.3 to 1.4)
	BWSTT	1.3 (1.2 to 1.3)	1.4 (1.3 to 1.8)
LVIDs (cm)	ACET	2.8 (2.1 to 4.1)	3.1 (3.0 to 3.2)
	BWSTT	3.4 (2.5 to 3.6)	3.0 (2.5 to 3.1)
PWs (cm)	ACET	1.4 (1.2 to 1.6)	1.4 (1.3 to 1.4)
	BWSTT	1.3 (1.2 to 1.5)	1.5 (1.2 to 1.7)
RWT	ACET	0.43 (0.38 to 0.51)	0.46 (0.43 to 0.47)
	BWSTT	0.41 (0.36 to 0.53)	0.44 (0.41 to 0.54)
Estimated LV mass (g)	ACET	130 (118 to 190)	150 (120 to 180)
	BWSTT	147 (110 to 193)	155 (118 to 184)
Estimated LV mass index (g/m^2)	ACET	64 (62 to 89)	76 (58 to 91)
	BWSTT	80 (58 to 92)	79 (65 to 86)

Values are median and quartiles (25% to 75%). Effects from Mann-Whitney U test performed for between-group comparisons. Between the baseline and post-training echocardiography for the SCI groups, a Wilcoxon signed-rank test for within-group comparisons. A, late diastolic mitral filling velocity; CO, cardiac output; d, diastolic; E, early diastolic mitral filling velocity; E', early myocardial relaxation tissue Doppler velocity; EDV, end-diastolic volume; ESV, end-systolic volume; IVS, interventricular septum; IVRT, isovolumetric relaxation time; LV, left-ventricle; LVID, left ventricular internal diameter; PW, posterior wall; RWT, relative wall thickness; s, systolic; S', systolic myocardial contractile tissue Doppler velocity; SV, stroke volume. Between-group comparison (i.e., ACET versus BWSTT): *$p<0.05$. Within-group comparison between pre- and post-training: †$p<0.05$.

Table 8-3. Echocardiographic indices for left ventricular mechanics between pre- and post-training between exercise groups

	GROUP	PRE-TRAINING	POST-TRAINING
Systolic Peak			
Basal Rotation (°)	ACET	-7 (-9 to -6)	-8 (-10 to -7)
	BWSTT	-9 (-11 to -8)	-10 (-11 to -9)
Apical Rotation (°)	ACET	10 (8 to 13)	13 (9 to 15)
	BWSTT	11 (8 to 14)	9 (8 to 11)
Twist (°)	ACET	18 (15 to 22)	21 (17 to 24) †
	BWSTT	22 (17 to 23)	20 (17 to 23)
Torsion (°/cm)	ACET	2.15 (1.79 to 2.33)	2.34 (2.10 to 2.46)
	BWSTT	2.60 (1.46 to 2.68)	2.45 (1.99 to 2.90)
Longitudinal Strain (%)	ACET	-19 (-21 to -18)	-19 (-20 to -19)
	BWSTT	-21 (-22 to -19)	-20 (22 to -19)
Global Radial Strain (%)	ACET	35 (31 to 41)	36 (27 to 47)
	BWSTT	30 (25 to 36)	32 (25 to 51)
Global Circumferential Strain (%)	ACET	-25 (-29 to -21)	-26 (-31 to -25)
	BWSTT	-25 (-26 to -23)	-22 (-25 to -19)*
Basal Rotation Rate (°/s)	ACET	-64 (-79 to -46)	-53 (-81 to -44)
	BWSTT	-90 (-54 to -106)	-67 (-98 to -61)
Apical Rotation Rate (°/s)	ACET	81 (54 to 105)	93 (84 to 117)
	BWSTT	77 (50 to 120)	68 (54 to 109)
Longitudinal Strain Rate (s^{-1})	ACET	-0.73 (-0.84 to -0.64)	-0.74 (-0.83 to 0.68)
	BWSTT	-1.04 (-1.09 to -0.89)	-0.72 (-0.81 to -0.65)
Global Radial Strain Rate (s^{-1})	ACET	1.64 (1.46 to 2.33)	1.90 (1.49 to 2.32)
	BWSTT	2.36 (1.39 to 3.51)	2.09 (1.87 to 2.99)
Global Circumferential Strain Rate (s^{-1})	ACET	-0.91 (-0.98 to -0.81)	-1.80 (-2.10 to -1.68) †
	BWSTT	-1.01 (-1.30 to -0.73)	-0.93 (-1.13 to -0.85)*

Diastolic Peak			
Basal Rotation Rate (°/s)	ACET	57 (45 to 84)	60 (45 to 86)
	BWSTT	69 (50 to 79)	59 (54 to 105)
Apical Rotation Rate (°/s)	ACET	-88 (-112 to -64)	-92 (-124 to -81)
	BWSTT	-91 (-132 to 60)	-95 (-120 to -65)
Longitudinal Strain Rate (s^{-1})	ACET	1.17 (1.00 to 1.35)	1.17 (0.71 to 1.35)
	BWSTT	1.11 (0.94 to 1.38)	1.08 (0.89 to 1.48)
Global Radial Strain Rate (s^{-1})	ACET	-2.08 (-2.58 to -1.95)	-2.15 (-2.70 to -1.38)
	BWSTT	-1.91 (-2.10 to -1.83)	-2.25 (-2.53 to -1.97)
Global Circumferential Strain Rate (s^{-1})	ACET	1.15 (1.03 to 1.49)	2.09 (1.58 to 2.47) †
	BWSTT	1.30 (1.18 to 1.39)	0.96 (0.91 to 1.06)

Values are median and quartiles (25% to 75%). Effects from Mann-Whitney U test performed for between-group comparisons. Between the baseline and post-training echocardiography for the SCI groups, a Wilcoxon signed-rank test for within-group comparisons. Between-group comparison (i.e., ACET versus BWSTT): *p<0.05. Within-group comparison between pre- and post-training: †p<0.05.

8.4 Discussion

This is the first study to use echocardiography to characterize changes in LV mechanical, structural, and global functional indices following six months of ACET or BWSTT exercise training. The novel finding of the present investigation was 72 sessions of ACET improved early diastolic filling velocities and LV mechanical indices, specifically mid systolic circumferential strain rate. However, participants performing passive leg exercises in the upright position using BWSTT did not demonstrate any significant improvements in LV indices post-training, which is contrary to our original hypothesis. Though RPE was significantly different between groups,

both forms of exercise could be interpreted as moderate intensity.[273] However, the higher RPE for ACET may provide some insight to the LV alterations following the intervention.

8.4.1 Left Ventricular Structural and global Functional Indices following Six months of Exercise

The changes noted in our study may indicate the onset of improved LV structure and global function. ACET revealed an increase in E on the post-training echocardiogram. There was a significant difference between ACET and BWSTT for deceleration time and E/A ratios on the post-training echocardiogram. Maggioni and collegues[180] found that individuals with motor- and sensory-complete (AIS A) paraplegia (T1-L3), have similar training responses as the non-injured population after five years of consistent aerobic training. Specifically, cross-sectional findings of ventricular hypertrophy comparing trained and untrained SCI suggested that following a regimen of regular aerobic physical activity may have a positive effect on the heart.[180] Turiel and colleagues[123] found that only six weeks of BWSTT was needed to show improvements in indices of diastolic function [i.e., isovolumetric relaxation time (IVRT), deceleration time, early over late diastolic filling (E/A) ratio]. However, it is important to note that these participants were motor-incomplete (i.e., SCI was less severe), and were in the acute phase of SCI.[123] Gibbons and colleagues[181] recruited individuals with motor-complete SCI between C4-T10 for a functional electrical stimulation rowing study and found positive outcomes on LV internal diameter in diastole (LVIDd), SV, E/A ratio, and early diastolic filling over early myocardial filling velocity (E/E') ratio, (i.e., indices of systolic and diastolic function).

8.4.2 Left ventricular mechanics following six months of exercise

Echocardiography plays a significant role in determining LV function, but it detects alterations when cardiac remodeling has already occurred. The application of strain imaging, by revealing myocardial deformation during the cardiac cycle, provide a solution to these short comings.[274] Speckle tracking echocardiography software for the application of strain imaging has been shown to potentially identify early changes in LV function by the measurements of mechanical indices.[275,276] As the LV contracts, muscle shortening occurs in the longitudinal and circumferential dimensions (negative) and lengthens in the radial direction (positive). Strain rate measures the time course of deformation and may be associated with the rate of change in pressure (dP/dt), which is a measure known to describe contractility.[277]

Relevant to the current study, among SCI individuals who underwent ACET, increases in mid systolic and diastolic circumferential strain rate were observed. Circumferential strain rate has been shown to be a good predictor of long-term LV remodeling.[278] Endurance training has been shown to increase resting myocardial mechanics in the non-injured population.[279] Furthermore, our data suggest that increases in LV twist may represent the previously unknown myocardial remodeling that occurs following 72 sessions of ACET in individuals with high-level SCI. Though previous work has shown a lower LV twist when comparing trained to untrained individuals with tetraplegia,[182] which may be the result of a longer training stimulus.[280] The limitations of this cross-sectional study does not confirm a cause-and-effect regarding an exercise stimulus. Increased LV twist has been previously reported in non-injured individuals following a period of endurance exercise training.[281] Another study showed that regular physical activity in non-injured heart failure patients following six months of exercise has been associated with significant afterload reduction, which has also been shown to increase LV twist.[282] As

previously discussed in a review of LV twist mechanics, physiology and disease state should be taken into account when evaluating cardiac mechanics, and further studies are warranted to draw conclusions.[166]

The significantly higher magnitude of strain values post-training compared to pre-training for the ACET group suggest that ACET influences LV mechanics. On the other hand, and contrary to our hypothesis, the upright posture and passive leg motion during BWSTT may not be sufficient to significantly alter LV mechanics after 72 sessions of training three times per week. Although both strain and strain rate are preload dependent,[283] it has been suggested in pre-clinical and clinical models, that strain rate might be more sensitive parameter to evaluate cardiac responses to exercise and ventricular unloading compared to strain.[284,285] Though mechanisms for our findings remain speculative, it appears that ACET may have experienced other training adaptations to LV indices, such as plasma volume expansion,[148,286] perhaps attributing to an increased preload (i.e., volume loading of the heart). In non-injured individuals undergoing exercise training, the heart exhibits an associated dilatation of the LV secondary to chronic volume loading of the heart with endurance activities.[287] The present study offers further insight into the response of LV mechanics to exercise for the SCI population, which may be helpful for identifying subclinical improvements in myocardial systolic or diastolic function.

8.4.3 Exercise in Individuals with High-level Chronic Motor-complete SCI

SCI at or above the sixth thoracic level has greater cardiovascular consequences compared to a lower level thoracolumbar injury.[104] Specifically, the diminished supraspinal sympathetic control over the splanchnic vascular bed causes the autonomic dysregulation of BP,[288] and can alter cardiovascular responses to exercise.[289] Consequently, abnormal BP control

after SCI can also be characterized by severe acute episode of elevated BP known as AD.[83] These dramatic swings in BP can result in shear injury to the blood vessel, leading to cardiovascular complications.[217] The long-term effects of these BP changes are unknown in individuals with SCI, however it has been shown that even in a non-athlete high-level SCI, regular exercise can help regulate BP,[226] and perhaps improve cardiac function after a period of training.[290]

Though there were no overt differences in LV structure and systolic indices following 72 sessions of ACET or BWSTT exercise training in these individuals, the literature suggests that changes in systolic indices are preceded by changes in LV mechanics.[260] While rodent models have showed promising improvements in LV structural and functional indices following passive hind-limb cycling compared to upper-limb exercise (i.e., swimming),[135] this study did not report LV mechanics. It is important to note that these rodents underwent 60 minutes of passive leg cycling 5 days/week, a greater frequency and volume than the intervention in the current study. Lastly, the four week exercise intervention in this rodent model study is comparable to almost two years of exercise training for humans.[291] Therefore, it remains to be seen whether a larger volume or duration of passive lower-limb exercise is sufficient to improve LV indices in humans with SCI.

Recent studies have shown that activity-based therapies in rehabilitation are an effective means to improve walking function post-injury and can facilitate general health maintenance.[292] Perhaps the gain of function may not be limited to motor function, and may have benefits on the cardiovascular system, leading to better cardiac function[64] and overall cardiovascular health.[237] Therefore task-specific practice can be integral for therapeutic interventions targeting recovery, and should be explored in future studies.[293]

8.4.4 Limitations

Studies with a larger sample sizes are needed to explore the responses of LV mechanics to different exercise modalities and intensities in different SCI subgroups for more compelling evidence. The study only focused on outcomes of LV indices at rest and post-exercise training, and overlooked the effects on right ventricular indices.[294] As this was a secondary study of a larger trial which was powered for its primary outcome, our small sample size limited our statistical approach. That being said, we did successfully complete 72 training sessions on a high-level SCI cohort with motor-complete injuries, providing compelling evidence to continue investigation in multi-center studies with longer follow-up durations to evaluate the long-term effects of exercise in the general SCI population.

8.5 Conclusion

It is crucial for people with SCI to engage in exercise to improve their overall cardiac health. Though previous findings would suggest benefits of BWSTT for the cardiovascular system, the findings in our current study suggest that cardiac function for individuals with high-level SCI does not improve following a thrice weekly, 72-session BWSTT exercise program. ACET, on the other hand, increased early diastolic filling velocity and LV mechanical indices, which provides preliminary evidence that ACET may prove to be a more viable training modality to improve cardiac function in this population. Further investigations should examine the utility of activity-based therapies over a longer duration to enhance the clinical relevance of our findings.

CHAPTER 9. GENERAL DISCUSSION AND CONCLUSIONS

9.1 Overall Summary of Findings

Prior to the undertaking of this thesis, cardiac structure and function had only been evaluated in chronic SCI populations, resulting in a paucity of knowledge regarding changes in the first year following injury. This lack of knowledge and a recent meta-analysis[98] quantifying echocardiographic measures between chronic SCI and the non-injured population meant that questions regarding when these cardiac changes occur still persisted. Moreover, this highlighted the importance of establishing a timeframe for therapeutic intervention before these deleterious cardiac changes occur. Though SCI is rare in incidence, attention should be given to this condition as individuals with SCI have a three to five fold increased odds of developing CVD compared to non-injured individuals.[6] I postulated that cardiac consequences following SCI may begin within the first year following injury, due to the myocardial unloading as a result of physical inactivity, further compounded by the potentially diminished supraspinal sympathetic control to the heart in individuals with higher level injuries. Targeted clinical echocardiography immediately following SCI may provide further insight into the progression of cardiac decline over time. Additionally, this information can provide clinicians with the knowledge to initiate certain cardiac rehabilitation strategies when these changes begin to occur. Finally, performing ACET as an intervention may impact cardiac performance more than BWSTT for motor-complete chronic high-level SCI. This has further implications as the resources needed for BWSTT (i.e., equipment and training staff) are a more expensive and resource intensive training modality for individuals with SCI.

In **Chapter 4**, we systematically reviewed the literature and found reduced cardiac

indices immediately following non-injured myocardial unloading conditions (NIMU; i.e., bed rest and spaceflight) and heart transplantation. Comparatively, the majority of SCI studies in the wider literature assessed participants in the chronic stage of injury, highlighting the need to investigate cardiac structure and function within the first months following SCI. Echocardiographic indices in individuals with sub-acute SCI (i.e., ~3 months) were reported in **Chapter 5**, where we cross-sectionally determined there were no differences in LV structure, function, and mechanics, between these individuals and non-injured matched healthy controls. In comparison, individuals with chronic SCI showed 14% lower mean EDV, 24% lower mean S' (i.e., systolic myocardial velocity), 19% higher E/E' ratio (i.e., diastolic function), and 27% lower mean LV twist (i.e., mechanics), compared to the sub-acute group.

Using the results from **Chapter 4 and 5**, we wanted to determine if there were any cardiac alterations due to the immediate autonomic imbalance following high-level SCI. In **Chapter 6**, we used 24-hour Holter monitoring to show the occurrence of arrhythmias within the first weeks following SCI up to six months post-injury. The number of SA node arrests and SVT arrhythmias were significantly lower at the six-month time point compared to the first month following cervical SCI. Arrhythmias in the thoracic SCI group were not observed as frequently as the cervical SCI group. Furthermore, the observed differences between cervical and thoracic SCI noted in the first weeks following injury were no longer significant at the six-month time point. These longitudinal alterations in the incidence of cardiac arrhythmias, along with findings from **Chapter 5**, suggested that it was worth exploring temporal changes in cardiac structure and function up to six months following SCI.

In **Chapter 7**, we used echocardiography to track and observe changes in cardiac indices between three- and six-months following SCI. We compared these measures between cervical

and thoracolumbar injuries due to the differences in autonomic innervation to the heart. These data provide further insight into whether the comparative decline in cardiac structure and function seen in SCI can be attributed to reduced physical activity or the diminished supraspinal sympathetic control. In individuals with cervical SCI, the EDV and SV underwent a median reduction of 17% and 20%, respectively, by the six-month time point compared to the three-month time point. To our knowledge, this was the first study to longitudinally track cardiac indices in the sub-acute phase post-injury, stratifying for NLI. This suggests that structural and functional cardiac decline may occur earlier than the chronic stage of SCI, particularly in individuals with cervical SCI.

Focusing on improving or restoring cardiac function in the chronic stage of SCI would have tremendous benefits to the quality of life in these individuals, as inactivity-related illnesses appear to correlate to the increased morbidity and mortality from CVD. In **Chapter 8**, we used a sample from a larger, multi-centre randomized clinical trial to explore the effect of two exercise modalities (i.e., ACET and BWSTT) on cardiac function using echocardiography. While BWSTT had promising effects on challenging the cardiovascular system,[122,295] we found that ACET was more beneficial as LV mechanical indices improved following 72 sessions of exercise training. No cardiac changes were observed following 72 sessions of BWSTT, suggesting that further research with this passive lower body cycling is needed. Though the recommended exercise guidelines were met for individuals with SCI to improve cardiometabolic health,[113] there were no changes to LV structure or systolic function, even with active exercising, suggesting further optimization strategies may be necessary.

9.2 Strengths and Limitations

This thesis is backed by several key strengths in its novel data. Firstly, a comprehensive scoping review was completed to inform the knowledge gap on echocardiographic measures during sub-acute SCI. Secondly, a trained sonographer performed the echocardiograms and analyzed the data in **Chapters 5, 7, and 8**. While much of the literature reporting on cardiovascular consequences following SCI has examined vascular function and BP control,[228] we explored the necessary area of cardiac function in the sub-acute period of injury. Thirdly, for the observation of arrhythmia occurrences in **Chapter 6**, the use of a continuous 24-hour recording of a Holter monitor increased the opportunity to record infrequent but recurrent arrhythmias compared to a brief clinical electrocardiogram test.[242] Fourthly, longitudinally tracking the changes in cardiac structure, function, and mechanics between three- and six-months post-injury in **Chapter 7** was the first study, to our knowledge, to track the same individuals in the sub-acute period following cervical and thoracolumbar SCI. Therefore, this thesis provides an evaluation of cardiac function during the recovery and rehabilitation period following injury for the first time, providing insight into cardiac alterations during the most crucial time post-injury. Finally, this thesis used a randomized clinical trial to explore the impact of two different exercise modalities on cardiac indices (**Chapter 8**). The exploratory nature of these findings warrants future studies with larger cohorts.

While this thesis has several strengths, the results should be interpreted while considering its limitations. While the use of a rigorous scoping literature review was systematic in its approach, the results did not determine if these changes following SCI are more representative of reduced physical activity or diminished autonomic control. We simplified assumptions on reduced physical activity by limiting our comparison to bed rest or spaceflight (i.e., microgravity

conditions). This was done in order to understand the differences between the cardiac deconditioning mechanisms while synthesizing information to identify knowledge gaps in the literature. A further limitation of this thesis is that though the sub-acute SCI sample used in **Chapter 5** is larger than most sample sizes reported in other SCI studies, cause-and-effect relationships cannot be determined as the study is cross-sectional in design. Exploring the occurrences of arrhythmias in the sub-acute SCI population in **Chapter 6** consisted of unbalanced groups, with a much larger sample of cervical SCI compared to thoracic SCI. Given the equal variance determined by Levene's test, a Bonferroni correction was applied to account for this. However, there was still a general loss of power from the underrepresented thoracic group. The sample size of our longitudinal echocardiography in **Chapter 7** was small, limiting the statistical power and generalizability of the results. However, the design of the study provided a step to track cardiac structure, function, and mechanics in the first six months following injury (addressing the limitation from **Chapter 5**). Our first echo assessment was three months post-injury and it is possible after weeks of bed rest that deleterious changes in cardiac structure and function might have already begun, as suggested with the NIMU group in **Chapter 4**. Future studies may want to consider an earlier assessment in the days/week post injury, though this may not be feasible given the abrupt and unpredictable nature of SCI and emergency clinical care. However, the three-month time point was chosen as this allowed an element of consistency in assessments between participants and allowed the injury to stabilise prior to initiating inpatient rehabilitation. Furthermore, there are logistical issues with gaining access to individuals in the early stages post-SCI as their medical care is the utmost priority. Though an exploratory randomized clinical trial, a larger cohort of individuals for the comparison of exercise modalities in **Chapter 8** on cardiac indices would provide stronger conclusions about the benefits and

drawbacks of each exercise strategy. Finally, autonomic testing was not reported; as a result, it can only be speculated that the supraspinal sympathetic control was disrupted with the high-level injuries. As the prevalence of arrhythmias were higher for cervical SCI in **Chapter 6** and a number of cardiac indices were compromised over time in the cervical SCI group compared to the thoracolumbar group in **Chapter 7**, the assumption of worsened cardiac indices in high-level SCI is further supported by previously documented pre-clinical work.[296]

9.3 Implications and Impact

This work has significant implications for cardiac function and health for the SCI population. We explored cardiac changes in individuals in the first six months following injury. Current literature has reported significant differences in cardiac structure and function in individuals with chronic SCI compared to non-injured controls.[98] The results presented in **Chapter 5** suggest a more urgent timeline for cardiac rehabilitation intervention post-SCI. We have shown that cardiac structure, function, and mechanics are not different initially post-SCI. Given ACET only showed an improvement in LV mechanics, perhaps an earlier intervention to prevent the decline would be advantageous rather than attempting to restore the cardiac capacity. Therefore, this thesis proposes investigating cardiac rehabilitation programs prior to cardiac decline, rather than attempting to reverse the cardiac consequences in the chronic period of injury (as explored in **Chapter 8**).

Clinicians should be aware of common cardiovascular dysfunctions following SCI described in **Chapter 1**, such as resting supine BP, OH, AD, and cardiac arrhythmias. We have further demonstrated the occurrences of arrhythmias following cervical SCI to decrease by the six-month timepoint in **Chapter 6**. This has implications for making clinical decisions on

whether the use of devices such as pacemakers are necessary for the individual. If the occurrences of arrhythmias decrease in the months following injury, a pacemaker device may not be warranted. Therefore, clinicians may want to perform regular Holter monitoring for individuals in the months following SCI to ensure that these individuals are not at serious risk of cardiac arrest or stroke due to episodes of tachycardia or atrial fibrillation.[297] Furthermore, arrhythmogenic occurrences may have an impact on an individual's fatigue in addition to the consequences of OH.[298]

This thesis identified the initial months following cervical SCI as the most critical. The notable cardiac decline in LV structure, function, and mechanics at six months compared to three months post-injury in **Chapter 7** confirms our reasoning in **Chapter 5**, suggesting that the sub-acute period following SCI would be the optimal window of opportunity for a therapeutic intervention. Considering the previous notion that cardiac consequences present in the chronic stage of injury,[98] clinicians may want to consider serial echocardiography immediately following SCI, particularly for individuals injured at the cervical level.

Finally, **Chapter 8** highlighted that ACET may be a more efficient exercise strategy than BWSTT for improving cardiac function in individuals with chronic high-level SCI. This has implications for the cost-effectiveness of utilizing a specific training modality for an individual. ACET has long been established as the most common exercise modality for individuals with SCI to improve functional capacity (i.e., aerobic fitness and power output) or metabolic health,[299] with the additional benefit of being inexpensive and accessible for volitional exercise.[300] Though the limitations of BWSTT included the high cost of equipment and requirement for a group of volunteers (i.e., labour intensive),[301] the promising effects on challenging the cardiovascular system[122,295] led to the hypothesis that the passive movement of the legs would increase venous

return to the heart. The limited improvement with ACET and lack of improvement with BWSTT may suggest that either the frequency, volume, or intensity of exercise required to improve cardiac function may need to be higher for individuals with chronic high-level SCI. Volumes of physical activity and exercise for individuals with SCI are lower than the recommendations for non-injured individuals[302] or for individuals with other disabilities.[303] To achieve cardiac benefits, as seen in pre-clinical models,[135] a greater exercise volume or intensity than that of this current randomized clinical trial may be necessary. Therefore, in order to optimize the cardiac adaptations in this population following exercise, a longer training period and other strategies may be needed. Further investigations are warranted as a paucity of data regarding exercise prescriptions for optimal cardiac benefits in this at-risk population remain. Furthermore, the findings may suggest the importance of harnessing the heart to improve cardiac function after high-level SCI, and that perhaps the passive loading of the heart in humans is not sufficient.

9.4 Future Directions

This research provides a solid foundation for investigating cardiac structure, function, and mechanics during the sub-acute period following SCI and exploring exercise strategies for chronic high-level SCI. However, much can still be done to better understand cardiac alterations during the sub-acute period and responses to exercise interventions. A scoping review in **Chapter 4** used complete bed rest and spaceflight to relate myocardial unloading to SCI, however, as individuals with SCI are not completely sedentary, a future literature review may want to investigate the impact of reduced step-count models (i.e., studies that quantify reduced physical activity) in a non-injured population to better understand the effects of reduced physical activity in the SCI population.

This thesis has provided a foundation to investigate immediate and acute cardiac responses to high-level SCI. Gaps regarding declining cardiac function in the first year following SCI indicate we are only beginning to focus on optimal rehabilitation strategies, with most of the current literature focused on pre-clinical studies. Our research in **Chapters 5, 6, and 7** highlights the need to close these specific gaps in the literature, especially with longitudinal testing. This information can be applied to rationalize increased efforts to follow-up with newly injured SCI individuals in hospital and provide follow-up examinations in rehabilitation and beyond. In addition to this, as outlined in **Chapter 1**, individuals with SCI are living longer with the advances in modern medicine. Therefore, investigating individuals over a five- or ten-year follow-up period may be useful for future investigations.

Finally, we have demonstrated cardiac mechanics may improve following a 72-session program of ACET for middle-aged individuals with high-level chronic SCI. These results were not seen in individuals who underwent the same number of sessions for passive BWSTT. Time after injury, as noted previously, could play an important role in determining when these rehabilitation exercise strategies should be performed (i.e., acute, sub-acute, or chronic) and this remains an area of further research.[304] Autonomic dysfunction caused by the disruption of descending input to the sympathetic nervous system in high-level SCI leads to an inability to challenge the cardiovascular system.[305,306] Combined with the limited physical activity, these individuals with high-level, severe SCI are at the greatest risk for a sedentary lifestyle due to paralysis and reduced upper body function.[5] The recent, evidence-based exercise guidelines that were published for people with SCI[113] stipulated the amount of exercise needed to improve fitness and cardiometabolic health, though further research on the long-term adherence to these exercise guidelines should be explored to observe the practicality and efficiency of improving

cardiac function over time. Ultimately, further controlled studies are warranted to explore the effects of exercise, perhaps in combination with pharmaceutical approaches, for optimal rehabilitation on cardiac function outcomes following SCI. Recently, a porcine model has shown that administering dobutamine, which works directly on cardiac β-receptors, restored the heart's pressure-generating potential and contractile control, for example.[261]

Given the compromised sympathetic nervous system during exercise, growing evidence in the current literature suggests the application of neuromodulation may be necessary to induce sympathetic activation for cardiac adaptations[237,307] and effectively normalize BP.[308] Neuromodulation (i.e., spinal cord stimulation) may be a strategy to activate the spinal circuitry and has recently received attention to target neurological dysfunctions.[309] Exercise rehabilitation strategies that incorporate the use of neuromodulation may be effective.[310] However, to build on the findings in **Chapter 5 and 7**, there is a window of opportunity to mitigate or potentially prevent the cardiac decline that we have observed (i.e., in the sub-acute period post-injury). Alternatively, activity-based therapy (ABT) is commonly used to improve motor control and can aid in overall health maintenance,[292] including improved BP control and cardiac function,[64] thereby potentially reducing the risk of CVD in the SCI population. Neuromodulation and ABT combined may be more effective to improve cardiac structure and function in the sub-acute SCI population. To investigate the effects of spinal cord stimulation (i.e., transcutaneous[238]) and ABT (i.e., active-arm passive-lower body exercise; AAPLE[311]) on cardiac indices, the research design in **Figure 9-1** has been proposed.

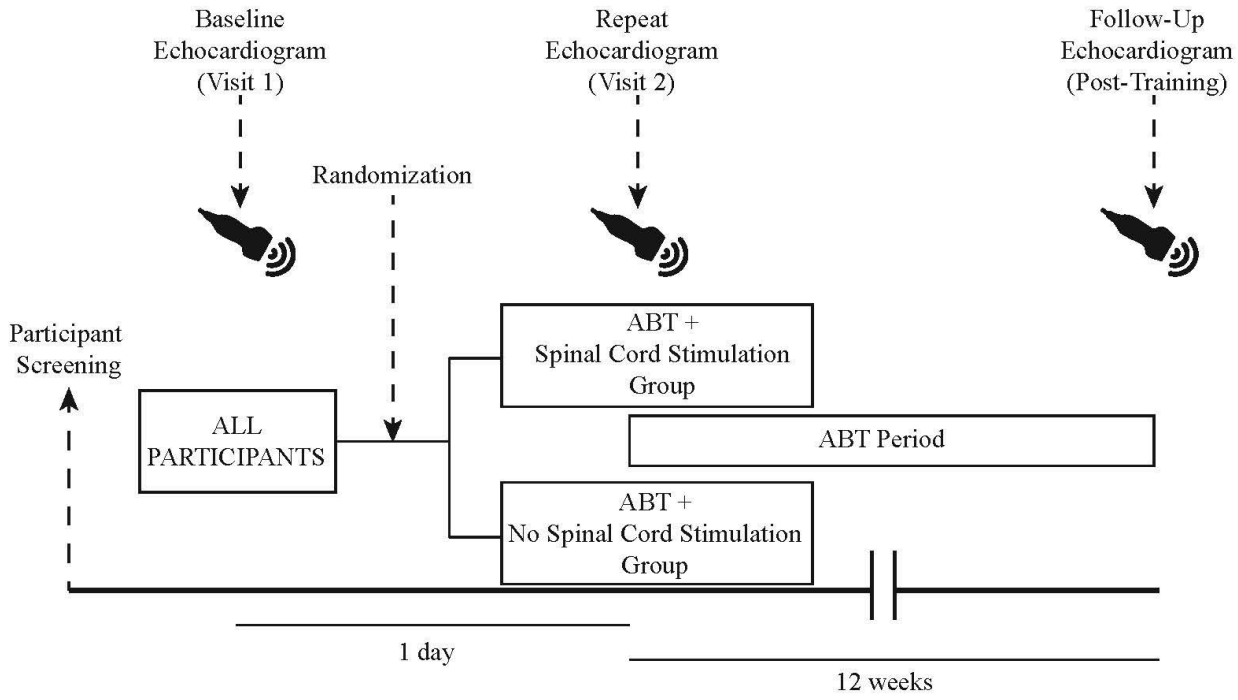

Figure 9-1. Schematic of a possible study design to assess cardiac adaptations to ABT + spinal cord stimulation and ABT + no spinal cord stimulation

To briefly summarize this proposed study, participants will be recruited based on similar inclusion and exclusion criteria described in **Chapter 8**. Cardiac indices will be assessed using echocardiography at baseline. Baseline echocardiography will be performed as participants are passively tilted head-up (HUT) to induce an orthostatic challenge.[312] This will be monitored by a physician to ensure participant safety in the occurrence of an adverse event (i.e., fainting due to OH). As discussed in **Chapter 1** and throughout this thesis, the disrupted sympathetic control to the vasculature in high-level SCI reduces cardiac preload, resulting in cardiovascular consequences. Spinal cord stimulation has been shown to restore hemodynamic stability after SCI.[313] BP will be measured using a continuous (beat-by-beat) monitor (Visit 1). Participants will then be randomly assigned to one of two groups; ABT (i.e., AAPLE[311]) + spinal cord stimulation (i.e., transcutaneous[238]) and ABT + no spinal cord stimulation. Participants in the

ABT + spinal cord stimulation group will undergo a repeat echocardiogram with HUT one day later with spinal cord stimulation (this will also be the mapping visit). Participants in the ABT + no spinal cord stimulation will also undergo a repeat echocardiogram, but with no stimulation. Participants will then undergo 12 weeks of ABT (with spinal cord stimulation or no spinal cord stimulation depending on group allocation) with a follow-up echocardiogram performed upon completion of training (no spinal cord stimulation for both groups). It would be interesting to see if the combination of ABT + spinal cord stimulation improves cardiac indices over time, with the stabilization of BP.[238] As learned in **Chapter 8**, there can be challenges in losing participants to training for various reasons. However, the potential to improve cardiac function with a combination of two treatments could have an impact on rehabilitation strategies following SCI.

9.5 Final Conclusions

This thesis systematically identified a knowledge gap in the literature and consequently explored changes in cardiac measures during the sub-acute period of SCI as a result. Assessment of cardiac performance during sub-acute SCI using 24-hour Holter monitoring revealed a decrease in the incidence of arrhythmias in cervical SCI at six months post-injury. Using echocardiography, the maladaptive cardiac remodelling between the three- and six-month time points for cervical SCI highlight the importance of initiating an early therapeutic intervention. Our findings suggest the first six months after injury might be the most crucial period to maintain cardiac function. The cardiac assessment following active upper-body and passive lower-body training in chronic high-level SCI found that ACET may be a more effective strategy for cardiac exercise adaptations compared to BWSTT. To our knowledge, there is currently no documented literature on the cardiac effects of exercise, assessed via echocardiography, in the months

following high-level motor complete SCI. This potentially indicates a critical time period for a future avenue of investigation.

In building upon the conclusions of this thesis, future research should be geared to developing rehabilitation strategies to preserve cardiac function in the months following injury, before the onset of cardiac decline. This will likely help reduce the risk of CVD for the SCI population. Furthermore, rehabilitation strategies for individuals with chronic high-level SCI may find improved cardiac function with ACET. Future studies should use larger samples to enhance and support these preliminary findings. Continuing to investigate the onset of cardiac decline with different injury levels and autonomic severity will help to inform guidelines to building effective rehabilitation strategies.

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