Neuromodulation for Restoration of Spinal Autonomic Functions that Increase Exercise Capacity after Spinal Cord Injury: A Systematic Scoping Review

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Abstract: Spinal cord injury results in varying degrees of motor and autonomic dysfunction. Cardiovascular and metabolic diseases are much more prevalent with an earlier onset in persons with spinal cord injury compared to the general population. Physical activity is widely accepted method for maintaining appropriate body weight, composition and overall health. Unfortunately, those living with a cervical or high thoracic spinal cord injury experience mild to severe dysautonomia, limiting their exercise performance and subsequent health benefits. Electrical spinal cord stimulation has been a therapeutic strategy investigated in recent years and has demonstrated beneficial effects on motor function as well as autonomic functions related to bladder, bowel and sexual function. Within the last 15 years, spinal stimulation studies aimed at improving motor function began to include anecdotal reports of improved autonomic functions, such cardiovascular control, metabolism, and exercise performance. This area of research is relatively new, and the neural mechanisms mediating these positive effects and the optimal parameters and stimulus locations have yet to be elucidated. We therefore performed a systematic scoping review to identify what has been reported about the effects of spinal cord stimulation on autonomic functions related to exercise outcomes to help identify knowledge gaps. A total of 1815 unique records were screened for eligibility following an electronic database search of Medline, EMBASE, Scopus, CINAHL and SportDiscus. Based on our inclusion criteria, 21 studies were included in this review. Of these 21 articles, 9 were transcutaneous stimulation studies and 12 were epidural stimulation studies. Improvements in blood pressure regulation, exercise output, thermoregulation, and body composition were reported in multiple studies. However, stimulation locations and parameters were highly variable and the number of participants relatively small. Therefore, further pre-clinical mechanism-based research and studies systematically testing different stimulus locations and parameters with larger numbers of participants are necessary to establish optimal stimulation interventions to improve exercise related autonomic functions.

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Table of Contents

Abstract……i
Acknowledgement……...ii
Table of Contents……iii
List of Tables……...v
List of Figures……vi
List of Key Abbreviations……vii
1. PART 1: Introduction
1.1. SCI definition, statistics and effects post injury……...8
1.2. The autonomic nervous system……9
1.2.1. Neural control of the cardiovascular system……11
1.2.3. Common cardiovascular disorders experienced by those with an SCI……13
1.3. Catecholamine release from adrenal glands and sympathetic ganglia……15
1.4. Spinal cord injury affects thermoregulation……...16
1.4.1. Effects of spinal cord injury on exercise performance……17
1.5. Locomotion……18
1.6. History of electrical spinal stimulation……...19
1.6.2. Potential neural mechanisms and pathways activated by electrical spinal stimulation…...21
PART 2: Scoping review
2.0. Hypothesis…….22
3.0. Objectives……22
4.0. Methods…….23
4.1. Identify the research question…….23
4.2. Identify relevant studies…….23
4.3. Study selection…….24
4.4. Chart the data…….24
4.5. Summarizing the results. ……...24
5. Results……...25
5.1. Articles retrieved…….25
5.2. Characteristics of articles and participants……25

5.3. Stimulator locations and parameters…..……..26
5.4. Outcomes reported…..…….27
5.5. Outcomes / findings…..……...28
6. Discussion…..…….32
6.1. Safety and tolerability…..……33
6.2. Study limitations…..……34
7. Conclusion…..……35
8. Figures…..……...……37
8.1. Figure 1. Study selection process (PRISMA-P flow diagram) …..……..…37
8.2. Figure 2. Representation of electrode placement used in TSCS studies…….38
8.3. Figure 3. Representation of epidural implant placement used in ESCS studies…….....39
9. Tables…..……40
9.1. Table 1: Participant characteristics for all studies……..40
9.2. Table 2: TSCS stimulation locations and parameters…….42
9.3. Table 3: ESCS stimulation locations and parameters……..47
9.4. Table 4: Outcomes / findings reported in TSCS studies…….52
9.5. Table 5: Outcomes / findings reported in ESCS studies…….53
10.0. References…….55

List of Tables

Table 1. Participant characteristics for all studies

Table 2. Transcutaneous stimulation locations and parameters

Table 3. Epidural stimulation locations and parameters

Table 4. Outcomes / findings reported in transcutaneous stimulation studies

Table 5. Outcomes / findings reported in epidural stimulation studies

List of Figures

Figure 1. Study selection process (PRISMA-P flow diagram)

Figure 2. Representation of electrode placement used in the transcutaneous stimulation studies

Figure 3. Representation of epidural implant placement used in the epidural stimulation studies

List of Key Abbreviations

AD – Autonomic dysreflexia

ANS – Autonomic nervous system

ATP – Adenosine triphosphate

AV Node – Atrioventricular node

CNS – Central nervous system

CPG – Central pattern generator

EKSO suit – Exoskeleton assisted walking device

ESCS – Epidural spinal cord stimulation

IML – Intermediolateral column

NTS – Nucleus tractus solitarius

OH – Orthostatic hypotension

PNS – Peripheral nervous system

PRISMA – Preferred reporting items for systematic reviews and meta-analyses

RMR – Resting metabolic rate

RVLM – Rostral ventral lateral medulla

SA Node – Sinoatrial node

SCI – Spinal cord injury

SNS – Somatic nervous system

TSCS – Transcutaneous spinal cord stimulation

PART 1: INTRODUCTION

1.1 SCI Definition, Statistics, and Effects Post Injury

Spinal cord injury (**SCI**) is physical damage to the spinal cord resulting in disruption of the neural signals to and from their target organs below the level of injury (Nas et al. 2015). This injury can be divided into two types, traumatic and non-traumatic. A traumatic SCI results from an external physical impact, like an automobile or sporting accident. Whereas a non-traumatic SCI is a consequence of a medical condition such as a tumor or other degenerative disease which compresses and damages the cord. This injury can be classified into two main types depending on the area of the lesion. In paraplegia, the injury occurs at the level of thoracic vertebrae two and below and affects only the lower limbs. In tetraplegia, the lesion occurs in the cervical spine and affects all four limbs as well as the organs to varying extents depending on the level of lesion.

This devastating injury affects over one million North Americans, including over 85,000 Canadians (Noonan et al. 2012). Beyond the lifetime estimated costs of between 1.1 and 4 million dollars per individual, the effects of the injury are far reaching. These include the more apparent physical effects and the less evident psychosocial outcomes affecting the individual, family, friends, and caregivers ('Spinal cord injury facts and figures at a glance' 2014). Though much research is being conducted on the regeneration of spinal cord function, the reality is that most persons living with a SCI will live the rest of their life without recovering from their injury. Compared to the general population, individuals with a spinal cord injury, in particular those with a cervical level injury, have much higher rates of obesity, type II diabetes, and risk for cardiovascular disease. This may partially be explained by very low resting energy expenditure values in some individuals with tetraplegia, even after normalizing to lean tissue mass (Shea et al. 2018; Sedlock and Laventure 1990; Monroe et al. 1998).

Exercise is a widely known way of maintaining appropriate body composition and cardiovascular function. Unfortunately, persons living with a SCI (especially tetraplegia) are unable to exercise at a sufficient intensity and duration to fully receive these benefits. This is mainly due to their disrupted autonomic response as a result of the injury (Cowley 2018).

In addition to a loss of motor function and sensation, SCI causes loss of the ‘automatic’ control of tissues and organs needed for a normal exercise response. This includes an inability to

increase heart rate, sweat in response to heat, activate the adrenal glands, increase mobilization of energy substrates and reduce blood flow to organs of digestion, and many other activities that normally occur to support exercise. If a person has a 'complete' injury above T1, all of these abilities are lost. For people with injury at L1 or below, these functions are preserved. With injury at T6, there is normal control of the heart and partial loss of these other functions. Because of these functional losses, people with injury above T1 (tetraplegia) are only capable of extremely low rates of exercise performance. Their maximal or peak oxygen uptake is extremely limited (< 20 ml O2 /min/kg) and their cardiovascular fitness classification is 'very poor' (Cowley 2018). Thus, there is a clear need for methods to improve the ability to perform physical activity in those with tetraplegia. In doing so, it may be possible to prevent the early onset of metabolic and cardiovascular related diseases that occur at much higher rates in the SCI population.

One potential method with reported beneficial effects in modulating autonomic function is electrical spinal stimulation. Both epidural and transcutaneous stimulation have demonstrated the ability to beneficially influence bladder, bowel and sexual function (Parittotokkaporn et al. 2020; Harkema, Legg Ditterline, et al. 2018; Herrity et al. 2017). Recent investigations are starting to report improvements in outcomes related to exercise capacity and blood pressure regulation (Phillips et al. 2018; Nightingale et al. 2019). However, studies investigating exercise related autonomic functions have only recently begun to appear in the research literature, and the degree to which spinal stimulation can improve these outcomes is unclear. In addition, different studies have used varying stimulation locations and parameters and reported a wide range of outcomes. Thus, the optimal parameters remain to be elucidated. Being that this is a relatively new area of study, we performed a systematic scoping review. The purpose of this review is to help summarize the stimulation parameters used, their outcomes, and what knowledge gaps still exist. More specifically, we focused on studies that have utilized electrical spinal stimulation to improve autonomic function as it relates to physical activity.

1.2 The Autonomic Nervous System

The human nervous system can be divided into two main branches; the central nervous system (**CNS**) and the peripheral nervous system (**PNS**). The prior being composed of the brain

and the spinal cord, and the latter consisting of the nerves not residing in the CNS. The PNS can further be divided into the somatic nervous system (**SNS**) and the autonomic nervous system (**ANS**). The somatic system uses voluntary control to move the skeletal muscles of the body. The autonomic nervous system is a control system in the body that involuntarily regulates many physiologic processes and provides control to organs and tissues such as the heart, smooth muscle, and glands in order allow humans to appropriately react to circumstances and maintain homeostasis.

The ANS is further organized into the sympathetic, parasympathetic, and enteric systems. Together, these three systems work in conjunction to respond to different internal and external stimuli. Portions of the brain such as the hypothalamus and medulla are also critical in the control of the ANS. The sympathetic system serves to increase or decrease activity to organs and tissues in response to excitement, fear, or danger. For example, when encountering a dangerous animal, activation of the sympathetic system will lead to increased heart rate, pupillary dilation, increased sweating, decreased blood flow to digestive organs, and increased blood flow to skeletal muscles in order to prepare the body to flee or fight. On the contrary, the parasympathetic system functions to regulate activity of organs and tissues when in a state of recovery or rest. Such actions will slow the heart rate, constrict the pupils, and promote digestion.

Both the sympathetic and parasympathetic divisions contain two distinct groups of neurons that are located between the central nervous system and the target organ. Within the grey matter of the CNS, preganglionic neurons are found within the intermediolateral column (**IML**) of the grey matter with their axons exiting via the ventral roots of the spinal cord or cranial nerves. These axons will synapse on to postganglionic neurons, located in areas of the PNS, parallel to the spinal cord, called the paravertebral ganglia (sympathetic chain) or prevertebral, found anterior to the spinal cord (celiac, superior, and inferior mesenteric ganglia). These preganglionic fibers are cholinergic and release acetylcholine to communicate with the postganglionic neurons. From there, the axons of postganglionic neurons will innervate target organs such as the heart and blood vessels using epinephrine. The exceptions to this are the sweat glands and piloerector muscles which require acetylcholine to activate their receptors in order to stimulate sweating and stand the body hair up (Kandel et al. 2013).

The parasympathetic preganglionic neurons are found at the level of the brainstem within the cranial nerves and within sacral spinal segments S2-S4. These neurons are long and extend almost the full distance to the organ of interest. This, as opposed to sympathetic preganglionic neurons which are very short, with long post ganglionic neurons. Upon activation, parasympathetic preganglionic neurons release acetylcholine, which upon binding to the nicotinic receptors of the postganglionic neuron will again release acetylcholine into the synaptic cleft. Acetylcholine will then bind to and activate the muscarinic receptors on the target organ cells resulting in parasympathetic activation. Cranial nerve X innervates the SA node of the heart, leading to decreased heart rate, conduction, and contractility. Nerves exiting at spinal segments S2-S4 innervate the bladder, bowel and sexual organs.

Sympathetic preganglionic neurons are found in the thoracic (T1-T12) and upper lumbar region (vertebral level L1-L3) of the spinal cord. (Schramm et al. 1993). Anatomically, these neurons occupy the spinal gray matter with the majority of them localized to the lateral horns or the IML cell column while a small proportion of them can be found near the lateral region of the central canal (Kandel et al. 2013). The sympathetic region of the spinal cord innervates numerous organs that are responsible for allowing an individual to be physically active for both short and long periods of time. Some of these important actions include increasing activity of the heart, systemic blood vessel constriction, sweat gland activation in response to heat, catecholamine release from the adrenal glands, fatty acid release from fat stores, and glycogen breakdown in the muscles and liver. These actions are crucial for anyone exercising for short, but more importantly long periods of time. Any limitations or dysfunction due to disease or spinal injury can have a major effect on the ability to increase sympathetic output and support the exercise response. It is no surprise then that even world class athletes with tetraplegia have significantly lower exercise capacities, typically demonstrating peak VO_2 values of less than 20 mm O_2/kg/min (Cowley 2018).

1.2.1. Neural Control of the Cardiovascular System

The heart is an incredible organ with many important physiologic roles both at rest and during activity. The main function of the heart is to circulate blood which contains oxygen and nutrients to the rest of the body's organs and tissues in order to meet metabolic demands. During

initial stages of exercise, the increase in heartrate is mediated by parasympathetic withdrawal. At higher intensities, sympathetic outflow to the heart and peripheral vasculature increases, directing blood flow to the metabolically active skeletal muscle tissues. The heart also contains both baroreceptors and chemoreceptors in the aortic arch and carotid sinuses respectively for sensing changes in blood pressure, oxygen and carbon dioxide concentration (Dampney 2016).

Amazingly, the heart has its own autorhythmic conduction system, intrinsic to itself. The sinoatrial node (**SA node**), located in the right atrium depolarizes this chamber first. In addition, this current also spreads to the left atrium, subsequently leading to the contraction of both atria and the pumping of blood to the ventricles below. This depolarization spreads inferiorly to the atrioventricular node (**AV node**), AV bundle, bundle of His, and finally to the Purkinje fibers resulting in the contraction of both ventricles and the pumping of blood into both the pulmonary (to the lungs for oxygenation) and systemic (rest of the body) circulation (Gordan, Gwathmey, and Xie 2015).

Both the sympathetic and parasympathetic systems also exert control over the heart, each having antagonistic effects on the muscle. This allows for constant and rapid adjustments in response to both internal and external stimuli. The sympathetic system innervates the heart with neurons exiting from thoracic vertebrae T1-T5. Prior to their exit, these neurons receive synaptic input from neurons exiting the lower brain stem, specifically the nucleus of the solitary tract (**NTS**) and the rostral ventral lateral medulla (**RVLM**) as well as the hypothalamus (Dampney 2016). Afferent input from baroreceptors, chemoreceptors, and other peripheral receptors (such as in skeletal muscle) modulates the activity of the brain stem neurons and subsequently the amount of the sympathetic output via neurons innervating the heart. Furthermore, feedforward control from the areas of the forebrain and midbrain can also have influence on the level of neuronal activity. Increased sympathetic activity via any of these routes leads to increased heart rate, cardiac contractility, and cardiac output.

Increased parasympathetic activity to the heart has opposing effects to sympathetic activity. The vagus nerve (cranial nerve X) directly innervates the SA node of the heart providing tonic inhibition, thus slowing the heart rate (Gordan, Gwathmey, and Xie 2015). Reduction in parasympathetic activity to the heart will increase the heart rate, but this effect is limited to low intensity activity where a large increase in cardiac activity is not needed (Cowley 2018).

Increased sympathetic activity not only increases activity of the heart, but also other organs and vessels whose output is important for maintaining homeostasis at rest and during physical activity. Changes in blood pressure occur naturally throughout the day and following changes in body posture. When rising from a lying down position or standing up from sitting, blood immediately begins to pool in the lower half of the body due to gravitational force. This leads to a sudden decrease in blood pressure which is sensed in the baroreceptors of the aortic arch of the heart. This information is sent via afferent fibers to the NTS and then to the RVLM in the brainstem. These stimulated medullary fibers will descend and synapse on to sympathetic preganglionic neurons within the mid to lower region of the thoracic spinal cord. The neurons in this region synapse on postganglionic neurons which directly innervate the blood vessels of the peripheral vasculature, which when stimulated lead to vasoconstriction and a subsequent increase in blood pressure back up to a normal range. Accompanying this action is an increase in cardiac sympathetic activity and resulting cardiac output which further compensates for the drop in blood pressure (Sherwood 2013).

In the contrasting situation, where there is a sudden increase in blood pressure from baseline, the rising pressure increases the firing rate of the baroreceptors resulting in increased stimulation of the NTS. Subsequently, this increases the inhibitory activity of the tonically active sympathetic output to the peripheral vasculature, ultimately leading to vasodilation and reduced blood pressure. During this time, the SA node of the heart will receive decreased sympathetic activity, thereby slowing the heart rate and decreasing cardiac output. These baroreceptor reflex pathways are extremely important in maintaining homeostasis throughout the day and during changes in activity level. Individuals without these complete pathways can suffer numerous direct and indirect health complications as a result of these interrupted reflex pathways.

1.2.3. Common Cardiovascular Disorders Experienced by Those with an SCI

Beyond the obvious motor effects of a spinal cord injury, the resulting autonomic dysfunction can be quite dramatic. In particular, individuals with a cervical SCI experience more severe autonomic disorders than those with a lower thoracic or lumbar injury. (Krassioukov and Claydon 2006). For example, a person with a cervical injury will have absent or limited descending control of the lower limb vasculature preventing them from responding appropriately

to sudden changes in blood pressure. For this reason, these individuals will commonly experience episodes of both hypotension (orthostatic hypotension; **OH**) and sudden hypertension (autonomic dysreflexia; **AD**).

Orthostatic hypotension is defined as a drop in systolic blood pressure of 20 mm Hg or more a drop in diastolic blood pressure of 10 mm Hg or more, with or without the presence of any symptoms when rising from supine to and upright position (Kaufmann 1996). The typical symptoms that occur include nausea, dizziness, light headedness, blurred vision, dyspnea (heavy breathing) and syncope (loss of consciousness) (Frisbie and Steele 1997). It is also common for individuals with an SCI to not experience any symptoms during an OH event. For example, one study examining the occurrence of OH during physical therapy in individuals (n=14) during the acute stage following an SCI, found that 41% of the study participants who experienced OH during a session were asymptomatic (Illman, Stiller, and Williams 2000). This provides evidence to the importance of monitoring blood pressure during any type of intervention within this patient population.

These hypotensive events can occur for a variety of mechanistic reasons. The first is that the descending signals from the brainstem to the neurons innervating the vasculature are interrupted due to injury, therefore the blood vessels are incapable of vasoconstricting in response to a change in posture and a person experiences sustained low blood pressure. Secondly, catecholamine levels are lower in individuals with tetraplegia compared to those with paraplegia. This is because the adrenal medulla, which releases epinephrine and norepinephrine, is innervated by spinal nerves exiting the mid thoracic region of the cord (Sato 1987). In the early period following an SCI, cardiovascular deconditioning occurs due to imperative bed rest for prolonged periods. This inactivity likely induces changes in the sensitivity of the baroreceptor reflex making it less responsive to changes in blood pressure (Vaziri 2003). Coupled with lower plasma levels due to hyponatremia, maintaining stable blood pressures in those with a cervical or high thoracic SCI can be quite burdensome and remains a significant issue for many individuals living with an SCI.

Another potentially dangerous disorder these individuals may encounter is autonomic dysreflexia, in which a sudden rise in blood pressure (increase in systolic blood pressure of at least 20%) occurs usually in response to a painful or irritating stimuli such as a distended bladder or bowel (Karlsson 1999). Bradycardia typically accompanies this sudden rise in blood pressure,

however this is not always the case. For example, one survey of 40 medical records reported that during autonomic dysreflexic events, only 10% of cases showed bradycardia, while tachycardia was reported in 38% of cases (Kurnick 1956; Kewalramani 1980). Symptoms generally include a pounding headache, flushed face, piloerection, facial sweating, paresthesia (tingling), and a desire to void. Such episodes can be extremely dangerous, potentially triggering seizures and brain hemorrhages (Kursh, Freehafer, and Persky 1977). These events occur mainly in people with an injury at the level of T6 and above and more often during the chronic stages following the injury.

Prior to an AD event, a triggering stimulus will activate the afferent nerve fibers entering the dorsal root of the cord. This stimulus will generate an exaggerated reflexive response that will project to the sympathetic preganglionic neurons leading to increased sympathetic tone and vasoconstriction below the level of injury. The resulting large increase in blood pressure will be sensed by the baroreceptors in the aortic arch. This will stimulate compensatory vasodilation in the vessels rostral to the injury site leading to symptoms such as facial flushing, sweating, and headache. However, because the injury limits descending inhibition of the sympathetic system below the lesion, blood pressure will remain elevated in the lower portion of the body (Krassioukov 2009). To restore blood pressure back to a normal range, the triggering stimulus must be identified and removed or managed, or the sympathetic action itself blocked.

Other Important Exercise Related Autonomic Functions Affected by SCI

1.3 Catecholamine Release from Adrenal Glands and Sympathetic Ganglia

Cardiovascular control in those with a cervical or high thoracic injury is one of the key organ systems affected following an SCI. This limited sympathetic output from the spinal cord also affects other organs whose activity is important during physical activity. Vasoconstriction, along with increases in heart rate and stroke volume increases during exercise, is not only controlled by sympathetic activation of the vasculature, but also mediated by circulating catecholamines released from the adrenal glands (Cowley 2018). It has been demonstrated that this release is absent in athletes with a cervical injury, even during sustained exercise such as a half-marathon (Ogawa et al. 2014), whereas those with low thoracic and lumbar injuries show

minimal differences in catecholamine levels and aerobic performance (Schmid et al. 1998). These stark differences can be explained by the fact that the adrenal gland is innervated by sympathetic preganglionic neurons exciting the spinal cord at the mid thoracic level. Therefore, any disruption in the delivery of this signal will limit the required response from the adrenal gland, further limiting the vasoconstrictive response that supports the physiological response to exercise.

Both epinephrine and norepinephrine act on target cells and have crucial downstream effects in the ability to meet the increased energy demands of both the heart and skeletal muscles during exercise. Firstly, the integrated action of these catecholamines act on adrenergic receptors on the heart, veins, lymphatics, splanchnic vessels, and muscular arteriolar beds in order to increase blood flow to active skeletal muscles (Koeppen and Stanton 2018). Secondly, upon binding to the β1 receptors of the heart, epinephrine stimulates an increase in heart rate (positive chronotropic effect), cardiac contractility (positive inotropic effect) and subsequent cardiac output. Thirdly, catecholamines promote glycogenolysis in the skeletal muscles and lipolysis in adipose tissue to provide adequate energy during longer periods of physical activity. Glucose metabolism at rest is also influenced by the spinal sympathetic system. In fact, individuals with tetraplegia demonstrate a completely absent epinephrine secretion in response to resting hypoglycemia due to their inability to activate the adrenal medulla (Palmer et al. 1976). Additionally, lipolysis of white adipose tissue has been shown to be directly mediated through sympathetic neuronal pathways. As such, even during sustained periods of exercise, people with tetraplegia show no changes in lipid metabolism (Campbell, Williams, and Lakomy 2004). Beyond regulating the release of energy stores, catecholamine release also stimulates bronchiolar dilation, increasing gas exchange in the lungs. The increased supply of oxygen during exercise promotes adenosine triphosphate (**ATP**) production in cells, which is the cell's energy currency. Finally, epinephrine and norepinephrine act on the visceral smooth muscle to decrease gastrointestinal motility and urinary tract activity, thereby conserving energy for use by active muscles. Based on these important actions of catecholamines, any disruption in their release can significantly affect one's ability to sustain physical activity for any significant length of time, thus also limiting the health benefits they will receive from such bouts of exercise.

1.4. Spinal Cord Injury Affects Thermoregulation

Perspiration is a healthy physiological response to an increase in body temperature. This process allows for the release of heat, thus maintaining a healthy core temperature range. The sweat glands are innervated sympathetically by neurons exiting the thoracic and lumbar cord regions, with the specific pattern of innervation typically following that of the dermatomes (Nathan and Smith 1987). In order to sweat during exercise in the upper portion of the body, one must have intact innervation to the superior cervical ganglion, which receives input from the sympathetic preganglionic neurons exiting the T1-T5 region of the spinal cord. Although not the focus of this thesis, persons with autonomically complete injury above T1 are also unable to mount appropriate physiological responses to decreased temperature, and are essentially poikilotherms; severely lacking the ability to regulate body temperature in response to ambient conditions (Cowley 2018; Guttmann, Silver, and Wyndham 1958; Altus, Hickman, and Nord 1985; Khan et al. 2007; Handrakis et al. 2017) As such, the inability to sweat significantly impairs the intensity and duration of exercise. Pre-cooling or cooling during activity in warm conditions can act to counter the increase in core temperature seen in tetraplegia (Webborn et al. 2005). Without such interventions, core temperatures can increase even following the completion of exercise in a warm environment (Price and Campbell 1999).

1.4.1. Effects of Spinal Cord Injury on Exercise Performance

The exercise responses of trained endurance athletes with varying levels of SCI clearly indicate that impaired sympathetic function has detrimental effects on aerobic performance. Bhambhani and colleagues demonstrated this when they compared the peak exercise responses in endurance athletes with tetraplegia and paraplegia. They reported that athletes with paraplegia on average had absolute and relative peak VO_2 values 78% greater than those with tetraplegia as well as maximum heart rates that were 72% greater (Bhambhani et al. 1994). Unfortunately, even with endurance training, athletes with tetraplegia have limited ability to improve these outcomes as demonstrated by the small differences in VO_{2peak} values in trained vs. untrained tetraplegics (Eriksson, Löfström, and Ekblom 1988). On the other hand, those with low level-paraplegia can significantly improve their aerobic endurance with appropriate training (Lovell et al. 2012).

As mentioned previously, the heart is sympathetically innervated by postganglionic neurons exiting from T1-T5 region of the spinal cord. At higher intensities, when parasympathetic withdrawal is insufficient to increase heart rate, sympathetic output to the heart increases. Individuals with cervical or high thoracic injuries will have absent or limited ability to stimulate this required increase. As such, heart rate max in people with tetraplegia is very low (110-130 bpm) along with very limited cardiac contractility and stroke volume (Bhambhani et al. 1994). Subsequently, the heart is unable to meet the increasing metabolic needs of the exercising muscles and tissues making it extremely difficult for the individual to maintain activity of that intensity. From this evidence, it is clear that the exercise response following a spinal cord injury is heavily dependent on the level and completeness of the lesion and the ensuing effects on sympathetic output (Cowley 2018).

1.5. Locomotion

Moving, whether it be walking, swimming, or flying is essential for the ability of an animal to survive. These repetitive rhythmic movements are largely controlled via a network of neurons found within the spinal cord, known as central pattern generators (**CPGs**). This term was coined in the 1960s following the work done by Thomas Graham Brown whose experiments determined that the basic patterns for stepping are generated by spinal cord and require no peripheral afferent input to do so (Guertin 2009). Decades later, it is now understood that the spinal cord contains essential rhythm generating elements that may be reasonable targets for rehabilitation interventions (Cowley, Zaporozhets, and Schmidt 2010).

Though locomotion is often characterized as relatively simple rhythmic movements, animals must have the ability to adapt to their environment. Spinalized animals can indeed develop the ability to walk again following injury, but they do not have the ability to maintain balance in the same way an intact animal does. Supraspinal control provides descending input to adapt to a changing environment. In a similar manner, supraspinal inputs help mediate acute responses to changes in either the internal or external environment, via brainstem autonomic control centres (Kandel et al. 2013). It is therefore important to recognize the rhythmic generating capacity of the spinal cord exclusively as well as the descending supraspinal and ascending afferent input that modulates motor output.

The intrinsic capacity of the spinal cord to generate overground locomotor activity has been demonstrated in animal models for decades. Electrical activation of spinal neurons below lesion have been increasingly investigated clinically since 2011 (Harkema et al. 2011) Such interventions take advantage of remaining intact or semi-intact sensory and motor pathways, further highlighting the amazing role of the spinal cord in producing movement and mediating autonomic functions.

1.6. History of Electrical Spinal Stimulation

Electrical stimulation has been utilized as a therapeutic treatment in human beings dating back to as early as Ancient Rome, where accidental contact with torpedo fish was found to relieve lower-limb pain from gout (Gildenberg 2006). Since then, the use of electrical stimulation has been used for many other therapeutic purposes. Epidural stimulation of the spinal cord involves the surgical implantation of a small electrode placed on the dorsal surface of the cord above the dura. This was first used in the 1960s for the treatment of pain (Shealy, Mortimer, and Reswick 1967) and in the 1970s for improved sensory and motor function in individuals with Multiple Sclerosis (Cook and Weinstein 1973). It wasn't until the early 1980s that epidural stimulation was used in spinal cord injured subjects which showed improvements in both motor function and bladder control (Campos et al. 1981). Further investigations would go on to show reductions in spasticity using specific stimulation parameters and noting differences in effects based on body position (ie. sitting vs. standing) (Dimitrijevic, Illis, and Nakajima 1986; Dimitrijevic, Gerasimenko, and Pinter 1998). It was during this time that individualized parameters were becoming a focus, which highlighted the variability of the remaining spinal pathways following injury. It would be lamentable to ignore the progress in the animal world that was also occurring during these times. Beginning in 1992, scientific groups were demonstrating the ability to elicit stepping movements in decerebrate cats using supra-threshold epidural stimulation (Iwahara et al. 1992). The Edgerton group would build on these findings using similar methods to produce bilateral stepping in spinal rats as well as movement in the presence of proprioceptive input in a follow-up study using sub-threshold stimulation (Ichiyama et al. 2005; Gad et al. 2013). Autonomic functions were also shown to be affected by stimulation, as demonstrated by Gad and colleagues who demonstrated the initiation of bladder voiding in paralyzed, step-trained rats with

epidural stimulation (Gad et al. 2014). These results became even more translatable to humans when the Courtine group reported improved locomotion in rhesus monkeys using epidural stimulation a few years later (Capogrosso et al. 2016).

Around this same time, transcutaneous spinal cord stimulation (**TSCS**) was being investigated as a less invasive and potentially effective way of activating similar spinal circuits as epidural stimulation. Minassian and colleagues applied TSCS over the lower thoracic region of the spinal cord and reported marked improvements in spasticity and voluntary motor activity in individuals with incomplete SCIs (Hofstoetter et al. 2014; Hofstoetter et al. 2015). These results suggested that TSCS may offer similar benefits to epidural stimulation, while being more cost effective and permitting the repositioning of electrodes for optimal results. Further investigations determined that multisite stimulation had interactive and synergistic effects on spinally evoked motor potentials (Gerasimenko et al. 2015). Around the same time, Angeli and colleagues demonstrated the novel ability to produce voluntary movement in motor and sensory complete spinal cord injured persons using epidural stimulation immediately following surgical implantation (Angeli et al. 2014). Amazingly, similar results were reported two years later in which TSCS (both with and without peripheral afferent feedback via treadmill training) was able produce rhythmic stepping in 4 individuals with chronic, clinically complete SCI (Minassian et al. 2016).

These results chiefly demonstrate the incredible effect that spinal cord stimulation can have on motor function following an SCI. However, it was during the early 2000s that participants and investigators were beginning to report anecdotal improvements in other autonomic functions besides those related to bowel, bladder and sexual function, such as improved blood pressure control, sweating ability, and exercise performance. These initial findings have led researchers to investigate these outcomes further. Nonetheless, changes in autonomic function of this type using neuromodulatory strategies is a new and emerging area of study. Being that improved autonomic control is so highly sought after by those living with an SCI, future systematic investigations examining the use of spinal cord stimulation on autonomic functions related to physical activity outcomes will be of great importance to those in the SCI community.

1.6.2. Potential Neural Mechanisms and Pathways Activated by Electrical Spinal Stimulation

Electrical spinal stimulation promotes functional recovery after spinal cord injury, but the exact mechanisms and pathways activated are not explicitly known. It is thought that both epidural and transcutaneous electrical stimulation preferentially activates dorsal root afferent fibres, thereby increasing the resting membrane potential of the activated spinal circuitry (West et al. 2018). Depending on the electrode placement, it is possible that stimulated dorsal root afferents may activate sympathetic preganglionic neurons leading to cardiovascular and vasomotor regulation (Harkema, Wang, et al. 2018b). Other autonomic functions may be affected in a similar fashion via interneuronal communication within the spinal cord.

Several other more long-term mechanisms have been proposed based on the size and anatomical locations of afferent neurons and the use of computational modeling studies supported by electrophysiological and pharmacological data (Bouyer and Rossignol 1998; Rossignol, Dubuc, and Gossard 2006; Capogrosso et al. 2016). Firstly, it has been proposed that electrical spinal stimulation promotes plasticity by strengthening the monosynaptic connections between electrically stimulated afferents and motoneurons within the lumbar cord segments, thereby increasing motor output (Eisdorfer et al. 2020). More specifically, group Ia proprioceptive afferents are thought to be the most important in achieving these effects because they form direct monosynaptic connections onto motoneurons innervating agonist muscles as well as synapsing onto interneurons responsible for muscle antagonist inhibition. Takeoka and colleagues demonstrated the important role of these neurons in the recovery of spinal mice. Animals without functional muscle spindles were unable to regain proper control of their affected hindlimbs, whereas wildtype mice demonstrated spontaneous locomotor recovery (Takeoka et al. 2014). They further corroborated this using a genetic model in which incomplete spinal mice with ablated proprioceptive afferents caudal to the injury site showed complete regression to their injured state, even in after they had shown initial improvements in locomotor performance following their cord lesions (Takeoka and Arber 2019). While electrical stimulation may enhance the activity of these existing neurons, it may also induce axonal sprouting allowing for the formation of new synapses (Retamal et al. 2018; Xu et al. 2020). Though it is currently unknown if these new synapses are formed between Ia afferents and motoneurons, if this is the case, it should be that it would not only enhance motoneuron output to agonist muscles, but also increase activation of muscle synergists

which would increase overall force output during movement. Secondly, it is possible that electrical stimulation indirectly targets propriospinal neurons (**PNs**) via peripheral sensory afferent activation, subsequently improving locomotor output. These neurons are a specific type of interneuron whose cell body is found within a particular spinal segment with its axon projecting several spinal segments either ipsilaterally (same side) or contralaterally (crossing over) (Flynn et al. 2011). They receive both descending supraspinal and sensory input and have been deemed important for locomotor control and coordination. They also demonstrate the ability to reorganize following an SCI by upregulating growth factors that allow it to sprout, elongate, and circumnavigate the injury site (Fernandes et al. 1999; Siebert, Middelton, and Stelzner 2010; Taccola et al. 2018; Wang et al. 2018). It is therefore proposed that electrical stimulation may indirectly facilitate this process while also reactivating spared PNs that may be dormant following injury as demonstrated by successful recovery of some voluntary control in chronic SCI individuals using electrical stimulation (Harkema et al. 2011; Angeli et al. 2014). Further understanding of the neural mechanisms and pathways involved will likely be achieved using animal models and genetic technology such as chemogenetics and optogenetics. Such tools allow investigators to target specific pathways and subpopulations of neurons, label affected neurons, and identify other pathways that have been indirectly influenced by electrical stimulation.

PART 2: SCOPING REVIEW

2.0. Hypothesis

There is insufficient research evidence to determine if electrical spinal stimulation can be used to improve autonomic function related to physical activity outcomes in people with a spinal cord injury.

3.0. Objective

Identify the state of the literature regarding stimulation parameters that improve autonomic function related to physical activity outcomes and determine what knowledge gaps exist.

METHODS

We utilized the 5-stage methodological framework developed by Arksey and O'Malley to conduct this scoping review (Arksey and O'Malley 2005). These stages included: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) summarizing the results. This scoping review followed the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). The purpose of a scoping review is to identify what is known about a topic and what the current knowledge exist in the literature. Given that electrical stimulation of the spinal cord for the purpose of improving exercise performance is a relatively new area of research, a scoping review is a useful method to help direct future scientific studies.

Stage 1: Identify the Research Question

The research team worked together to develop the research question: what is known about spinal cord stimulation and autonomic function, as it relates to physical activity, following a spinal cord injury?

Stage 2: Identify Relevant Studies

With the help of a Health Sciences U of M librarian, the research team developed the literature search strategy. Search terms were selected based on key words used in past articles related to our topic of interest. Examples of these terms include: spinal cord injury, SCI, tetrapleg*, parapleg*, electrical spinal stimulation, epidural stimulation, and transcutaneous stimulation. Searches were conducted using the following databases: Medline, EMBASE, Scopus, CINAHL, and SportDiscus. Articles were limited to those written in the English language and involving adult human participants (if an available limiter). Relevant articles were uploaded to an online screening platform, Covidence.

Stage 3: Study Selection

Upon uploading references to Covidence, all duplicates were removed. The screening process consisted of two steps involving three reviewers. In the first step, titles and abstracts were screened for relevance. In the second step, full texts articles were reviewed. Each article was required to receive two votes in agreeance to be successfully screened. Studies were excluded if they were: (a) conference abstracts, (b) using electrical stimulation that was not applied to the spinal cord (ie. functional electrical stimulation), (c) including participants under the age of 18, (d) using non-human participants, (e) including participants without a SCI (exclusively), and (f) investigating the effects of electrical spinal stimulation on autonomic functions not related to exercise (ie. bladder or sexual function). Conflicts about screening were discussed amongst team members until a unanimous decision was made. This search strategy and screening process is outlined in the PRISMA flowchart in Fig. 1.

Stage 4: Chart the Data

Prior to data extraction, the authors discussed all information that was to be extracted from the included articles. Participant data extracted included the number of participants, gender, age, time since injury, AIS (American Spinal Injury Association impairment scale) classification, and neurological level of injury. Transcutaneous and epidural stimulation data were managed separately. Extracted data included author(s), publication date, title of article, study design, intervention protocol, electrode placement, electrode size (transcutaneous studies only), frequency, intensity, waveform, pulse length, treatment length, and primary outcomes.

Stage 5: Summarizing the Results

Results were first categorized based on how many studies focused mainly on changes in autonomic function or motor function. It was then determined how many studies reported on specific autonomic outcomes (ie. six epidural stimulation studies reported on blood pressure at rest). Specific outcomes were then further categorized into main findings (ie. increase in blood pressure at rest) which included how many studies reported a finding and how many participants experienced the specific outcome.

RESULTS

Articles Retrieved

Our searches of the above listed databases yielded a total of 1964 articles. Following deduplication, 1815 studies remained. The titles and abstracts of these articles were screened for relevance. From this, 134 articles passed to the full text screening stage. Following the full text screening phase, 20 studies were included for this scoping review. One additional study was included following the initial screening phase. Figure 1 (PRISMA flowchart) outlines the process of study selection.

Characteristics of Articles and Participants

Of the 21 articles included in this review, 11 were case reports, 8 were case series, 1 was a parallel design, and 1 was a double-blind crossover design. Publication dates ranged from the year 2000 to 2020. The number of participants ranged between 1 and 25, with the total study sample size equaling 96 (n = 70 participants received transcutaneous stimulation; n = 26 participants received epidural stimulation). The average number of participants in each study was relatively small at approximately 5. Nine of the studies used transcutaneous stimulation as the intervention, while the remaining twelve used epidural stimulation. Of important note, a reported total of 51 males participated in 21 studies while only 10 women were reported as participants in the included studies. 28 participants were classified as AIS A, 17 as AIS B, 16 as AIS C, and 6 AIS D. Two studies (Shelyakin et al. 2000, n = 25 participants; DiMarco et al. 2018, n = 1 participant) did not disclose the level of injury completeness of their participants. Out of the 96 participating individuals, 45 had tetraplegia, 23 had paraplegia, and the remaining were not reported. 6/9 transcutaneous stimulation studies included anecdotal reports on autonomic function(s) and 3/9 systematically examined autonomic outcome(s). In the epidural stimulation studies, 5/12 reported anecdotally on autonomic function(s) whereas 7/12 were systematic/planned studies of autonomic outcome(s). Of note, all anecdotal reports on autonomic function appeared in 2000 and onward, while the systematic/planned examination of the effects of spinal electrical stimulation on autonomic function did not appear in the literature until 2018. The remaining relevant participant characteristics information is included in Table 1.

Stimulator Locations and Stimulus Parameters

As shown in Figure 2, in studies that used transcutaneous spinal cord stimulation (**TSCS**) as their intervention, four studies placed the stimulating cathode over the cervical vertebrae (C3-C7), 3 studies over the thoracic vertebrae (T2-T12), one over the lumbar vertebrae (L1-L2), and one study did not specifically report the area of stimulation, but rather stated "along the vertebral column" (Shelyakin et al. 2000). It is interesting to note that these wide array of electrode placements all elicited changes in sympathetic output. Two studies using dual site cervical stimulation (C3-C4 & C6-C7) reported improvements in sweating ability (n = 2 participants) with no detrimental effects on heart rate or blood pressure (Gad et al. 2018; Inanici et al. 2018b). Similarly, three studies stimulating over C5-T2 (Murray and Knikou 2017) or between T11-12 and/or Co1 (Sayenko et al. 2019; Gad et al. 2017) also reported improvements in perspiration with stimulation. Changes in blood pressure were reported in studies stimulating over T11-T12 and/or Co1 (Gad et al. 2017), T2-T4 (Wu et al. 2020; Sachdeva et al. 2021), and T7-T8 (Sachdeva et al. 2021; Phillips et al. 2018).

There was less variability reported in the placement of the anodes. The iliac crests were the most common placement for the anodes (n = 7 studies), followed by the clavicles (n = 1 study), and anterior portion of the neck corresponding the C4-C5 vertebral level (n = 1 study).

Six of the nine studies used round cathode electrodes with diameters ranging between 2-3.2 cm. Of the remaining studies, two reported using 10x5 cm rectangular electrodes while one study reported using a 600 mm^2 cathode of unknown shape. The primary and anecdotal outcomes measured in each study are also indicated in Table 2.

In studies that administered epidural stimulation (Figure 3), implants were surgically placed ranging between the vertebral levels of T9-L1. Implants are comprised of 16-electrode arrays in which the electrode configurations (which are cathodes, anodes, or inactive) can be adjusted to target specific participant needs.

Only two studies using transcutaneous stimulation did not report the waveform used. Of the remaining seven studies, three reported using monophasic pulses, two reported using biphasic waves and two reported using both biphasic and monophasic pulses. Two studies further specified using rectangular shaped pulses (Murray and Knikou 2017; Inanici et al. 2018b). Waveform was not commonly reported in the epidural stimulation studies. The two studies that did report waveform noted the use of a biphasic stimulation pattern.

The most common frequency used during transcutaneous stimulation was 30 Hz (n = 5 studies). Frequency use ranged between 0.2-30 Hz with three studies utilizing a 10 kHz carrier wave. One study did not report the frequency used (Shelyakin et al. 2000).

Frequency used during epidural stimulation ranged between 2-400 Hz. The frequency values varied depending on the targeted outcome (ie. standing, stepping, blood pressure control while seated) and the individual's level of injury and stage of rehabilitation.

The intensity of stimulation used in transcutaneous studies ranged between 4-250 mA. Only one study did not specifically report the intensity levels used. Instead, they reported that this parameter was chosen based on participant feedback and optimum efficacy (Gad, 2017).
Different from transcutaneous stimulation studies, intensity in the epidural studies was more often reported using voltage. The intensity applied ranged between 1-10 V and varied for each participant. One study (Darrow et al. 2019) reported the intensity range between 2-15 mA and one study did not report on the intensity used (Edgerton and Harkema 2011).

The pulse length most commonly used in the transcutaneous studies was 1 millisecond (n = 5 studies). One study reported using 2 milliseconds (Wu, 2020), while two studies did not report the pulse length used (Gad, 2017; Shelyakin, 2000).

Pulse length used in the epidural studies varied widely. The numbers reported ranged between 200-300,000 microseconds. Further detail on epidural stimulation locations and parameters is provided in Table 3.

Outcomes Reported

The autonomic outcomes most commonly reported in both transcutaneous and epidural studies were blood pressure (4/9 TSCS; 4/12 ESCS) and heartrate (5/9 TSCS; 3/12 ESCS). Exercise performance outcomes (RPE, VO_{2peak}) were reported in 4/12 ESCS studies.

In the transcutaneous studies, blood pressure was most often recorded for the purposes of safety to ensure that stimulation was not eliciting uncontrolled changes (5/9 studies). However, in three of the nine studies, blood pressure was a primary outcome measure as the focus of these studies were changes in autonomic function with stimulation. Blood pressure was measured during a range of activities and positions including at rest (n = 1), during standing (n = 1), during an orthostatic or autonomic dysreflexia induced challenge (n = 2), following exercise (n = 1), and

during physical therapy (n = 1). Heart rate was often measured for safety reasons, but not specifically reported in the results. Six out of nine studies reported changes in heartrate, while the remaining studies made note of recording this variable but did not publish their data. Of the six studies that documented changes in heart rate during stimulation, only three published specific values. Improvements/regained ability to perspire with stimulation was reported in two out of nine transcutaneous studies.

Outcomes / Findings

Transcutaneous Studies

Blood Pressure Outcomes

Of the six primarily motor function studies with only anecdotal reports of autonomic outcomes, changes in blood pressure at rest were mentioned in one study indicating seven persons with increased blood pressure and two persons with decreased blood pressure. Blood pressure was not altered in the remaining 4 participants (Wu et al. 2020). Stimulation was delivered at T2-T4 (anodes over anterior region C4-C5) spinal level in this study. Of the primarily motor studies reporting on blood pressure during or after locomotor training, one study reported increased blood pressure (post step training at baseline: 138/95 mm Hg; post step training + TSCS: 145/87 mm Hg) when walk training occurred with TSCS (n= 1 participant, TSCS at T11 and/or Co1) (Gad et al. 2017). Of the three studies with autonomic outcomes as a primary focus, two examined the effect(s) on blood pressure regulation and reported that TSCS normalized blood pressure responses to either an orthostatic challenge or an autonomic dysreflexia challenge (n = 6 participants). Stimulation was delivered over T7-T8 vertebrae in both studies (Phillips et al. 2018; Sachdeva et al. 2021).

Heart Rate Outcomes

Of the six studies with motor outcomes as the primary focus, an increase in heart rate at rest during stimulation was reported in two studies, totaling 26 participants. Of note, Shelyakin et

al. 2000 did not report how many participants had an SCI and how many had tuberculous spondylitis, but rather grouped all participants together (n = 25) for results. However, Wu et al. 2020 reported a decrease in heart rate at rest in 7/13 participants (TSCS at T2-T4; anodes over anterior region C4-C5). None of the studies with autonomic outcomes as the primary focus examined resting or activity-based heart rate responses to TSCS.

Similar to blood pressure, most reports on sweating were anecdotal, in studies whose primary outcome was motor function (3/6 primarily motor function focus studies). Recovery of perspiration (after only 1 session of stimulation or only when stimulation was being delivered) with stimulation was reported in three studies (n = 7 participants). Stimulation was delivered at T11-T12 and/or Co1, L1-L2, or with dual site stimulation over C3-C4 and C6-C7 in these studies. Specifically, sweating at rest increased in one study, while sweating during standing and/or stepping improved in two studies (n = 4 participants). One study (Gad et al. 2018) reported an increase in sweating ability in two participants, but did not specify if the sweating occurred at rest or in response to activity or heat. A summary of these findings can be found in Table 4. None of the studies with autonomic outcomes as the primary focus examined the effect(s) of TSCS on sweating.

Epidural Studies

Blood Pressure Outcomes

Blood pressure outcomes were reported anecdotally in 5/12 studies. In the 7/12 studies with autonomic outcomes as the primary focus, two studies (Darrow et al. 2019; Aslan et al. 2018) investigating the effects of epidural stimulation (implant placed over T12 (Darrow et al. 2019) or T11-L1 (Aslan et al. 2018)) on blood pressure regulation reported the normalization of blood pressure during an orthostatic challenge in four individuals with orthostatic intolerance. These two studies further tested this response in participants with no orthostatic intolerance and reported no significant changes in blood pressure due to stimulation, while at rest or during the orthostatic challenge. In another study, Harkema and colleagues also investigated these effects in individuals who regularly experienced orthostatic hypotensive events (Harkema, Wang, et al. 2018c). They

reported reproducible and significant increases in mean arterial pressure and the normalization of cardiovascular parameters in direct response to stimulation (implant placed over T11-L1 vertebrae) while seated. Each participant received personalized stimulation configurations (anode-cathode selection, voltage, frequency, and pulse width) chosen to maintain blood pressure within a normal range without stimulating skeletal muscle activity in the lower limbs. These values were determined during 2-3 preparatory sessions prior to the full-length intervention sessions. Upon removal of the stimulation, blood pressure returned to low baseline values. A summary of all autonomic outcomes can be found in Table 5.

Heart Rate Outcomes

Heart rate responses to epidural stimulation tended to be more variable than blood pressure responses. One participant in the Harkema et al. 2018 study demonstrated a significant decrease in heart rate (average decrease of 8 bpm from baseline) during stimulation, while the other three participants showed no significant changes. All participants in this study demonstrated orthostatic intolerance. In another orthostatic intolerant participant group (n = 3), Aslan et al., 2018 reported increases in heartrate while supine (3/3 participants) and during standing (2/3 participants) while stimulation was on. Interestingly, one participant in their study group without orthostatic intolerance (n = 4) also demonstrated an increase in heartrate of up to 50% from baseline (2 Hz; 10 V) using a rostral configuration while supine during the intervention. This finding was not further commented on.

Exercise Related Outcomes

Only one study to date has investigated the effect of spinal cord stimulation on exercise performance measures. Specifically, Nightingale et al., 2019 was the only study to investigate the direct effects of both high and low intensity epidural stimulation on peak exercise outcomes such as VO_{2peak}(L/min), ventilation (L/min), and peak oxygen pulse (ml / beat; used as an indirect measure of stroke volume) (Nightingale et al. 2019). In one male participant with a cervical level injury (AIS B), they reported remarkable increases in relative VO_{2peak} (15-26%) and peak oxygen pulse (8-21%) during a progressive arm ergometry test to failure with stimulation when compared

to a test with no stimulation. Peak ventilation also significantly improved while rating of perceived exertion (**RPE**) for a given output of 60 Watts was reduced with stimulation. Mean arterial pressure following the exercise test was on average 6 mm Hg higher with stimulation than without.

Terson de Paleville and colleagues investigated the effects of epidural stimulation on various metabolic and exercise performance outcomes, but did so in conjunction with a stand and step training program (Terson de Paleville, Harkema, and Angeli 2019). As this data was collected at four time points (before, during and after the training program with stimulation), the direct effects of the stimulation (versus training effects) could not be determined. Nonetheless, the results are still clinically relevant. Two participants (AIS A (T5); AIS B (C5) demonstrated small improvements in VO_{2peak} at the end of the 40 weeks of training (Participant 1: 23.5 → 26.9 ml / kg / min; Participant 2: 11.0 →14.5 ml / kg / min). Increases in body mass due to increases in lean tissue mass were reported along with decreases in body fat percentage and android / gynoid fat ratio following the training + stimulation intervention. The latter measure is considered an important risk indicator for cardio-metabolic disease with a reduced ratio being more favorable. Additionally, resting metabolic rate (**RMR**), the rate of energy expenditure at rest (kcal / day), was increased in two participants (the remaining two participants had incomplete data) upon completion of their training program.

In a similar experimental paradigm, Gorgey et al., 2020 examined the effects of epidural stimulation in combination with a twelve-week training program using an exoskeleton assisted walking device (**EKSO suit**) (Gorgey et al. 2020). Though any changes cannot be directly attributed training, stimulation or a combined effect, trunk region and total body fat mass was reduced while no significant changes in lean mass were reported. Furthermore, RPE increased significantly when the EKSO suit assistance during stepping decreased and with the stimulation on. It is proposed that these increases reflect an increase in exercise intensity while reducing the assistance.

More direct effects of spinal stimulation on metabolic outcome measures were observed in studies performed by Herman et al., 2002, Carhart et al., 2004, and Ganley et al., 2005 in which gas exchange data during partial weightbearing walking was examined both with and without epidural stimulation (at T10-T12 vertebral level) in 4 participants. All three studies demonstrate significant decreases in oxygen consumption during walking with stimulation indicating a reduced energy cost, even when controlling for distance and duration. Moreover, CO_2 production was also

reduced implying an increase in fatty acid oxidation and potentially less blood lactate accumulation and associated bicarbonate titration (Carhart et al. 2004). One study indicated an increase in fat oxidation by up to 8x during walking when compared to unstimulated walking of equal distance (Herman et al. 2002). This same group noted that although partial weightbearing training alone improved spasticity, RPE remained very high at 8/10. With stimulation, there was an immediate improvement in stepping pattern, characterized by well-organized and smoother movements at higher treadmill speeds, as well as reduced RPE to 2/10. Perceived exertion decreased during walk training with stimulation in the other two studies as well, when compared to training without stimulation.

DISCUSSION

The purpose of this scoping review was to identify the state of the literature regarding the effects of spinal cord stimulation on autonomic function in outcomes related to physical activity. We identified 21 articles, of which 9 focused on transcutaneous spinal cord stimulation and 12 focused on epidural stimulation. Though all included articles made some mention of the effects of stimulation on autonomic function, the main focus of the majority of articles was on improving motor function. In total, 11/21 articles focused on the effects of stimulation on motor function, 7/21 specifically focused on changes in autonomic function, while the remaining 3 focused on the effects on both autonomic and motor function. The main observation of this scoping review is that spinal cord stimulation (either transcutaneous or epidural) can modulate autonomic outcome measures.

During the early reports (2000-2016), autonomic outcomes were reported in studies in which they primarily focused on changes in motor function, and the reported effects on ANS function were generally for the purpose of safety and tolerability. This typically included measures such as blood pressure or heart rate. However, baseline data for variables such as those just mentioned are important to include in order to provide meaningful context to any changes that may have occurred with stimulation. For example, Wu (2020) reported that 7 participants demonstrated sustained increases in blood pressure of 20% or greater during the intervention. Without baseline data, it is difficult to discern the significance of this finding as it is possible that this may be a beneficial response for this group or a dangerous increase potentially resulting in autonomic

dysreflexia. Other more generalized outcomes included the regained ability to sweat during the intervention in 3 transcutaneous studies (n = 6 participants). These outcomes were all self-reported by the participants and not objectively measured. Future studies would benefit from including more objective measures of perspiration such as skin conductance.

All studies, but one (Shelyakin et al. 2000) included information on the neurological level of participant injury as well as the AIS classification. These are important characteristics to note as they can help to interpret results of a specific study and allow future investigations to determine patient specific parameters. For example, it would be expected for a person with a cervical injury to have some form of cardiovascular dysfunction and reduced ability to regulate blood pressure during an orthostatic or autonomic dysreflexic event. In comparison, an individual with a lower thoracic or lumbar injury should have intact innervation to these cardiovascular regulating regions of the spinal cord and therefore should not present with orthostatic hypotension or autonomic dysreflexia. Knowing this, future investigations should aim to assess autonomic function prior to administering any interventions using the current International Standards to Document Remaining Autonomic Function After Spinal Cord Injury (Contributors et al. 2012). If an appropriate number of participants can be recruited, they should further be grouped by baseline autonomic function. Specifically, participants demonstrating orthostatic hypotension at baseline should be grouped together and those without orthostatic hypotension should be placed in a different group. By doing so, it can be better discerned whether the targeted stimulation influenced specific functions of interest and if those effects were to be expected. The findings of this scoping review supports the concept that spinal stimulation may ameliorate negative consequences of autonomic dysregulation of the vasculature in those with impaired autonomic function and, importantly, does not induce inappropriate cardiovascular responses in those with sympathetically intact systems.

Safety and Tolerability

No serious, unresolvable issues regarding safety and tolerability were reported in any of the studies. One case study utilizing at home epidural stimulation (implant over T9-11) for the purposes of maintaining airway pressure reported the temporary development of autonomic dysreflexia during the initial use of stimulation. However, this was resolved in 5-6 weeks with continued use (DiMarco et al. 2018).

In the transcutaneous studies, stimulation was generally well tolerated and did not overheat or cause damage to the skin, even with multiple testing sessions. Painless hyperemia (skin redness) under the electrodes was reported in 2/9 studies. This redness disappeared several minutes after the removal of the stimulation. Some discomfort was expressed at the highest stimulation intensities (150-200% motor threshold) in one study (Wu et al. 2020). Some participants (n = 7) also reported mild nausea, neck pain, sore throat, light headedness, metallic taste in their mouth, and a sense of feeling flushed. This study was unique in that it was the only one to place the anode in the mid cervical region, possibly explaining these effects. All events resolved within minutes or less. Three participants in one study experienced unintentional bladder voiding during one session of stimulation (T11-T12 or L1-L2). However, this did not occur during the other testing sessions using the same stimulation parameters and configurations (Sayenko et al. 2019).

Based on these reports, electrical spinal stimulation offers a safe and tolerable method to improve motor and autonomic function in individuals with a spinal cord injury. Future investigations should continue to monitor variables such as level of discomfort, skin damage, and changes in blood pressure and heart rate to ensure that no severe health outcomes occur with stimulation.

Study Limitations

A major limitation of this scoping review is that the vast majority of studies reporting on autonomic exercise related outcome measures were anecdotal, rather than specific, systematic investigations of autonomic functions. Thus, this scoping review demonstrates the need for future systematic investigation of the effect(s) of spinal cord stimulation on exercise-related autonomic outcome measures in persons with SCI, and particularly those with high level SCI (cervical injury). This is because it is quite likely that persons with injury below about T4-T6 probably demonstrate ‘normal’ sympathethic autonomic regulation of function related to exercise. Thus, the need for more targeted sample selection and more specific sympathetic exercise-related outcome measures is warranted.

Additionally, the average number of participants in all of the studies combined was 5. 11/21 studies were case reports and only 3 studies had more than 10 participants. With small sample sizes, it is difficult to determine the true effectiveness of a stimulation protocol. This also

potentially limits the internal and external validity and reliability of such studies. Nonetheless, the clinical relevance of case reports is still important given that both spinal cord injury and electrical spinal stimulation are independently complex necessitating individualized approaches.

Another common limitation identified by numerous studies, was combined treatment strategies of both locomotor training in conjunction with stimulation. In most cases, this was not done using a cross-over case design. Even when this study design was used, the order of received treatment was not randomized (ie. physical therapy for 4 weeks following by physical therapy + stimulation for 4 weeks), preventing the possibility of determining the effects of order on outcomes (Gad et al. 2017; Inanici et al. 2018a).

Double-blind, placebo-controlled trials are widely regarded as the gold standard of clinical studies. However, it is well recognized that this 'gold standard' is almost universally unachievable within the SCI research realm because of the low incidence of injury overall and the widely varying characteristics of the injury level and extent. Further, in the case of electrical stimulation, participant blinding is essentially impossible. Sham stimulation is sometimes used in which a known pulse configuration that is intentionally ineffective is delivered to the participant. Yet, even sensory complete individuals can detect the presence of stimulation which could affect certain outcomes. Additionally, we currently do not have a thorough enough understanding of the spinal circuitry that is activated with spinal stimulation. As a result, we would be mistaken to conclude that any stimulation, regardless of the parameters, does not influence these pathways. Consequently, this will continue to be a difficult area of potential bias to address.

CONCLUSION

Electrical spinal cord stimulation is a therapy with the capacity to improve both motor and autonomic function in those living with a spinal cord injury. Improvements have been demonstrated in recent reviews on both motor function and autonomic functions related to bowel, bladder, and sexual function (Megia Garcia et al. 2020; Parittotokkaporn et al. 2020). However, the potential to modulate other autonomic functions, such as those related to exercise performance, including cardiovascular function, BP regulation, temperature regulation, metabolic substrate mobilization and use, and exercise performance generally have only recently been investigated. This scoping review demonstrates that both transcutaneous and epidural stimulation may improve

such outcomes. However, given the widely varying stimulus locations and parameters, and the mainly anecdotal reports of improved autonomic function, more systematic and targeted examination of the capabilities of spinal stimulation to influence exercise-related autonomic outcome measures is warranted. As such, the specific parameters and stimulus locations that are most effective for improving a specific autonomic function (or constellation of functions) remains to be elucidated. Nonetheless, there are some identified patterns in the studies included in this scoping review. Blood pressure regulation via transcutaneous stimulation was improved in two studies (Phillips et al. 2018; Sachdeva et al. 2021) using electrodes over the thoracic region with a stimulation frequency of 30 Hz. Epidural stimulation has demonstrated similar effects with implants placed over the lower thoracic and upper lumbar vertebral regions using a range of frequencies, intensities, and electrode configurations specific to the individual and activity. This is reasonable, considering the sympathetic preganglionic neurons reside in this region of the spinal cord. Future transcutaneous stimulation studies would benefit from testing the effects of a variety of electrode locations on specific autonomic functions. Though the adjustment of electrode placement is not feasible with epidural implants, individualized stimulation programs (anode-cathode configuration and activity/patient specific stimulation parameters) will give better insight into immediate and long-term effects of spinal stimulation. In addition, pre-clinical mechanistic studies are needed to determine the possible neural substrates mediating these improved outcomes so that clinical studies can better develop more targeted and effective spinal cord stimulation strategies. Investigations of this manner further highlight that the application of spinal stimulation for the purposes of modulating autonomic function, in particular cardiovascular function, are in its infancy.

Future advancements in this area may provide individuals with an SCI an appealing tool for enhancing their exercise response so that they may benefit from physical activity and increase their odds of preventing or delaying the onset of numerous metabolic and vascular diseases.

FIGURES

Figure 1. Study Selection Process. PRISMA-P flow diagram outlining the article selection process.

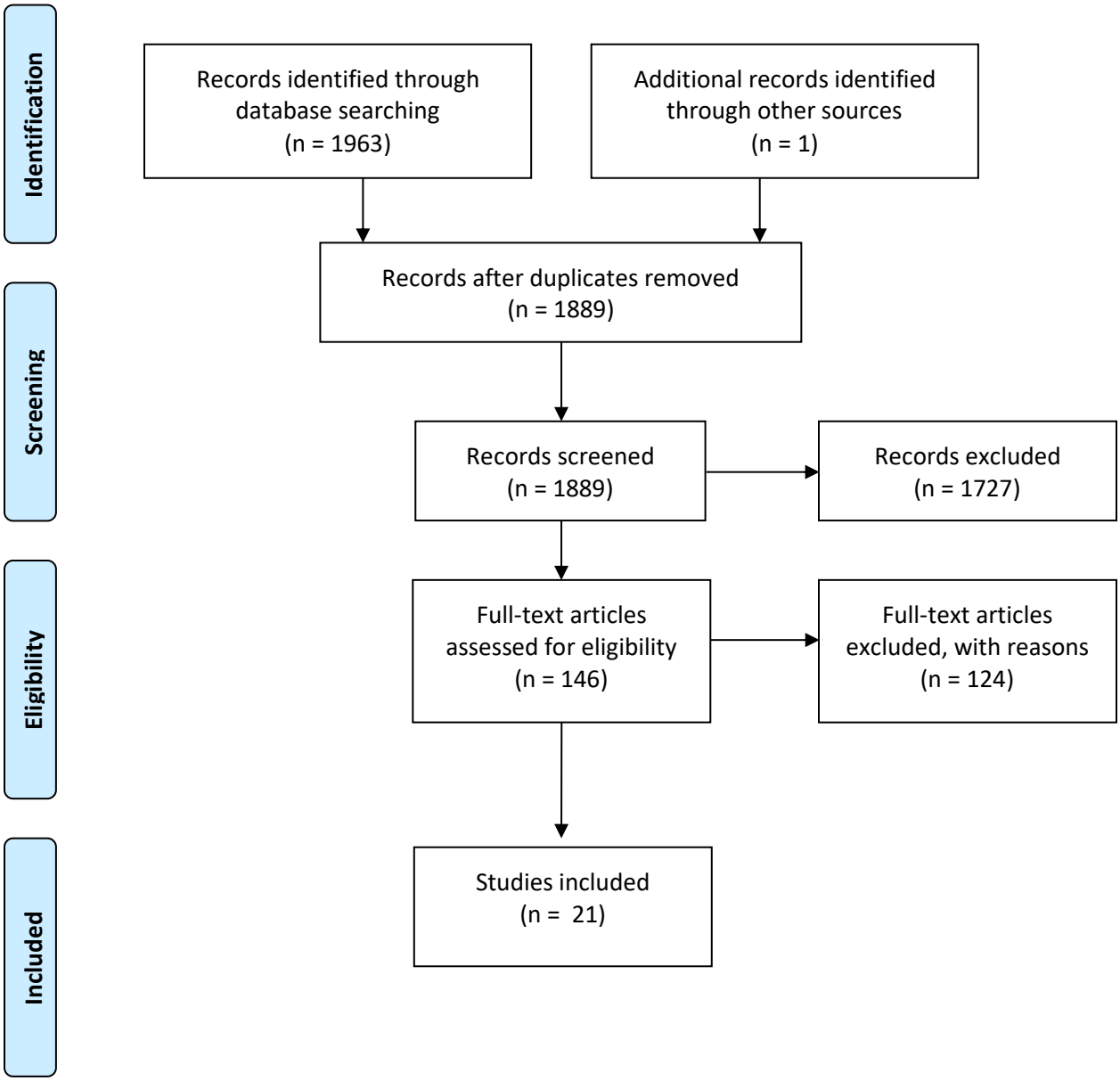
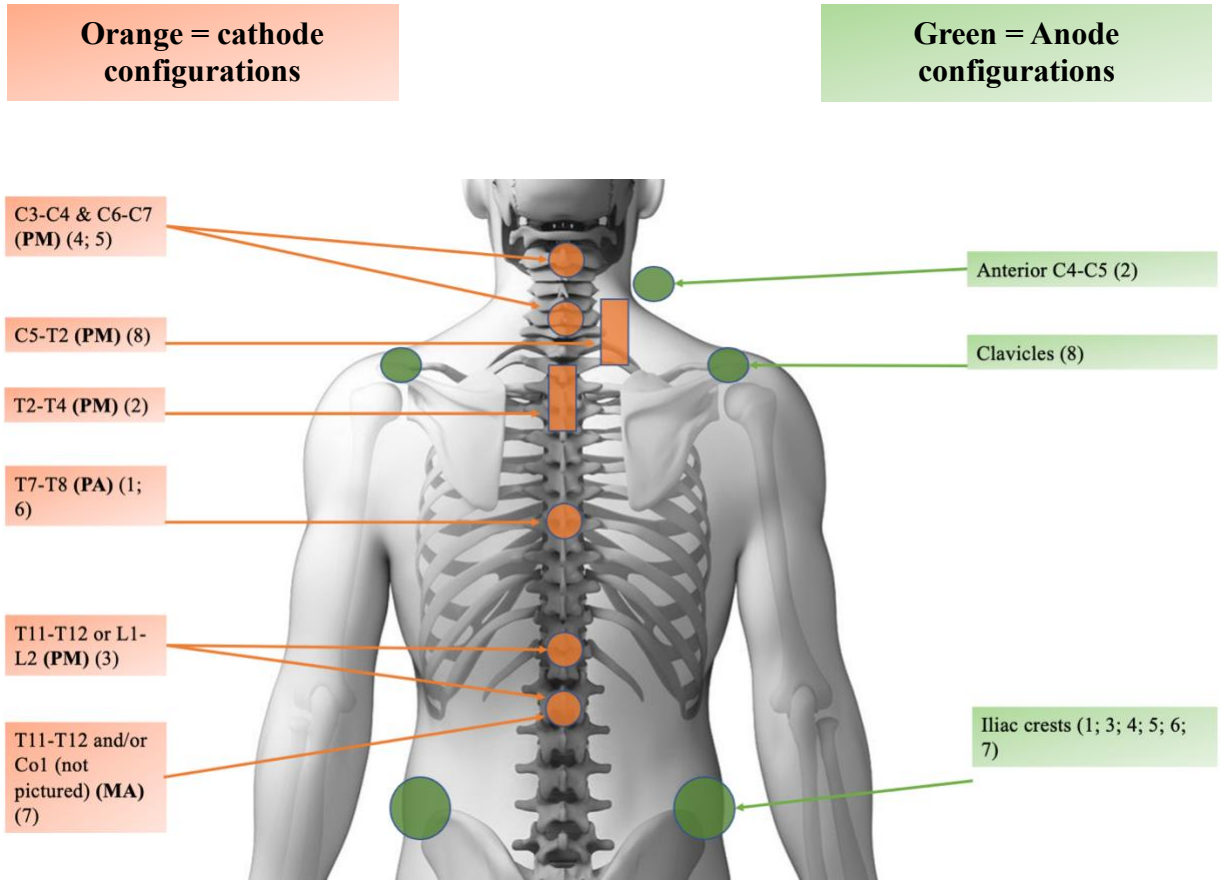


Figure 2. Representation of electrode placement used in the transcutaneous stimulation studies.

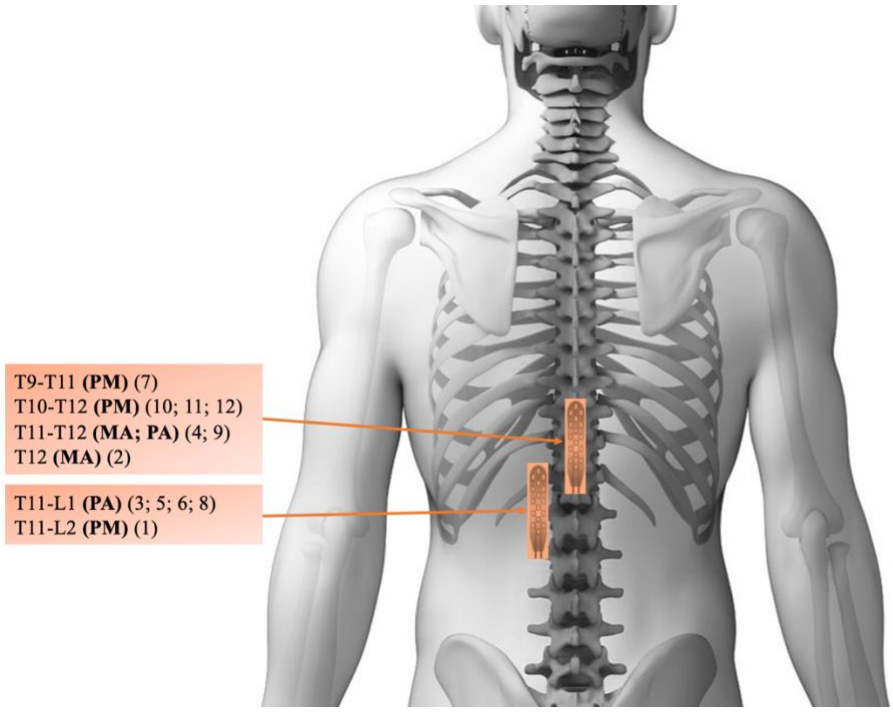


Human spine picture credit: (Holwerda 2017)

Abbreviations
PM = Primarily motor focused study
PA = Primarily autonomic focused study
MA = Both motor and autonomic focused study

References
1 (Sachdeva et al. 2021); 2 (Wu et al. 2020); 3 (Sayenko et al. 2019); 4 (Gad et al. 2018); 5 (Inanici et al. 2018); 6 (Phillips et al. 2018); 7 (Gad et al. 2017); 8 (Murray et al. 2017)

Figure 3. Representation of epidural implant placement used in the epidural stimulation studies.



Human spine picture credit: (Holwerda 2017)

Abbreviations
PM = Primarily motor focused study
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References
1 (Gorgey et al. 2020); 2 (Darrow et al. 2019); 3 (Nightingale et al. 2019); 4 (Terson de Paleville et al. 2019); 5 (Aslan et al. 2018); 6 (West et al. 2018); 7 (DiMarco et al. 2018); 8 (Harkema et al. 2018); 9 (Edgerton et al. 2011); 10 (Ganley et al. 2005); 11 (Carhart et al. 2004); 12 (Herman et al. 2002)

TABLES

Table 1. Participant Characteristics for all Studies

Study	Participants (n)	Gender (M = male; F = female)	Age (Years)	Time Since Injury	AIS Classification (n)	Level of Injury	Study Type
Sachdeva et al., 2021	1	1 M	36	3 years	A	C4	CR
Wu et al., 2020	15	10 M, 3 F	21-65	1-20 years	B (3), C (5), D (7)	C2-C8	CS
Gorgey et al., 2020	1	1 M	NR	NR	A	C7	CR
Nightingale et al., 2019	1	1 M	33	5 years	B	C5	CR
Sayenko et al., 2019	15	12 M, 3 F	23-53	2-13 years	A (11), B (1), C (3)	C4-T12	DB CO
Darrow et al., 2019	2	2 F	48; 52	5-10 years	A	T4, T8	CS
Terson de Paleville et al., 2019	4	4 M	22-31	28-31 months	A (3), B (1)	C5-T5	CS
Aslan et al., 2018	7	7 M	26.7 +/- 4.1	2-3.5 years	A (4), B (3)	C5-T4	PAR
Phillips et al., 2018	5	4 M, 1 F	23-32	3+ years	A (3), B (2)	C5-C6, T2	CS
Harkema et al., 2018	4	3 M, 1 F	24-35	3.8-8 years	A (3), B (1)	C4	CS
DiMarco et al., 2018	1	1 M	50	2 years	NR	C4	CR

Inanici et al., 2018	1	1 M	62	2 years	D	C3	CR
Gad et al., 2018	8	NR	NR	1-21 years	B (3), C (5)	C7 and above	CS
West et al., 2018	1	1 M	Early 30s	NR	B	C5	CR
Gad et al., 2017	1	1 M	35-40	7 years	A	T9, L1	CR
Murray et al., 2017	1	1 M	27	9 years	C (upper limbs), B (lower limbs)	C6-C7	CR
Edgerton, 2011	1	1 M	23	NR	B	C7-T1	CR
Ganley et al., 2005	2	2 M	43; 48	3.5; 8 years	C	C5-C6, T8	CS
Carhart et al., 2004	1	1 M	43	3.5 years	C	C5-C6	CR
Herman et al., 2002	1	1 M	43	3.5 years	C	C5-C6	CR
Shelyakin et al., 2000	25	NR	NR	NR	NR	NR	CS

Abbreviations: NR (not reported), CR (case report), CS (case series), PAR (parallel group design)

Table 2 – Transcutaneous Stimulation Locations and Parameters

Study	Protocol	Electrode Placement	Electrode Size	Frequency	Intensity	Waveform	Pulse Length	Changes Exercise Related Autonomic Outcomes With Stimulation
(Sachdeva et al. 2021)	Digital anorectal stimulation (**DARS**) was used to trigger AD. TSCS was used prior to AD event in attempt to prevent AD and during AD to interrupt episode.	T7-T8 (cathode), iliac crests (anodes)	30 mm diameter cathode; two 5x9 cm anodes	30 Hz	20-30 mA	Biphasic square pulses	2 ms	**TSCS used prior to DARS** ↓ SBP rise by 82% ↓ DBP rise by 65% when TSCS turned on prior to DARS 68% less reduction in HR **TSCS used to interrupt AD due to DARS** ↓ SBP by 49% ↓ DBP by 56% No significant change in HR
Wu et al., 2020	TSCS and TMS was delivered at	T2-T4 (cathode),	5x10 cm	0.2 Hz	4.4 - 102 mA	Biphasic	2 ms	↑ MAP by 20% or more for at

	rest in seated position.	C4-C5 (anode - anteriorly), distal clavicles are connected to common ground						least 15 mins (n = 7) ↓ MAP by 20% or more for at least 15 mins (n = 2) ↑ HR by 20% or more for at least 15 mins (n = 1) ↓ HR by 20% or more for at least 15 mins (n = 7)
Sayenko et al., 2019	All participants received TSCS, no stimulation, and "sham" TSCS during self-assisted standing. 1 testing day (2 hours) (all participants), 12 training sessions (2 hours) (6 participants)	T11-T12 or L1-L2 (cathodes), illac crests (anodes)	3.2 cm diameter (cathode), two 7.5 x 13 cm (anodes)	0.2-30 Hz with 10 kHz carrier wave	Up to 150 mA	Monophasic	1 ms	↑ sweating below lesion during first session (n = 3) ↑ SBP by more than 60 mm Hg during first session (no further incidents following first session) (n = 1)
Gad et al., 2018	4 week (2x/week) hand grip strength program with TSCS.	C3-C4 & C6-C7 (cathodes), illiac crests (anodes)	Two 2.0 cm diameter round (cathodes), two 5 x 10	30 Hz with 10 kHz carrier wave	10-250 mA	Biphasic and monophasic	1 ms	↑ sweating ability in 2/8 participants

			cm (anodes)					
Inanici et al., 2018	TSCS + physical therapy for 4 weeks followed by physical therapy alone for 4 weeks, followed again by TSCS + physical therapy for 1 week.	C3-C4 & C6-C7 (cathodes), illiac crests (anodes)	Two 2.5 cm diameter round (cathodes), two 5 x 10 cm (anodes)	30 Hz with 10 kHz carrier wave	80-120 mA	Biphasic, rectangular	1 ms	BP ranged between 88/58 and 121/85 mm Hg HR ranged between 66-98 bpm.
Phillips et al., 2018	25 mins resting in supine followed by OH challenge (tilt table) with TSCS when SBP dropped by 20 mm Hg.	T7-T8 (cathode); illiac crests (anodes)	30 mm diameter cathode; two 5x9 cm anodes	30 Hz	10-70 mA	Monophasic	1 ms	↑ SBP, DBP, MAP and middle and posterior cerebral artery blood flow during OH challenge with TSCS (compared to no TSCS) No significant change in HR (remained elevated), CO, or SV with TSCS compared to no TSCS during OH challenge
Gad et al., 2017	Subject walked using exoskeleton assist device for 4	T11-T12 and/or Co1 (cathode –	2.5 cm diameter cathode,	30 Hz over T11 and/or	No # reported: Optimum	NR	NR	↑ HR during stepping by 10

	weeks (no stimulation), followed by 1 week of EKSO + stimulation, followed by 1 week of EKSO + buspirone, followed by 1 week of EKSO + stimulation + buspirone. Training = 1 hour /day, 5 days/week.	depended on efficacy and subject feedback), iliac crests (anodes)	two 5.0 x 10.2 cm anodes	5 Hz over Co1	efficacy & based on participant feedback			bpm (72-82 bpm) with TSCS ↑ HR during stepping by 66 bpm (72-138 bpm) with TSCS + buspirone ↑ BP from baseline walking (138/95) to walking with TSCS (145/87) ↑ BP from baseline walking (138/95) to walking with TSCS + buspirone (154/91) ↑ self-reported sweating during stepping with TSCS (3/5) and TSCS + buspirone (5/5)
Murray et al., 2017	14 sessions (55 mins) of TSCS while supine	C5-T2 (cathode); clavicles (anodes)	10.2 x 5.1 cm	0.2 Hz	5-68 mA	Monophasic, rectangular	1 ms	↑ sweating in upper back and armpits during TSCS

Shelyakin et al., 2000	20 sessions (20-50 mins) of micropolarization were administered to 25 patients in the late phase of SCI and in patients with tuberculous spondylitis (very minimal info on methods)	"Along the vertebral column"	600 mm squared	NR	Not greater than 10 mA	NR	NR	↑ HR from 95-100 (baseline) to up to 120 bpm (with TSCS) By end of 20 sessions, HR stabilized at 80-95 bpm (with or without TSCS – not clear)

Table 3 – Epidural Stimulation Locations and Parameters

Study	Protocol	Electrode Placement	Frequency	Intensity	Waveform	Pulse Length	Changes Exercise Related Autonomic Outcomes With Stimulation
Gorgey et al., 2020		T12-S2 spinal segments	40 Hz	6-7 V	NR	420 µs	↑ RPE ↓ regional and total body FM No change in lean mass
Darrow et al., 2019		T12	16-400 Hz	2-15 mA (position dependent)	NR	200-500 µs	Participant 1 (no OI): no change in BP during OH challenge Participant 2 (OI): BP normalization during OH challenge
Nightingale et al., 2019	6 progressive arm crank ergometry tests to failure (separated by 12 days), each with a different randomly assigned epidural stimulator setting or no stimulation (control)	T11-L1	40 Hz (abdominal program); 35 Hz (cardio program)	3.5-6.0 V	NR	420 µs (abdominal program), 300 µs (cardio program)	↑ VO2 peak (absolute and relative; 15-26%) ↑ ventilation (33 L/min no stim to 50 L/min HI stim ab program) ↑ peak oxygen pulse (21% HI ab program) ↑ MAP by 14 mm Hg at rest (cardio program) regardless of intensity ↓ RPE for given power output of 60 W (18/20 no stim to 14/20 HI stim; both stim programs equally effective)

Terson de Paleville et al., 2019	Epidural implant placed after 80 locomotor training sessions. After implantation individuals received 160 sessions of task specific training with epidural stimulation (stand and step).	L1-S1 spinal segment	10-40 Hz (standing); 25-45 Hz (stepping)	Voltage was individualized to participant	NR	NR	POST TRAINING WITH STIMULATION (INDIRECT EFFECTS OF STIMULATION) ↑ lean mass ↓ android / gynoid fat ratio ↑ RMR ↑ VO_{2peak}
Aslan et al., 2018	Applied stimulation during both supine to sitting OH challenge and sit to stand OH challenge.	T11-L1	2 Hz (supine); varied (standing)	0-10 V	NR	NR	**<u>Group 1 (OI)</u>** ↑ BP while supine BP within normative ranges during standing **<u>Group 2 (no OI)</u>** No significant changes in BP ↑ HR while supine up to 50% (n = 1)

West et al., 2018	Examined BP responses to head-up tilt OH challenge with and without stimulation.	T11-L1	35 Hz	3.5 V	NR	300 ms	BP normalized during OH challenge in person with OI ↓ HR during OH challenge with stim (88 bpm) when compared to OH challenge with no stim (110 bpm) Stimulation preserved SV and CO during OH challenge
DiMarco et al., 2018	The subject was instructed to apply stimulation every 30 s for 5–10 min, 2 or 3 times/day, in the home to help with expiratory airflow.	T9-T11	50 Hz	40 V	Biphasic	0.2 ms	↑ BP after first application to 175 mm Hg ↓ HR after first application to 55 bpm Changes disappeared with repeated use over 9 weeks.
Harkema et al., 2018	2 hours seated @ rest with no stim. Then five 2 hour sessions	T11-L1	30-65 Hz	3-7 V	NR	450 µs	↑ MAP in participants with OI (reproducible over 5 sessions) during stim session No significant change in HR (n = 3) ↓ HR (on avg. by 8 bpm) (n = 1) ↑ HR from baseline, post stim session in ALL participants

	with stim adjusted to maintain SBP between 110-120.						
Edgerton, 2011	Observations in the 18 months following epidural implantation	L1-S1 cord segment	NR	NR	NR	NR	More normalized BP control Temperature control improved ↑ lean mass
Ganley et al., 2005	3.5 months of PWBT followed by surgical implant. Retraining to presurgical level followed by training with stim for 100 sessions.	T10-T12	20-60 Hz	4 V	NR	800 µs	↓ O_2 consumption rate during walking (25-50%) ↓ CO_2 production during walking (indicative of FA oxidation) ↓ RER ↓ RPE ↑ muscular endurance
Carhart et al., 2004	12 weeks of PWBT prior to surgical implantation.	T10-T12	40-60 Hz	4 V	Biphasic	800 µs	↓ RPE ↓ energy cost of walking by 20-30% ↑ FA oxidation

	Retraining to presurgical level followed by training with stim for 3 months.						
Herman et al., 2002	PWBT (unknown length of time) performed prior to epidural implant. Retraining to presurgical level followed by further treadmill and overground training.	Upper lumbar enlargement (L2-S1)	20 Hz	Not specified; above sensory threshold, but below motor threshold	NR	0.8 ms	↓ RPE by 3x ↓ O_2 cost of walking by 27-36% ↑ FA oxidation by up to 8x

Abbreviations: RPE (rate of perceived exertion), FM (fat mass), OI (orthostatic intolerance), BP (blood pressure), HI (high intensity), ab (abdominal), MAP (mean arterial pressure), SV (stroke volume), CO (cardiac output), RER (respiratory exchange ratio), PWBT (partial weightbearing training)

Table 4 – Outcomes / findings reported in transcutaneous stimulation studies

Outcome	Studies	Participants (n)
↑ Blood pressure post walking	(Gad et al. 2017)	1
↑ Blood pressure at rest	(Wu et al. 2020)	7
↓Blood pressure at rest	(Wu et al. 2020)	2
Normalization of BP During OH or AD Challenge in those with autonomic dysregulation with no change in HR	(Sachdeva et al. 2021); (Phillips et al. 2018)	6
↑ Heart Rate at Rest	(Wu et al. 2020); (Shelyakin et al. 2000)	26
↑ Heart Rate Post Walking	(Gad et al. 2018)	1
↓ Heart Rate at Rest	(Wu et al. 2020)	7
No significant change in HR During OH or AD challenge in those with autonomic dysregulation	(Sachdeva et al. 2021); (Phillips et al. 2018)	6
↑ Sweating at rest	(Gad et al. 2017)	1
↑ Sweating while standing	(Sayenko et al. 2019)	3
↑ Sweating (not specified)	(Gad et al. 2018)	2
↑ Sweating during stepping	(Gad et al. 2017)	1

Table 5 – Outcomes / findings reported in epidural stimulation studies

Outcome	Studies	Participants (n)
BP normalization during seated OH challenge in those with orthostatic intolerance	(Darrow et al. 2019)	1
BP normalization during sit-to-stand OH challenge in those with orthostatic intolerance	(Aslan et al. 2018)	3
↑ BP at rest in those with OH intolerance	(Harkema, Wang, et al. 2018a)	4
↑ BP post exercise	(Nightingale et al. 2019)	1
No significant change in BP during OH challenge in those NOT demonstrating orthostatic intolerance	(Darrow et al. 2019)	1
No significant change in BP during standing in those NOT demonstrating orthostatic intolerance	(Aslan et al. 2018)	4
No significant change in BP while supine in those NOT demonstrating orthostatic intolerance	(Aslan et al. 2018)	4
↑ HR while supine in those with orthostatic intolerance	(Aslan et al. 2018)	3
↑ HR at rest while supine in those NOT demonstrating orthostatic intolerance	(Aslan et al. 2018)	1
No change in HR at rest while seated in those with orthostatic intolerance	(Harkema, Wang, et al. 2018a)	3
↓ HR at rest while seated in those with orthostatic intolerance	(Harkema, Wang, et al. 2018a)	1
↓ HR during OH challenge in those with orthostatic intolerance	(Aslan et al. 2018) (West et al. 2018)	2
↑ VO2 peak	(Nightingale et al. 2019)	1
↓ RPE during activity	(Nightingale et al. 2019); (Ganley et al. 2005); (Carhart et al. 2004); (Herman et al. 2002)	5

↑ RPE (due to increased intensity)	(Gorgey et al. 2020)	1
↑ Peak ventilation	(Nightingale et al. 2019)	1
↓ O_2 consumption during walking	(Ganley et al. 2005); (Carhart et al. 2004); (Herman et al. 2002)	4
↓ Body fat %	(Gorgey et al. 2020)	1
↓ RER (Respiratory Exchange Ratio) = increased F.A oxidation	(Ganley et al. 2005); (Carhart et al. 2004); (Herman et al. 2002)	4

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