

Effects of Transcutaneous Spinal Electrostimulation on Oxygen Uptake Kinetics in People Living with a Spinal Cord Injury

By

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General Abstract

Background. Spinal cord injuries (SCI) are complex neurological conditions that result in sensory, motor, and autonomic dysfunction. Autonomic dysfunction, sedentary behavior, chronic inflammation and deficits in oxygen delivery increase the risk of cardiovascular diseases (CVD). However, in the case of SCI, these diseases are primarily caused by inadequate or inappropriate activation of spinal neural regulatory circuitry rather than physical inactivity. Transcutaneous spinal electrostimulation (TSES) is a non-invasive intervention that may modulate acute spinally mediated cardiovascular responses. Currently, the effects of TSES on cardiorespiratory function and dynamic measures of aerobic performance such as $\dot{V}O_2$ kinetics remain poorly understood. **Objectives.** A systematic review evaluated the immediate effects of TSES on cardiorespiratory responses in adults living with a SCI, identified effective stimulation sites, and reported any adverse effects. An experimental study compared the effects of TSES versus no TSES on $\dot{V}O_2$ on-kinetics during constant workload exercise (CWL). **Methods.** The systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. For the experimental study, fourteen participants with SCI were recruited (7 tetraplegic, 7 paraplegic, with SCI at or below C4/5, aged 18-75 y, and ≥ 1 -year post-SCI) plus seven healthy, age, sex, and height matched neurologically intact (NI) references, to the tetraplegic group. Participants performed two $\dot{V}O_2$ peak tests and one CWL test with at least 48 hours between each test to prevent carryover effects. The two peak tests determined each participant's power output (PO) for the CWL exercise test (40-45% of the PO at peak $\dot{V}O_2$), and consisted of four bouts of exercise, each 5 minutes long (two bouts with TSES, and two without TSES). $\dot{V}O_2$ kinetics, consisting of the primary variable mean response time (MRT) and secondary variables time constant (τ), time delay (TD), and amplitude, were measured. **Results.** Systematic review findings demonstrated that when TSES is applied at the T11-L2 vertebral segments, blood pressure is safely and beneficially modulated. Experimental study findings revealed that when TSES is applied at T12 using 20 Hz, 900 μ s and an intensity around motor threshold, significant differences in $\dot{V}O_2$ on-kinetics in those living with SCI were not seen. Overall, TSES appears safe; however, an individualized approach may be required to optimize autonomic and cardiorespiratory outcomes in those living with SCI.

Keywords: spinal cord injury, transcutaneous spinal electrostimulation, oxygen uptake kinetics exercise capacity, cardiorespiratory fitness, tetraplegia, paraplegia, able-bodied.

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Abbreviations

ACerg	Arm crank ergometry exercise test
AD	Autonomic dysreflexia
ANS	Autonomic Nervous System
ASIA	American Spinal Cord Injury Association
ASIS	Anterior superior iliac spine
ATP	Adenosine triphosphate
BSCB	Brain spinal cord barrier
CERT	Consensus on Exercise Reporting Template
CNS	Central Nervous System
CO	Cardiac output
CO ₂	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
CPETmax	Maximal cardiopulmonary exercise testing
CRF	Cardiorespiratory fitness
CSF	Cerebral spinal fluid
CVD	Cardiovascular disease
CWR	Constant work rate
EC	Exercise capacity
ECG	Electrocardiogram
EES	Epidural Electrical Stimulation
EMG	Electromyography
FEV ₁	Forced expiratory volume in 1 second

FVC	Forced vital capacity
GLM	General linear model
HR	Heart rate
LMN	Lower motor neuron
MAP	Mean arterial pressure
MET Cart	Metabolic cart
MRC	Medical Research Council
MRT	Mean response time
MWC	Manual wheelchair user
MVC	Maximal voluntary contraction
NI	Neurologically Intact
NIRS	Near-infrared spectroscopy
NMDA	N-methyl-D-aspartate
NMES	Neuromuscular electrical stimulation
NOS	Newcastle- Ottawa scale
NS	No stimulation
NTSCI	Non-traumatic spinal cord injury
O ₂	Oxygen
PNS	Parasympathetic nervous system
PP	Paraplegic
PRISMA-P	Preferred reporting items for systematic review and meta-analysis protocol
PWC	Power wheelchair user
QoL	Quality of life

RNS	Reactive nitrogen species
ROS	Reactive oxidative species
RPE	Rating of perceived exertion
RPM	Revolutions per minute
RQ	Respiratory quotient
SAGER	Sex and Gender Equity in Research
SCI	Spinal cord injury
SCRC	Spinal Cord Research Centre
SD	Standard deviation
SV	Stroke volume
TD	Time delay
TP	Tetraplegic
TSCI	Traumatic spinal cord injury
TSES	Transcutaneous spinal electrostimulation
$\dot{V}E$	Minute ventilation
$\dot{V}O_2 \text{ max}$	Maximal oxygen uptake
$\dot{V}O_2 \text{ peak}$	Peak oxygen uptake
W	Watt(s)
τ	Tau

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THESIS ORGANIZATION

This thesis followed the sandwich format as outlined by the Faculty of Graduate and Postdoctoral Studies at the University of Manitoba, and is organized into six chapters, as described below:

Chapter 1. Introduction: This chapter describes the overview of spinal cord injury (epidemiology, incidence, prevalence, injury classification using the AIS scale, organ system dysfunction), the effects of spinal cord injury on exercise responses, therapies/techniques available for the management of organ dysfunction, and the clinical importance of improving exercise capacity via faster $\dot{V}O_2$ on-kinetics.

Chapter 2. Literature Review: This chapter provides a summary description of the anatomy and function of the spinal cord, incidence, prevalence and risk factors, economic and health consequences, pathophysiology, classification, limitations, respiratory impairment, peak oxygen uptake ($\dot{V}O_{2peak}$), and the effects of transcutaneous spinal electrostimulation on cardiorespiratory fitness and exercise capacity among those with SCI.

Chapter 3. General methodology: This chapter describes the general methodology, including participant recruitment and enrollment, inclusion and exclusion criteria, measurements, protocols, and data collection for my experimental aim. Specific details (e.g., data acquisition, data analysis, and statistics) are presented in Chapter 5. This thesis is a part of the Transcutaneous Spinal Electrical Stimulation to Improve Exercise Function after Spinal Cord Injury study, which was approved by the Health Research Ethics Board at the University of Manitoba (#HS22987-H2019:279). As part of a larger research project, many physiological measurements were collected, including muscle activity via electromyography (EMG), heart electrical activity via electrocardiogram (ECG), muscle oxygenation via near-infrared spectroscopy (NIRS), and ventilatory gas measurements via metabolic cart.

Chapter 4. Systematic Review: This chapter describes the current literature in the field of transcutaneous spinal electrical stimulation on cardio-autonomic and respiratory variables in the spinal cord injured population.

Chapter 5. Experimental Study: This chapter describes original work done in the spinal cord injured population to explore the effects of transcutaneous spinal electrical stimulation on $\dot{V}O_2$ on-kinetics.

Chapter 6. General Discussion: This chapter provides a summary of the main findings and contributions of this thesis.

1. CHAPTER 1: INTRODUCTION

Spinal cord injuries (SCI) are complex neurological conditions that result in sensory, motor, and autonomic dysfunction (Kao et al., 2025; Qin et al., 2025). SCIs can arise from traumatic or non-traumatic aetiologies (World Health Organization [WHO], 2024). SCI resulting from physical forces applied to the spinal cord is referred to as traumatic. The vast majority of traumatic SCI (TSCI) results from motor vehicle accidents, falls, and sport-related injuries (van Den Hauwe et al., 2020; National Spinal Cord Injury Statistics Center [NSCISC], 2022). Non-traumatic SCIs (NTSCI) result from tumors, infections, toxins, congenital conditions (malformed skeleton), genetic disorders (spinal muscular atrophy) or acquired conditions such as degenerative bone or vascular disorders (Molinares et al., 2022; WHO, 2024). The average age at injury onset has increased in recent decades due to rising numbers of NTSCIs, which occur most frequently in older adults living with degenerative spinal column conditions (Molinares et al., 2022; Safdarian et al., 2023; van Den Hauwe et al., 2020).

SCIs are classified based on the rostrocaudal level at which the injury occurred as well as the severity of injury (complete vs. incomplete) at that location (Alizadeh et al., 2019; American Spinal Injury Association, 2019). The majority of injuries (40 – 60%) occur at the cervical level (Singh et al., 2014), resulting in impairment of motor and/or sensory function known as tetraplegia (Marino et al., 2016). Injuries below this, at the thoracic, lumbar, and sacral levels, also result in loss of autonomic, motor and/or sensory function and are termed paraplegia (Marino et al., 2016). SCIs can be further classified as complete or incomplete, as described by the American Spinal Injury Association Impairment Scale (AIS), which ranges from AIS A to E (Rupp et al., 2021). A complete injury results in the absence of all motor and sensory functions below the level of the injury, whereas an incomplete injury results in some degree of preservation of motor and/or sensory function below the level of the injury (Moura et al., 2024;

Roberts et al., 2017). Additionally, reduction or removal of communication between the spinal autonomic centres and the brain results in a variety of autonomic dysfunctions, including a reduced ability to elicit increases in sympathetic functions, which are needed for appropriate exercise responses (Cowley, 2018). Further details on complete and incomplete injuries are described in Chapter 2.

Thus, beyond sensory and motor dysfunction, those living with SCIs face numerous physiological complications that affect quality of life (QoL) (decreased satisfaction with social life and sex life) and overall health (Krause & Bozard, 2012). Depending on their level of injury (those with tetraplegia most affected), many commonly experience autonomic dysfunction that may impair thermoregulatory, genitourinary (e.g. neurogenic bladder, urinary tract infections), gastrointestinal (e.g. constipation, bowel incontinence), respiratory (e.g. oxygen uptake [$\dot{V}O_2$], minute ventilation $\dot{V}E$) and cardiovascular (heart rate [HR], blood pressure [BP], cardiac output [CO]) function. Thus, during exercise, the cardiorespiratory response is compromised, limiting exercise capacity and performance (Krassioukov & West, 2014). Research within the general population has shown that those with faster $\dot{V}O_2$ kinetics, which reflects the speed at which $\dot{V}O_2$ uptake adapts to changes in exercise intensity, is indicative of a high exercise tolerance, whereas slow $\dot{V}O_2$ kinetics is associated with greater oxygen debt and reduced exercise tolerance (Poole & Jones, 2012). Those living with an SCI experience substantially lower resting oxygen consumption than neurologically intact individuals, which has been attributed to decreased overall muscle mass due to disuse atrophy of the lower limbs (Hopman et al., 1998; Schmid, Huonker et al., 1998). In terms of exercise responses, those with tetraplegia (untrained) have significantly lower $\dot{V}O_2$ peak compared to their paraplegic and neurologically intact counterparts (Schmid, Huonker et al., 1998).

Exercise responses are also limited amongst paralympic athletes living with SCI. Specifically, those living with tetraplegia lack the ability to activate descending exercise commands that support movement and exercise (e.g., increases in HR, BP, catecholamine release, as well as glucose and fatty acid mobilization) (Wheeler et al., 1994) and those living with paraplegia experience a smaller decrement as lesion level and exercise capacity have an inverse relationship (Coutts et al., 1983; Gass & Camp, 1979; Hullemann et al., 1972; Rhodes et al., 1981). Due to reduced exercise capacity and poorer exercise performance, paralympic athletes with higher level injuries (at or above T6) ‘boost’ to achieve more desirable exercise performance. ‘Boosting’ involves intentionally inducing autonomic dysreflexia (AD) for competition to try and increase blood pressure with the hope of enhancing exercise performance (Wheeler et al., 1994).

Exercise performance is just one of several bodily functions negatively affected by SCI, as those living with SCI also experience cardiovascular instability (Krause & Bozard, 2012; Moura et al., 2024; WHO, 2024), as well as impaired bowel and bladder function, leading to increased time needed to perform activities of daily living (e.g. emptying of bowel and bladder, bathing), negatively affecting quality of life (QoL) and in the longer term, overall health. The cardiovascular instability occurs in a variety of settings in response to different stimuli and includes orthostatic or post-prandial hypotension (OH) and autonomic dysreflexia (Moura et al., 2024). Risk of death is especially of concern if the cardiovascular dysfunction becomes severe with excessively high uncontrolled BP (Myers et al. 2007). Historically, respiratory and renal conditions were the most prevalent comorbidities and the biggest contributors to mortality among the SCI population (Myers et al., 2007). In the late 2000, CVD exceeds the morbidity and mortality rates associated with respiratory and renal dysfunction in those living with a chronic

SCI (Myers et al., 2007). Dysfunction in virtually every body system (e.g. low BP and HR at rest and exercise, inability to sweat, neurogenic bladder and bowel function) is the reality, leaving those living with SCI more susceptible to a variety of diseases associated with body homeostasis, metabolism, and immune responses (Cowley, 2018; Flett et al., 2022; Moura et al., 2024; Wulf & Tom, 2023).

Since there is no known cure for SCI, an alternate and reasonable strategy for improving health and quality of life after injury is to understand how to improve exercise function and capacity, including acute cardiovascular responses, such as $\dot{V}O_2$ kinetics. Ultimately, this may then lead to enhanced exercise capacity and performance in addition to cardiorespiratory fitness. Several therapies/techniques are being tested to determine whether they can attenuate organ dysfunction and physiological complications associated with an SCI, including medications, biologics (drugs or vaccines), cell-based treatments and cell-based transplants, as well as electrical stimulation (Wulf & Tom 2023). Some of these aim to reduce damage at the injury site itself (e.g., regeneration strategies), whereas others aim to alter neural activity below the injury site. To date, none of the cell-based or biologic therapies has resulted in substantive improvements in function after SCI. Two types of electrical stimulation (i.e., epidural, transcutaneous) have shown promising results for improving acute cardiovascular (e.g. BP, HR) and autonomic (bladder function, and locomotion) outcomes (Angeli et al., 2014; Flett et al., 2022; Harkema et al., 2011; Hubscher et al., 2018; Minassian et al., 2015; Parittotokkaporn et al., 2020).

Epidural (ESS) and transcutaneous (TSES) spinal stimulation are thought to modulate spinal circuitry below/caudal to the site of injury (Flett et al., 2022; Samejima et al., 2025). ESS requires surgically implanting electrodes in the epidural space of the spinal canal (an invasive

method), with the electrodes connected to a pulse generator to modulate neuronal excitability within the spinal cord (Shealy et al., 1967). Alternatively, TSES is a non-invasive approach that likely targets similar neural structures, as noted by Flett et al. (2022). In TSES, a surface electrode is applied to the skin over the vertebrae in the back, with different configurations for placement of the anode and cathode (Flett et al., 2022). There is emerging evidence that TSES may be useful for improving motor function and reducing spasticity (Angeli et al., 2014; Harkema et al., 2011; Minassian et al., 2015). Research is more limited on the effects of TSES for improving acute cardiac dysfunction, although case studies (Engel-Haber et al., 2025; Phillips et al., 2018) suggest it may be possible to use TSES to improve autonomic cardiovascular function (e.g. increased blood pressure during postural transitions to reduce orthostatic hypotension symptoms) in those living with an SCI. While it has been shown that TSES can improve autonomic cardiovascular function, current studies are mainly anecdotal reports, case studies and case series. Thus, the effects of TSES on dynamic measures of aerobic performance, such as $\dot{V}O_2$ kinetics, remain limited and poorly understood. This gap in evidence justifies further investigation into TSES as a potential strategy to improve exercise tolerance and cardiovascular health after SCI.

Research on TSES will help address gaps in the literature and identify the next steps needed to advance clinical treatments that improve autonomic function, exercise capacity, and aerobic metabolism in people with SCI. The focus of this thesis is to understand whether and how TSES may improve cardiorespiratory responses and, more specifically, oxygen uptake ($\dot{V}O_2$) kinetics via a systematic review and an experimental study, respectively. Using the PICO framework for stating my experimental aim, the following research question was formulated: in the spinal cord injured population (SCI), how does transcutaneous spinal electrostimulation

(TSES) affect oxygen uptake ($\dot{V}O_2$) kinetics when compared to no stimulation during a constant work rate arm crank ergometry exercise test? Thus, the experimental aim of this thesis is to determine if TSES can accelerate $\dot{V}O_2$ kinetics during a constant workload (CWL) exercise test at 40-45% of each participant's peak power at $\dot{V}O_2$ peak. More specifically, the primary variable of interest is $\dot{V}O_2$ mean-response time (MRT), and the secondary variables of interest are $\dot{V}O_2$ time constant (τ), time delay (TD), and amplitude of the $\dot{V}O_2$ response. It is hypothesized that implementing TSES will result in a faster MRT and τ , lower TD, and a larger amplitude of the $\dot{V}O_2$ response during CWL exercise when compared to the absence of TSES in people with SCI.

2. CHAPTER 2: REVIEW OF LITERATURE

This chapter provides a summary description of the anatomy and function of the spinal cord, incidence, prevalence and risk factors, economic and health consequences, pathophysiology, classification, limitations, respiratory impairment, peak oxygen uptake ($\dot{V}O_{2peak}$), and the effects of transcutaneous spinal electrostimulation on cardiorespiratory fitness and exercise capacity in those with SCI.

2.1 Anatomy & Function of the Spinal Cord

The spinal cord is a crucial part of the body's central nervous system, receiving and integrating information from the body (sensory input), brain (descending commands) and spinal interneurons. The spinal cord is the 'final common path' via somatic motor neurons and autonomic preganglionic neurons to all muscles, tissues, and organs of the body (Flett et al., 2022). For example, the isolated spinal cord is capable of generating weight-bearing locomotion in the absence of descending input from the brain and sensory input (Stuart and Hultborn, 2008). The spinal cord is a key integrating centre for all body functions, including locomotion, and regulation of cardiovascular, respiratory, digestive, bladder and bowel functions as described in Kandel et al. (1991). The spinal cord consists of columns of output neurons (motor neurons and sympathetic preganglionic neurons), networks of interneurons, and ascending and descending paths or tracts (Kandel et al., 1991; Salianni et al., 2017).

The functional outcome after SCI is related to the extent and location of damage to neurons within the grey matter and to the ascending and descending tracts in the white matter of the spinal cord. Given the spinal cord's importance, complexity, and delicate nature, it has strong structural protection (Khan & Lui, 2023). The vertebral column is divided into five regions: cervical, thoracic, lumbar, sacral, and coccygeal, each protecting the spinal cord and providing a

passageway for spinal nerves (Martini et al., 2018). The spinal cord is a cylindrical, elongated structure that is housed and protected within the vertebral canal, spanning from the foramen magnum as a continuation of the medulla oblongata to the L1-L2 vertebral level, where the spinal cord ends (Khan & Lui, 2023; Ganapathy et al., 2024). Additionally, it is insulated against movement and vibration by cerebrospinal fluid (CSF) and connective tissue layers known as the meninges (Khan & Lui, 2023). The meninges consist of 3 layers of tissue, the most superficial being the dura mater, then the arachnoid mater, followed by the deepest layer (immediately surrounding the spinal cord) known as the pia mater (Khan & Lui, 2023). The CSF is found between these layers in the subarachnoid space (the space between the arachnoid mater and the pia mater) (Khan & Lui, 2023). Figure 2.1 depicts an overview of the anatomy and one spinal reflex function of the spinal cord.

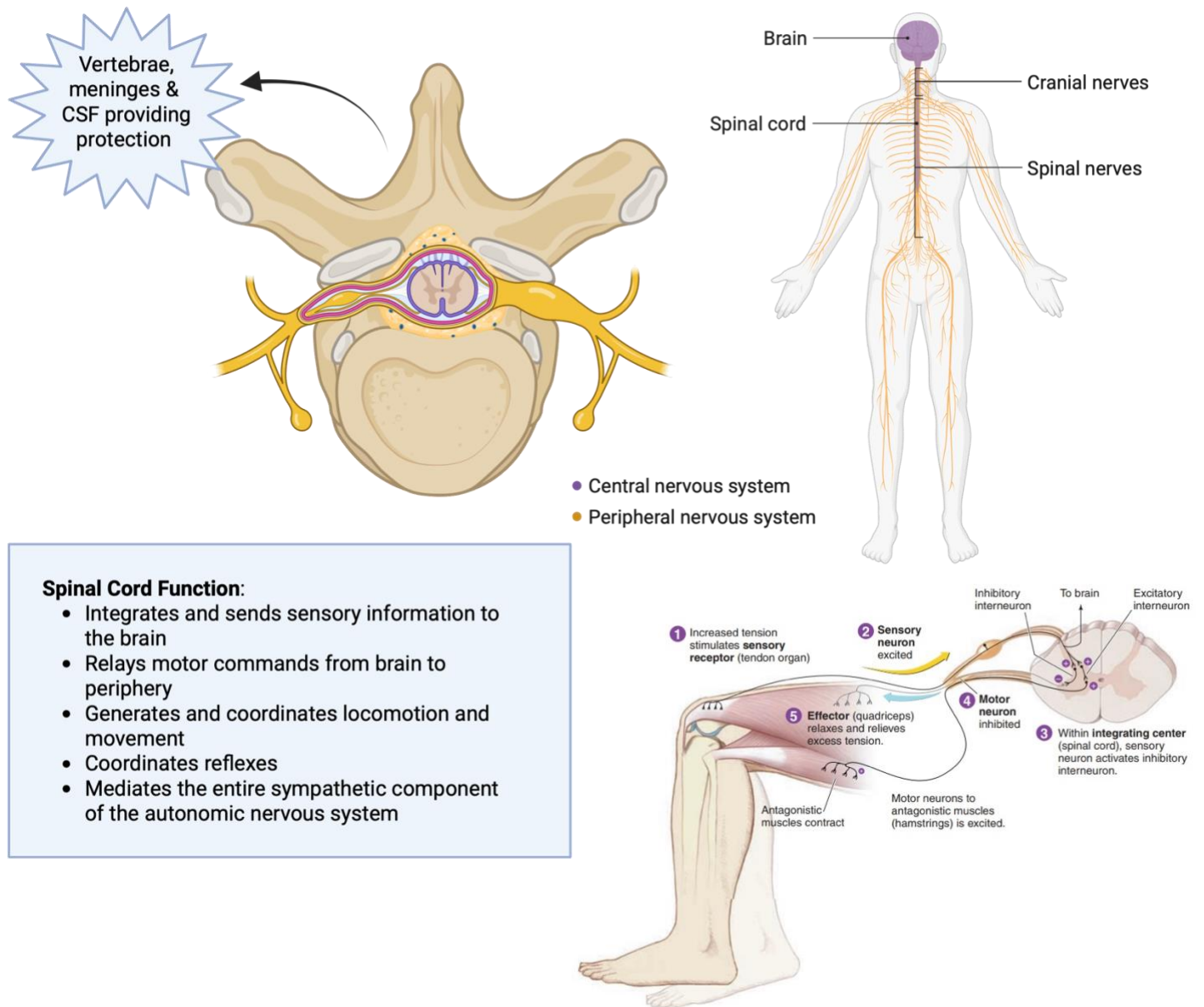


Figure 2.1 Anatomy and Function of the Spinal Cord. Created in <https://BioRender.com> by Sara Petkau with an incorporated image retrieved from “BrainKart.com” by BrainKart.com (n.d.).

2.2 Incidence, Prevalence & Risk Factors

In Canada, over 86,000 people live with SCI, while worldwide prevalence is estimated to be approximately 15.4 million (Noonan et al., 2012; WHO, 2024). SCIs are severe neuronal injuries that negatively affect sensory, motor, and autonomic nervous system function (Rupp et

al., 2021). Most SCIs are a result of traumatic aetiologies or at least traumatic injuries remain the most frequently reported (Lu et al., 2024; Mackiewicz-Milewska et al., 2025; WHO, 2024). Falls were the most common type of traumatic injury, accounting for 42% of all traumatic SCIs (TSCI), with those aged 45-75+ experiencing falls the most (Lu et al., 2024; Praxis Spinal Cord Institute, 2024; Thorogood et al., 2023). Vehicle accidents are the second most common cause, contributing to 27% of TSCIs, largely affecting those between 15 and 44 years of age (Praxis Spinal Cord Institute, 2024; Thorogood et al., 2023). The average age of SCI has increased as a greater proportion of injuries are fall-related among older adults (average age of 61), whereas those who acquire a SCI due to vehicle accidents have an average age of 48 years (Praxis Spinal Cord Institute, 2024; Safdarian et al., 2023; Thorogood et al., 2023; van Den Hauwe et al., 2020). In Canada, individuals aged 45 and older now account for 66% of TSCIs, while those under 45 make up 34% of cases (Thorogood et al., 2023). Older age at the time of injury impacts survival rates and therefore influences prevalence (Thorogood et al., 2023).

Non-traumatic SCI injuries (NTSCI) are lower in incidence and are typically caused by tumors, inflammation, vascular conditions, congenital/genetic disorders, infections, and degenerative spinal conditions (Lu et al., 2024; Praxis Spinal Cord Institute, 2024). Lu et al. (2024) found that although NTSCI has a lower incidence rate than TSCI, NTSCI cases have been steadily increasing worldwide and are gradually becoming a significant contributor to SCI. The average age of those acquiring an NTSCI is 60+ (older adults), with 65 years as the average age of those experiencing degenerative diseases, whereas 63 years is the average age at which a SCI is acquired due to a malignant tumour (Lu et al., 2024; Praxis Spinal Cord Institute, 2024).

2.3 Economic & Health Consequences of Spinal Cord Injury

The total estimated lifetime cost for a subset of largely healthcare-related costs associated with TSCI for those who acquired a SCI classified as paraplegia at 25 years of age is around \$3 million, whereas for high-level tetraplegia, that number is approximately \$6.2 million (NSCISC, 2024). Lifetime cost depends on the level and completeness of injury, as well as ongoing maintenance requirements for equipment (Diop & Epstein, 2024). Some studies include estimated costs for healthcare/rehabilitation, home adaptations, and loss of productivity for the individual and their families in the lifetime cost of SCI, but many other studies do not include these indirect costs (Diop & Epstein, 2024). Such indirect costs were estimated at an average of \$95,309 per year in 2024 (NSCISC, 2025). Furthermore, the estimated costs focus solely on those borne by the healthcare system and do not include those within social systems. For example, the costs associated with the loss of employment opportunities due to inaccessibility, and the costs to the individual and their families for needed medical supplies, mobility equipment, or housing and vehicle modifications are omitted from these calculations.

SCI is associated with health consequences as the body experiences autonomic dysfunction attributed to loss of bidirectional communication with the brain as well as descending regulatory input, an imbalance of the autonomic nervous system (general sympathetic nervous system blunting and parasympathetic nervous system dominance) combined with intermittent unchecked reflexive sympathetic outflow in response to noxious stimuli below the level of the injury (Henke et al., 2022). Depending on the level of injury, autonomic dysfunction leads to dysregulation in virtually all body systems, including the cardiovascular, respiratory, gastrointestinal, thermoregulatory, genitourinary, and visual systems (e.g. potential

impairment of pupillary light reflex, Horner's syndrome) (Henke et al., 2022; Moura et al., 2024; Wulf & Tom, 2023).

Individuals living with SCI are estimated to have three times the risk of developing CVD, and up to six times the risk of developing a stroke when compared to the general population (Vivodtzev et al., 2021). This increased risk of CVD and stroke is not only associated with a sedentary lifestyle but also caused by sensory and motor dysfunction, paralysis, and inability to mount appropriate autonomic responses during exercise (Flett et al., 2022). In the decades lived after SCI, the disordered autonomic regulation of cardiovascular and respiratory systems, thermoregulation, whole-body homeostasis, and metabolism at rest and in response to different environmental conditions may also contribute to sedentary-related disease development (Cowley, 2018; Flett et al., 2022). Together, these impairments lead to poor maximal oxygen consumption ($\dot{V}O_2$ max) and are thought to lead to sub-optimal $\dot{V}O_2$ (oxygen uptake) kinetics, resulting in low exercise capacity (EC) and cardiorespiratory fitness (CRF) (Deley et al., 2015; Flett et al., 2022; Mercier et al., 2020). CRF represents how well the cardiovascular and respiratory systems can work together so the body can efficiently transport and utilize oxygen to perform work (Ross et al., 2016), while EC is the maximum amount of physical exertion that an individual can sustain (Goldstein, 1990).

2.4 Pathophysiology of Spinal Cord Injury

The pathophysiological process of a spinal cord injury has two components, a primary phase and a secondary phase (Mensah et al., 2025). A SCI begins with a primary injury, which is any event that causes a contusion, dislocation or distraction to the spinal cord, causing immediate vascular and structural damage (Chen et al., 2016; Mensah et al., 2025). Secondary spinal cord injury is categorized by three distinct phases: the **acute, sub-acute, and chronic phases**

(Mensah et al., 2025). The **acute phase** occurs within the 24 hours after the primary injury and is characterized by neuronal cell death (Mensah et al., 2025; Moura et al., 2024). The **subacute** phase occurs 2 days to 2 weeks after the primary injury and is where the injury can worsen as neuronal cell death continues, and additional vascular injury persists (Mensah et al., 2025). The third and final phase is the **chronic phase**, which occurs around 14 days after the primary injury and can last up to six months (Mensah et al., 2025; Moura et al., 2024). During the **chronic phase**, there is irreversible neuronal damage due to impaired neurovascular remodeling, demyelination, hindered axonal regrowth, myelin regeneration, and neuronal cell migration (via the formation of cystic cavities) (Mensah et al., 2025). Beyond this time point, the SCI damage is considered permanent and stable, with no further neurological deterioration, although those with SCI are at increased risk of losing further function caused by syrinx development in the decades typically lived after injury (Krebs et al., 2016).

2.5 Classification of Spinal Cord Injury

Depending on the location and severity of injury, a variety of spinal cord syndromes can manifest as categorized using the American Spinal Injury Association Impairment Scale (AIS) scores and functional classifications. There are two main functional classifications: complete or incomplete (Alizadeh et al., 2019). During assessments, if there is no spared motor or sensory function below the level of the injury, then the injury is considered complete (Alizadeh et al., 2019). Historically, only sensory and motor function was considered in this definition, but in recent years, there has been an emerging understanding that autonomic functions are critical and need to be specifically assessed, leading to the development of the first autonomic basic data sets in the mid 2000s (Alexander et al., 2009; Krassioukov et al., 2012). Injuries that occur in the cervical spinal cord and result in paralysis of the legs, most of the trunk, and partial to complete

paralysis of the arms and hands, are classified as tetraplegia (Bryce, 2012; Herrmann et al., 2011; Yari et al., 2023). Paraplegia, on the other hand, is caused by spinal damage below the cervical region, in either the thoracic, lumbar, or sacral segments of the spinal cord, and depending upon the level and severity of injury, involves paralysis of portions, or all, of the trunk and lower limbs (Bryce, 2012; Herrmann et al., 2011). Figure 2.2 shows a schematic illustrating examples of complete paraplegia or tetraplegia vs. incomplete paraplegia or tetraplegia.

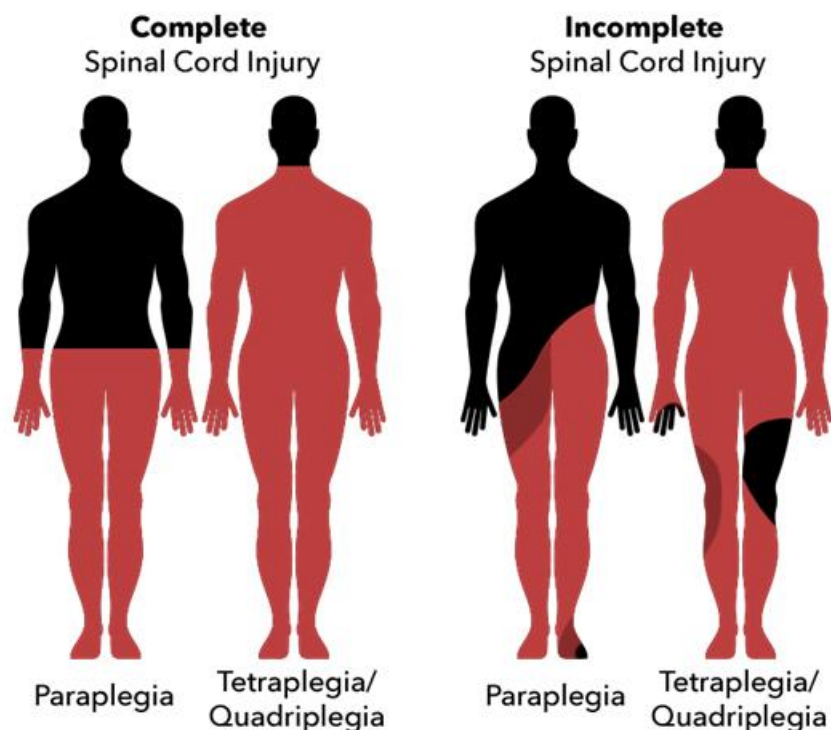


Figure 2.2 Illustration of some examples of complete vs. incomplete paraplegia and tetraplegia. Retrieved from “Total Community Care,” by Total Community Care (n.d.).

The AIS standardizes documentation of the level and extent of SCI, guides assessments and rehabilitation treatments, and helps determine if a SCI is complete or incomplete (American Spinal Injury Association, 2019). The AIS scale ranges from AIS A to E, where an AIS A indicates a complete injury with no motor or sensory function, and an AIS E indicates virtually

normal sensation and motor function of all muscles (Table 2.1; American Spinal Injury Association, 2019).

Table 2.1 American Spinal Injury Association (AIS) impairment scale.

AIS Score (A-D)	Sensory & Motor Function Status
AIS A	• No motor or sensory function • Complete injury
AIS B	• No motor function but some sensory function • Sensory incomplete
AIS C	• Some motor and sensory function • Motor incomplete • Less than half the muscles have Medical Research Council (MRC) grade three strength
AIS D	• Some motor and sensory function • Motor incomplete • At least half the muscles have Medical Research Council (MRC) grade three strength
AIS E	• Normal sensory and motor function

2.6 Selected Cardiovascular and Thermoregulatory Exercise Limitations of Persons with Spinal Cord Injury

The spinal cord provides input to all body systems, tissues and organs; therefore, a SCI can impair neural regulation across multiple systems that maintain whole-body homeostasis and metabolism over a range of activity levels and environmental conditions (Cowley, 2018; Flett et

al., 2022). Thus, the focus of this thesis is to investigate whether non-invasive spinal electrical stimulation can alter cardiorespiratory function and thereby exercise performance after SCI. Exercise is extremely important for overall health and is comprised of two broad categories: strength or resistance training and aerobic training (Pelletier, 2023). Strength/resistance training involves applying resistance to a muscle during contraction to ultimately build strength, anaerobic endurance, and the size of skeletal muscles (Gómez-Feria et al. 2023). Aerobic training, on the other hand, is any repetitive/rhythmic activity performed at a sufficient intensity and work rate for a sufficient period of time that elicits systemic changes in the cardiovascular, respiratory, and muscular systems. Regular exercise reduces the risk of chronic diseases such as CVD, type 2 diabetes, obesity, and cancer (Anderson & Durstine, 2019). For example, Vivodtzev & Taylor (2021) examined the benefits of exercise for those living with SCI and concluded that exercise consistently improved body composition, markers of systemic inflammation, and cardiovascular function.

Dysfunction of cardiovascular regulation is a possibility following SCI, and the level of injury determines whether and how these functions are impaired (Cowley, 2018). Sympathetic autonomic innervation of the heart and the vasculature supplying the upper body arises from T1-T5, whereas sympathetic innervation of the vasculature supplying tissues of the lower body and the adrenal medullae arises from T6-L2 (Kandel et al., 1991). SCIs below T6 result in relatively normal cardiac function and increasingly normal blood pressure regulation responses, which are essentially normalized with injuries at or below ~T10/12, as there is normal innervation to the heart in this region, and to the majority of the body's vascular bed (Cowley, 2018). However, injuries above T6 disrupt supraspinal regulatory control of spinal sympathetic regulatory regions, which are responsible for increasing cardiovascular function during movement and exercise and

for mediating blood pressure responses under different environmental conditions (Cowley, 2018; Hopman et al., 1993; Wulf & Tom, 2023). Those with injuries above T6 often initially present with hypotension or cardiac arrhythmias such as bradycardia, although bradycardia is typically in the acute phase of SCI, rendering it a temporary outcome of SCI (Krassioukov et al., 2007). Those with SCI above T1 are additionally impaired and lack sympathetic nervous system (SNS) innervation to the heart and therefore rely only on parasympathetic nervous system (PSNS) withdrawal to increase HR, resulting in a blunted HR response, limiting exercise capacity as reported by Bhambhani (2002) and reviewed in Cowley (2018). Individuals with SCI above T6 also face limitations to exercise, such as impaired thermoregulation, decreased venous return, stroke volume (SV), cardiac output (CO), and oxygen delivery (Bernardi et al., 2020; Cowley, 2018; Dela et al., 2003; Theisen, 2012). The lower the level of injury, the more autonomic function remains intact. For example, CO, SV, and temperature regulation are thought to be relatively normal compared to those who are neurologically intact by approximately T6-T8, and almost entirely intact by T12, as reviewed in Cowley (2018).

Impaired thermoregulation limits exercise in the heat and increases the risk of hyperthermia, especially for those individuals with complete tetraplegia (Hopman et al., 1993; Price & Campbell, 1999). Upper-body exercise has been shown to result in higher HR, increased peripheral resistance, and decreased SV (via decreased venous return) compared with lower-body exercise (Theisen, 2012). This is thought to be attributable to the absence of larger muscle mass (legs), its association with the skeletal muscle pump, and reliance on only upper-body muscles during exercise (Bernardi et al., 2020; Theisen, 2012). Hooker & Wells (1990) conducted a prolonged steady-state arm-crank ergometry exercise test that demonstrated a gradual elevation in HR among elite paraplegic (T4-T12 lesion) road racers, similar to findings

in neurologically intact (able-bodied) participants reported in previous work (Pimental et al., 1983).

Lesion level also plays a crucial role in exercise responses as those with a cervical level injury experience the greatest impairments, while those with a lower-level injury (below T6) maintain sufficient cardiac and vasomotor activity required to regulate arterial pressure during exercise demand, giving those with paraplegia a hemodynamic, thermoregulatory and metabolic advantage over those with higher level injury (Cowley, 2018; Currie et al., 2016; Figoni et al., 1990; Hopman et al., 1993). These advantages become more apparent during peak exercise. Figoni et al. (1990) applied peak functional neuromuscular stimulation (FNS) during a leg-cycling exercise test, in which individuals with tetraplegia developed exertional hypotension (failure to increase SBP by more than 10% above their resting value) more frequently than individuals with paraplegia. Additionally, those with paraplegia who developed exertional hypotension experienced it less severely as they were able to increase their SBP more than those with tetraplegia (120 mmHg vs. 128 mmHg, respectively). Figure 2.3 illustrates some possible exercise-related limitations for those living with SCI.

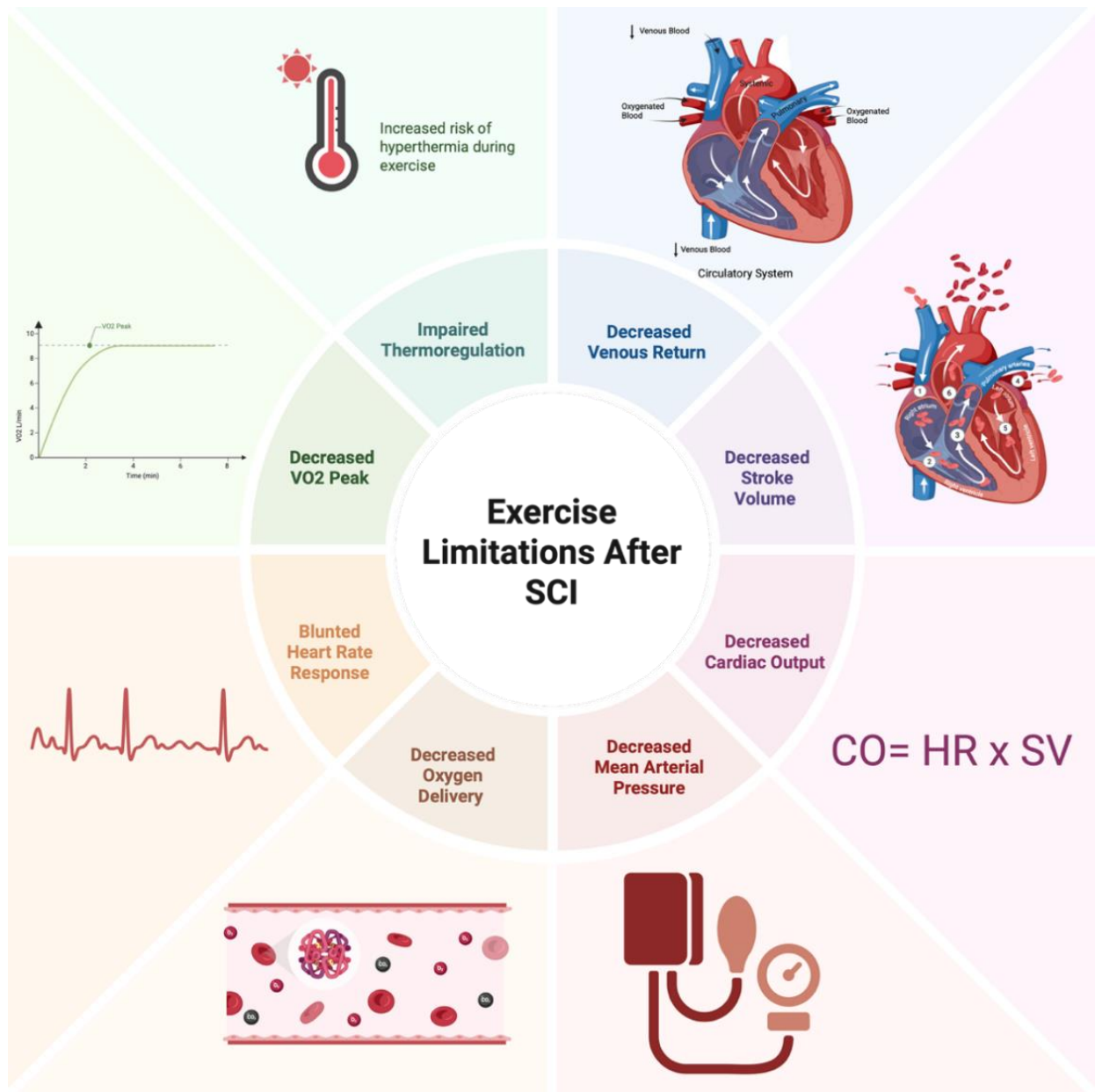


Figure 2.3 Several possible exercise limitations for those individuals living with SCI.

2.7 Respiratory impairment, peak oxygen uptake, and oxygen uptake kinetics of persons with SCI

$\dot{V}O_2$ peak is defined as the highest level of oxygen consumption attained during an incremental exercise test (Alexander et al., 2003). $\dot{V}O_2$ kinetics quantifies the time needed to adapt from rest to steady-state exercise (Manns et al., 2010). $\dot{V}O_2$ on-kinetics is comprised of three phases: 1) the cardio-dynamic phase, 2) the fast/fundamental phase and 3) the slow component phase (Burnley & Jones, 2007). The cardio-dynamic phase is the early fast increase in $\dot{V}O_2$, typically occurring within the first 15-25 seconds of exercise, and is largely attributed to an increase in cardiac output (CO) (Xu & Rhodes, 1999). Specifically, vasoconstriction of the vascular beds in the abdominal viscera, non-exercising muscles, and skin occurs, increasing venous return and thus CO (Clausen, 1976). The fast/fundamental phase shows the influence of muscle metabolic changes and occurs when $\dot{V}O_2$ increases exponentially towards steady state (Xu & Rhodes, 1999). The slow component is comprised of a continuous, relatively gradual increase in $\dot{V}O_2$ following the fast/fundamental phase and is only observed when exercise intensity is above the lactate threshold, causing $\dot{V}O_2$ to increase above the anticipated steady state $\dot{V}O_2$ value (Burnley & Jones, 2007). Gollie et al. (2017) reported impaired $\dot{V}O_2$ kinetics in those with SCI compared to the neurologically intact population. Those with higher-level injuries (tetraplegia and higher-level paraplegia) experience greater impairment in oxygen uptake (Coutts et al., 1983). This decrement in oxygen uptake may be attributed to reduced oxygen delivery to the functioning muscle mass, resulting from a low maximal heart rate and inadequate peripheral vascular control due to the lack of intact sympathetic innervation (Coutts et al., 1983).

Following SCI, impaired neuronal control negatively affects the respiratory muscles and respiratory function (Sheel et al., 2008). Respiratory dysfunction is dependent on the level, location, and time since injury (Sheel et al., 2008). Thus, with a spinal cord lesion at or above

C3, there is complete paralysis of muscles involved in ventilation, and ventilatory support is needed to sustain life (Sheel et al., 2008). A complete injury between C3 and C5 results in impaired function of the diaphragm and requires medical intervention for breathing at varying degrees depending on the level of the lesion (Berlowitz et al., 2016). A C5 injury generally results in breathing independently (Berlowitz et al., 2016). However, there is weakness of the diaphragm and respiratory muscles, further resulting in impaired inspiration and inability to cough (Berlowitz et al., 2016). Those with injury between C6 and C8 may have normal diaphragmatic function but varying degrees of pectoralis muscle paralysis, as well as the absence of intercostal muscles, thereby limiting maximum inspiratory and expiratory respiratory function as well as the ability to cough (Terson de Paleville et al., 2011). Individuals living with a complete T12 injury should not have any impairments pertaining to inspiration or expiration (Berlowitz et al., 2016). Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are diminished in individuals living with a SCI, with greater losses seen in those with higher-level injuries (Baydur et al., 2001).

An inverse relationship has been observed between maximal oxygen uptake ($\dot{V}O_2$ peak) and lesion level (Theisen, 2012). Eriksson et al. (1988) reported that those with lower injury levels exhibited higher $\dot{V}O_2$ peak than those with higher-level injury levels. However, nearly all participants who were trained and had high-level injuries (C7-C8) had higher $\dot{V}O_2$ peaks than those who were untrained with a similar lesion level (Eriksson et al., 1988). Peak performance is also impaired, with higher-level injury inversely related to peak performance despite similar training volumes (Bhambhani et al., 1994; Theisen, 2012). Gervasi et al. (2021) compared healthy, sedentary, age-matched able-bodied (neurologically intact) controls to those with a SCI

and reported that those with a SCI had a significantly lower $\dot{V}O_2$ peak ($12.2 \pm 2.8 \text{ mL.kg}^{-1}.\text{min}^{-1}$), compared to controls ($28.3 \pm 3.7 \text{ mL.kg}^{-1}.\text{min}^{-1}$).

Impaired $\dot{V}O_2$ on-kinetics have been reported during treadmill walking in participants with incomplete SCI. Participants with incomplete SCI had a time constant (Tau [τ]) that was 55% slower (54.6 seconds vs. 29.3 seconds) and a steady state amplitude that was 19% lower ($616.5 \text{ mL.min}^{-1}$ vs. $694.6 \text{ mL.min}^{-1}$) during treadmill walking than the neurologically intact control group (Gollie et al., 2017). At least part of the reduced amplitude of $\dot{V}O_2$ can be explained by the reduced stepping speed of those with SCI, since their stepping speed was 1/3 that of the controls. However, it is unknown whether the reduced on-kinetics also reflected underlying cardiovascular dysfunction or resulted from inadequate/inappropriate activation of the lower-limb muscles during stepping.

Fukuoka et al. (2002) compared $\dot{V}O_2$ on-kinetics between trained SCI participants and untrained neurologically intact control participants. They found that the trained SCI participants attained faster $\dot{V}O_2$ on-kinetics when compared to controls despite no changes in HR and a lower CO during supine arm crank ergometry. The authors attributed this improved $\dot{V}O_2$ on-kinetics to the small amount of lactate accumulation in the arms of participants with SCI during exercise compared to the neurologically intact control group. These results demonstrate that it is possible to measure $\dot{V}O_2$ on-kinetics during exercise in those living with SCI. However, it has not been systematically investigated. Therefore, this area of exercise physiology needs further systematic investigation regarding how and whether $\dot{V}O_2$ on-kinetics are altered after SCI, and if TSES can alter $\dot{V}O_2$ on-kinetic profiles. Transcutaneous spinal electrostimulation (TSES) may be a potential neuromodulatory intervention to improve cardioautonomic function. TSES may alter $\dot{V}O_2$ on-kinetics, via increased systemic vascular resistance (SVR), for those with a SCI.

Specifically, increased SVR allows for greater venous return and consequently cardiac preload. With greater cardiac preload, greater stroke volume can be observed, and thus CO will be increased. An increase in CO would allow for an increase in blood pressure which would facilitate greater delivery of oxygen rich blood to the working tissues, thus increasing the speed of $\dot{V}O_2$ on-kinetics.

2.8 Effects of Transcutaneous Spinal Electrostimulation on Cardiorespiratory Fitness and Exercise Capacity for Persons with Spinal Cord Injury

Given the cardiorespiratory limitations that those living with SCI face during exercise, interventions such as transcutaneous spinal electrostimulation (TSES) have recently been utilized, aiming to address these limitations (Engel-Haber et al., 2024). TSES is a non-invasive technique thought to modulate sympathetic spinal afferents (Angeli et al., 2014, Flett et al., 2022, Hofstoetter et al., 2018; West et al., 2018). TSES electrodes are placed on the skin directly over the spinal cord, to deliver an electrical current, which can be applied using a variety of waveforms (Taylor et al., 2021; Tefertiller et al., 2022). Stimulation parameters can be altered to produce different waveforms with differences in frequency, pulse shape, pulse width, and amplitude (Barrs et al., 2022). Studies investigating the effects of TSES on autonomic and cardiorespiratory function are very recent, with the earliest study conducted by Phillips et al. in 2018. To date, effective stimulation parameters and locations are unknown. This study is one of the few (currently 8 studies) examining autonomic function and its implications for cardiorespiratory outcomes. Additionally, we are the first study to explore the effects of TSES on $\dot{V}O_2$ on-kinetics in the SCI population.

Since this is an emerging intervention in the context of cardiorespiratory function and exercise, recent studies have been experimenting with stimulation parameters as well as

stimulation locations (Engel-Haber et al., 2024; Engel-Haber, 2025; Hodgkiss et al., 2024; Kumru et al., 2025; Lau et al., 2026; Phillips et al., 2018; Samejima et al., 2025; Solinsky et al., 2024). These efforts to optimize the likelihood of achieving improved acute responses for particular outcome measures (e.g., BP, HR) can be seen in the Engel-Haber et al. (2024) study, which mapped BP responses ($n = 8$, all with cervical SCI). During this study, participants were seated, and electrodes were placed sequentially over the following sites: C3/4, C4/5, C5/6, C6/7, C7/T1, T1/2, T11/12, L1/2, and S1/2. Stimulation of the lumbosacral sites (T11/12, L1/2, and S1/2) consistently led to an elevation in BP, whereas the cervical and higher thoracic sites did not (Engel-Haber et al., 2024). This result suggests that stimulation within the lumbosacral region may have a greater effect on blood pressure than stimulation at higher thoracic levels.

Another study with an experimental within-subjects research design examined postural changes in response to TSES ($n = 5$, all with SCI at or above T2), placing the electrode at approximately T8 (Phillips et al., 2018). The stimulation was delivered at 30 Hz as monophasic, 1 ms pulses when participants' systolic blood pressure (SBP) dropped by at least 20 mmHg during postural transition (known as orthostatic hypotension), and the amplitude of stimulation was increased from 10 mA up to 70 mA until BP was returned to resting levels (Phillips et al., 2018). Results showed normalized autonomic cardiovascular dysfunction, presenting as orthostatic hypotension (OH) attributed to the TSES but no restoration of HR, SV, or CO (Phillips et al., 2018). Phillips et al. (2018) proposed that sympathetic preganglionic neurons are excited, thereby increasing vascular tone and elevating BP. However, Phillips et al. (2018) acknowledged that the mechanism of action was not specifically analyzed and that it was beyond the scope of their study. Interestingly, collaborative animal research from the Cowley and Chopek labs has shown that at least one population of locomotor-related lumbar interneurons

(V3 INs) projects directly to and excites thoracic sympathetic preganglionic neurons, providing a potential neural substrate that may mediate increased activation of sympathetic target tissues during locomotor movement and exercise (Chacon et al., 2023; Dominguez-Rodriguez et al., 2026).

There have also been case reports ($n = 7$) of increased time to exhaustion, resting BP, and peak oxygen pulse, indicating greater SV and CO due to TSES (Hodgkiss et al., 2024). Since no changes were observed in leg muscle activity during the exercise trials, the authors concluded that the increase in BP was attributed to effects within the spinal cord that increased sympathetic responses, leading to increased vasomotor tone of blood vessels, thereby increasing vasoconstriction, resulting in increased venous return and thus BP (Hodgkiss et al., 2024). Thus, these findings suggest that TSES may improve cardiorespiratory outcomes, possibly through increased CO, leading to greater $\dot{V}O_2$, given their relationship ($\dot{V}O_2 = CO \times [a-vO_2 \text{ difference}]$) (Magder, 2021). However, this question requires further investigation.

SCI can cause autonomic dysfunction, disrupting cardiovascular and respiratory responses at rest and during exercise. TSES may be a viable option for improving cardiorespiratory responses to exercise in those living with SCI. The systematic review in this thesis provides the most up-to-date and relevant evidence on the effectiveness of TSES in improving various cardiorespiratory responses during exercise, as well as exercise capacity and cardiorespiratory fitness. Furthermore, this systematic review bridges the gap between the current literature and the experimental study in this thesis.

3. CHAPTER 3: GENERAL METHODOLOGY

This chapter describes the general methodology, including participant recruitment and enrollment, inclusion and exclusion criteria, measurements, protocols, and data collection for my experimental aim. Specific details (e.g., data acquisition, data analysis, and statistics) are presented in Chapter 5. This thesis is a part of the Transcutaneous Spinal Electrical Stimulation to Improve Exercise Function after Spinal Cord Injury study, which was approved by the Health Research Ethics Board at the University of Manitoba (#HS22987-H2019:279). As part of a larger research project, many physiological measurements were collected, including muscle activity via electromyography (EMG), heart electrical activity via electrocardiogram (ECG), muscle oxygenation via near-infrared spectroscopy (NIRS), and ventilatory gas measurements via metabolic cart.

Participants Recruitment and Enrollment

Participants were recruited via mailouts sent to members of Spinal Cord Injury Manitoba (Inc.), a non-profit, non-governmental organization that provides rehabilitation, information and advocacy services for Manitobans living with SCI. Participants then called or emailed expressing their interest in the study. Our team followed up with each person who called, screened each potential participant, and ensured they met the inclusion criteria (described later in the document). Participants who met all inclusion criteria were then invited to the lab for their first visit, where additional screening of exercise capacity on the SCI Fit arm-crank ergometer was conducted. If the SCI Fit was not accessible for the participant's chair, the participant did not pass ECG screening, or did not meet the exercise demands of the arm-crank ergometer (all participants that could not crank the arm ergometry were living with a C4/5 injury level), were

not included in the study (more details provided below). Figure 3.1 depicts the study recruitment process.

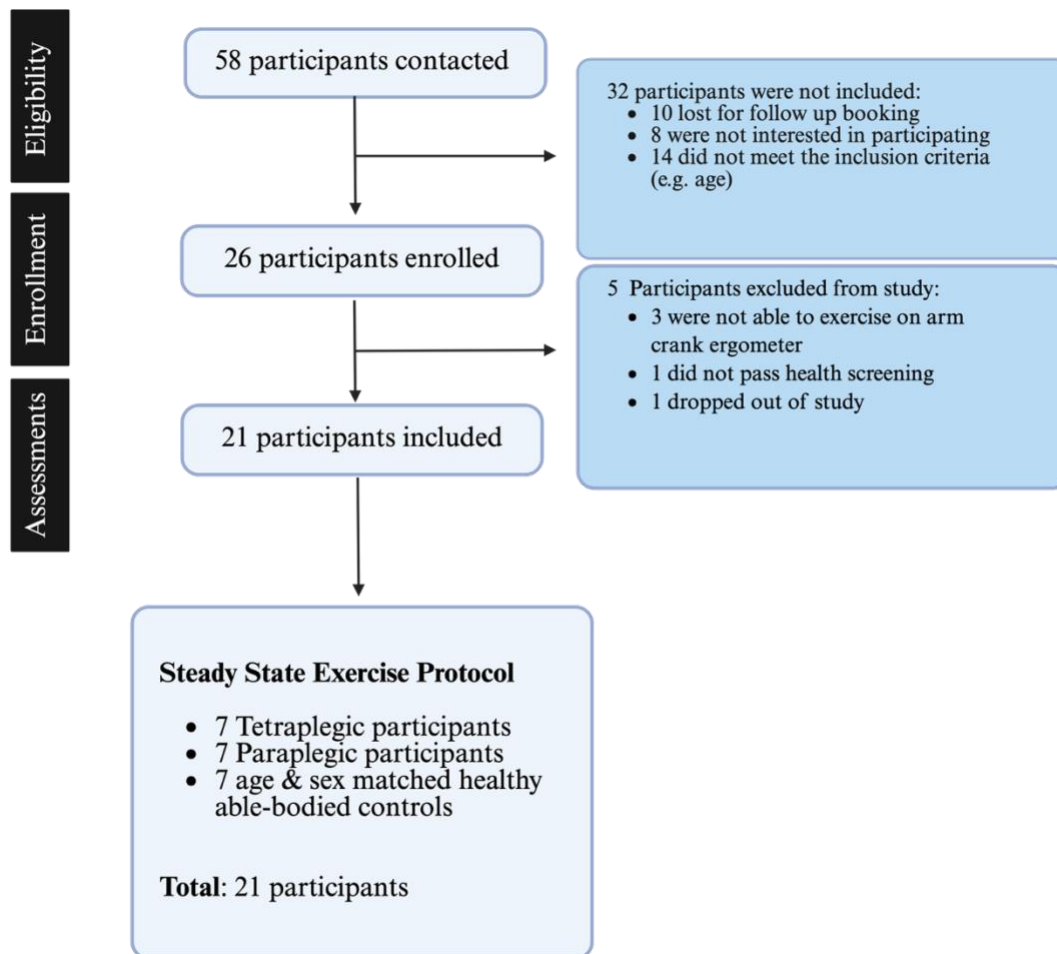


Figure 3.1 Recruitment flowchart.

Inclusion and Exclusion Criteria

The study details, including the testing procedures, underlying rationale, significance, and potential risks, were communicated to participants both verbally and in writing before they signed an informed consent form. The inclusion and exclusion criteria were established to

safeguard participant health and ensure the appropriateness of the exercise intervention. The inclusion and exclusion criteria are displayed in Table 3.1.

Table 3.1 Participant inclusion and exclusion criteria chart.

Inclusion Criteria	Exclusion Criteria
• 18-75 years of age • ≥ 1 year post injury (for SCI participants) • Injury level of C5-T12 accompanied by an AIS A-D • Medically stable and healthy enough to engage and complete exercise requirements (examined via health screening and PARQ+ Questionnaire)	• 1 or more ongoing serious injuries to the upper body • Pressure ulcer(s) that affect the ability to perform the exercise testing • Uncontrolled persistent high blood pressure ($>140/90$mmHg) • Presence of cardiovascular disease or an implanted electronic cardiac device (e.g., pacemaker, defibrillator) • Morbidly obese • Known to have thyroid dysfunction • Were actively diagnosed with cancer • Uncontrolled epilepsy • Presence of deep vein thrombosis (DVT) • Ventilator dependent • Presence of a cognitive impairment that would impair their ability to follow instructions sufficiently and perform study activities • Our SCI Fit machine was not accessible enough

Measurements

Data collection was conducted at the Spinal Cord Injury Research Centre in the Basic Medical Sciences Building at the Bannatyne Campus of the University of Manitoba. The

laboratory temperature was maintained at approximately 22°C, while humidity and barometric pressure remained at ambient levels. A minimum of two days was provided between test sessions to minimize potential carryover effects between the $\dot{V}O_2$ peak tests and the CWL exercise tests.

The height-adjustable SCI FIT arm ergometer (PRO01 Upper Body, SCIFIT, Tulsa, Oklahoma, USA) was used for the maximal and submaximal exercise protocols. All exercises were performed with the working muscles below shoulder height. The ergometer was set to allow participants to maintain $\sim 30^\circ$ of elbow flexion at maximum arm extension and a shoulder angle of $\sim 65^\circ$, ensuring that the highest point of the crank handle did not exceed shoulder height. In this configuration, participants' hands remained below shoulder level throughout all phases of the crank cycle. If necessary, the ergometer was adjusted to prevent contact between the crank handle and the participant's lap. Additionally, for some participants, depending on wheelchair configuration and lap height, a flexible strap was used to adjust leg positioning, thereby preventing contact between the crank handle and the lower extremities during exercise. Hand straps were available to participants as needed to ensure the arm crank was usable for those with limited hand function.

To collect muscle activity data, wireless muscle electromyography (EMG) surface sensors were applied to the right arm on the biceps, anterior deltoid, posterior deltoid and the triceps muscle to monitor their activity during arm cranking. Transcutaneous spinal electrostimulation (TSES) anodes were applied to the anterior superior iliac spine (ASIS), and the cathode (electrode delivering stimulation) was applied to T11/T12 of the spine. A 12-lead electrocardiogram (ECG) was utilized to monitor HR during exercise. However, since there may be electrical noise/interference from the TSES, HR data was also collected using a Garmin Forerunner 955 watch (Garmin Ltd., Olathe, Kansas, USA), which had been previously validated

in the lab (manuscript in preparation). Near-infrared spectroscopy (NIRS) sensors were placed on the left arm, specifically on the biceps and anterior deltoid, in addition to the left gastrocnemius muscle of the leg. NIRS sensors were used to determine muscle oxygenation during exercise. For participants with SCI, a sweat test was also conducted to monitor sweating throughout the test. The last device used was a metabolic (MET) cart.

The MET cart was used to record data regarding oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), respiratory rate (RR), and respiratory quotient (RQ). Breath-by-breath measurements were recorded using a metabolic cart (Quark Cardiopulmonary exercise testing [CPET], COSMED, Rome, Italy). Before calibrating and operating the CPET system, the metabolic cart was turned on for ~20 minutes to equilibrate with room conditions. Prior to testing, the CPET (metabolic cart) requires three different calibration processes: (1) turbine flowmeter calibration, (2) turbine flowmeter verification, and (3) gas calibration. The first two calibration processes assess levels and rates of inspiration and expiration produced by a calibrated syringe-pumping system, while the gas calibration ensures reliable measurements of O_2 consumption and CO_2 production by comparison with a calibrated gas cylinder standard. To complete the gas calibration, two gas mixtures in a tank with known concentrations (16% O_2 , 4.94% CO_2) were used as references, allowing the gas analyzer to adjust for any discrepancies from the expected values and calibrate the O_2 and CO_2 sensors. To analyze the fraction of air as O_2 and CO_2 , the CPET paramagnetic had a range of 0% to 25% for the O_2 analysis with an accuracy of $\pm 0.3\%$, and the nondispersive infrared sensor (NDIR), with a range of 0% to 10% for CO_2 analysis with an accuracy of $\pm 1\%$ (COSMED, 2022). The bidirectional digital turbine had a flow rate range of 0-16 $L \cdot s^{-1}$ and 0-300 $L \cdot min^{-1}$ for minute ventilation measurement, with an accuracy of $\pm 2\%$ (COSMED, 2022).

After calibration, participants' information, such as name, age, sex assigned at birth, race, body mass, and height were saved in the database. To set up the face mask for the participant, we first selected the appropriate mask size. The mask was then placed on the participant's face, tightened to ensure an airtight seal while remaining comfortable enough for the participant to complete the test. To assess whether the mask was airtight, participants or a member of our team (depending on the participant's functional capabilities) covered the turbine opening with the palm of their hand and had the participant exhale forcefully. If no air leaked out the side of the mask, then the two-way valve and turbine flowmeter were connected to the mask. This allowed the participants' breathing to be monitored with the metabolic cart, ensuring it was ready for data collection. Data collected using the MET cart were the focus of my thesis and were the sole device used to answer my research question (In the SCI population, how does TSES affect $\dot{V}O_2$ on-kinetics when compared to no stimulation during constant workload (CWL) arm crank exercise? The setup is illustrated in Figure 3.2 (C).

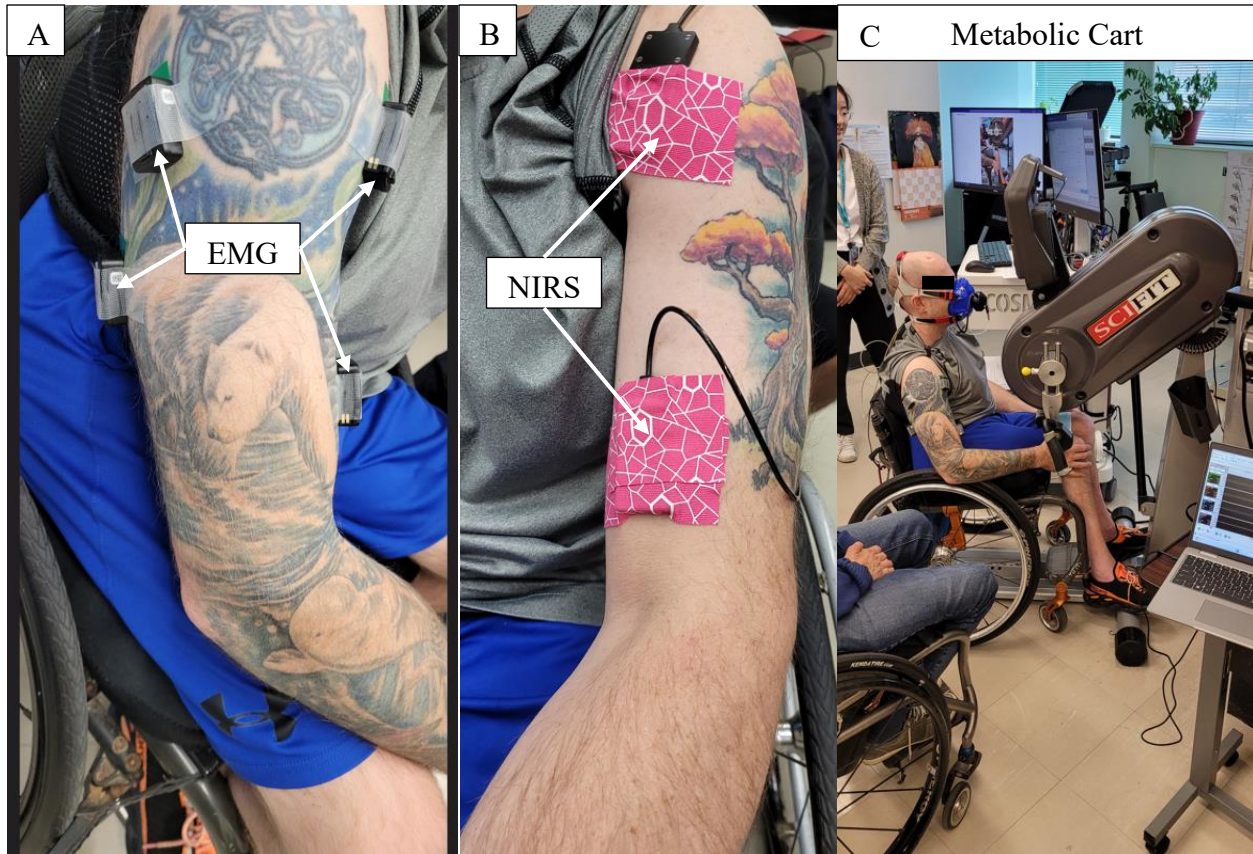


Figure 3.2 (A) Electromyography (EMG) electrode placement (anterior and posterior deltoids, biceps, and triceps). (B) Near-infrared spectroscopy (NIRS) optode placement (anterior deltoid and biceps). (C) Metabolic cart.

Protocols

This larger research project was designed to have 7 visits (Figure 3.3). However, for my thesis, I will only discuss visits 1-4 as they pertain to my research question (Figure 3.3).

Depending on the visit, participants spent 1-3 hours in the lab. Each visit is described below.



Figure 3.3 Study assessments for the entire project, visits 1-4 (red dashed box) are the focus of this thesis.

Visit 1: Each participant's first visit was used to confirm inclusion criteria, obtain informed consent, identify personal information such as age, date of birth, sex assigned at birth, date of injury, level of injury, AIS classification (including current motor function of those with incomplete injuries), ability to sweat in response to heat, anthropometric measurements (height, body mass, skin fold measurements of the biceps, anterior deltoid, and gastrocnemius for NIRS device) and medications used. Health screening was also performed along with the administration of the PARQ+ questionnaire and preliminary submaximal exercise testing. During the preliminary exercise testing, participants were instructed to crank at 60-70 rpm (depending on their strength) and then asked to rate the perceived load as easy, moderate, or difficult at each power output. During this time, participants were also asked to estimate how long they think they could maintain their cadence at a given workload. The participant's estimates of work rate difficulty and duration, along with our visual observations of their effort and strength, were used to determine the most appropriate starting work rate and increments during the maximal cardiopulmonary exercise testing (visits 2 & 3). Starting workload and stage increments were

individualized and designed to ensure a test duration of 6-10 minutes, consisting of 3-5 stages with increasing work rate in each.

Visits 2 & 3: Participants were instructed to arrive fasting, having abstained from alcohol and smoking for 48 hours before their test and to withhold caffeine on the day of the test. If participants forgot to abstain from caffeine on test day, we asked them to consume the same amount for their next visit. Following arrival and determination of fasting status and no alcohol or caffeine, participants completed a maximal cardiopulmonary exercise test (CPET_{max}) on an arm ergometer (60-70 rpm), using an initial work rate and increments deemed appropriate during the first visit. Simple randomization using drawing lots (shuffled deck approach) was established before these visits, prior to participants' arrival. For instance, two pieces of paper (one with "stim" written on it and the other with no "stim" written on it) were placed in a container and swirled around. One piece of paper was drawn to determine if the first CPET_{max} (visit 2) was with or without TSES. If the first CPET_{max}-1 (visit 2) was randomly assigned to have stimulation on, then visit 3 (CPET_{max}-2) was without stimulation. To minimize confounding variables, counterbalancing was implemented to ensure that 4 participants from each group had a visit 2 with stimulation and a visit 3 with no stimulation (and vice versa, as required). Participants were not aware of which condition they were receiving until the test began, and we did not tell them which condition they received to minimize potential biases. However, due to the nature of this study, it is not possible to conduct a truly blinded study, particularly for those with retained sensory function below their level of injury (AIS B and lower).

When participants arrived, they had their body mass measured (to monitor changes in body mass), followed by assessments of BP (brachial and radial measurements), and body temperature via an aural thermometer. Next, electromyogram (EMG) sensors were placed on the

bulk of the biceps, the anterior and posterior deltoids, as well as the triceps. Maximal voluntary contraction (MVC) testing for each muscle was performed twice, with a 1-minute break between trials, for a total of 8 trials (2 MVCs x 4 muscle groups).

TSES electrodes were placed on the participant, with the anodes being placed at the anterior superior iliac spine (ASIS) and the cathode being placed at T11/T12 (depending on participants' injury level). Sensory threshold was determined, followed by motor threshold, which was assessed via visual observation and palpation of muscles innervated at the stimulation site (i.e., Latissimus dorsi, erector spinae). Once the stimulation electrodes were placed and sensory/motor testing was complete, a five-minute warmup with 5-second bursts every minute was completed. Upon warm-up completion, BP measurements (brachial and radial measurements) along with aural temperature and a rating of perceived exertion (Borg scale) were collected. Following the completion of these measurements, a sweat test (Figure 3.4) was administered, a 12-lead EKG, a NIRS device, a Garmin watch, and a metabolic cart face mask were set up on the participant (Figure 4.2).

After setup was complete, a 2-minute resting baseline measurement was collected. Following the 2-minute baseline, a continuous peak exercise test was performed, consisting of ~6 to 10 minutes of exercise, 3-5 stages of work, each lasting 2 minutes, with a progressive increase in work rate per stage until volitional exhaustion was reached. The test was terminated when participants could no longer maintain their cadence despite repeated verbal encouragement from study staff. Whether each person achieved a peak test is confirmed post-hoc, by calculating whether each achieved at least 3 of the following: 1) 85% maximum HR, 2) $RQ > 1.10$, 3) $RPE \geq 17$ on the Borg 6-20 point scale, 4) plateau in $\dot{V}O_2$ despite increasing work rate, 5) inability to maintain the exercise rate (reduction in push rate or power output over 30 seconds that cannot be

increased with verbal encouragement). Once the test was terminated, participants remained seated for 10 minutes or until their RQ returned to baseline. RQ was calculated in real time as the ratio of CO₂ released/O₂ utilized (Patel & Bhardwaj, 2023). At rest, normal RQ is 0.8, a result of 200 mL.min⁻¹ CO₂ and 250 mL.min⁻¹ O₂ (Patel & Bhardwaj, 2023). Therefore, respiration was observed to ensure it returned to healthy resting levels, indicating adequate recovery. Blood pressure (brachial and radial), aural temperature, and peak RPE were recorded after test completion. For instance, as soon as the recovery was completed and the met cart mask was taken off, RPE was asked pertaining to the time period when they had to stop exercise and after they completed recovery, to ensure participants do not forget their RPE ratings. After the devices were removed from the participant (approximately 5 minutes later), BP and aural temperature were measured for the last time.

Sweating was detected using the starch-iodine test (Sato et al., 1988), in which iodine is applied directly to the skin of the neck. In brief, starch was gently applied over the iodine and sealed with a clear Tegaderm bandage to detect the presence or absence of sweat during exercise. Figure 3.4 depicts a sweating response after exercise. It is evident in the figure that sweating occurred in the first person (top image), as shown by the change in cornstarch coloration. The sweating can be identified by its dark purple/brown colour. The second person (in the bottom image) did not sweat, as their neck remained white.

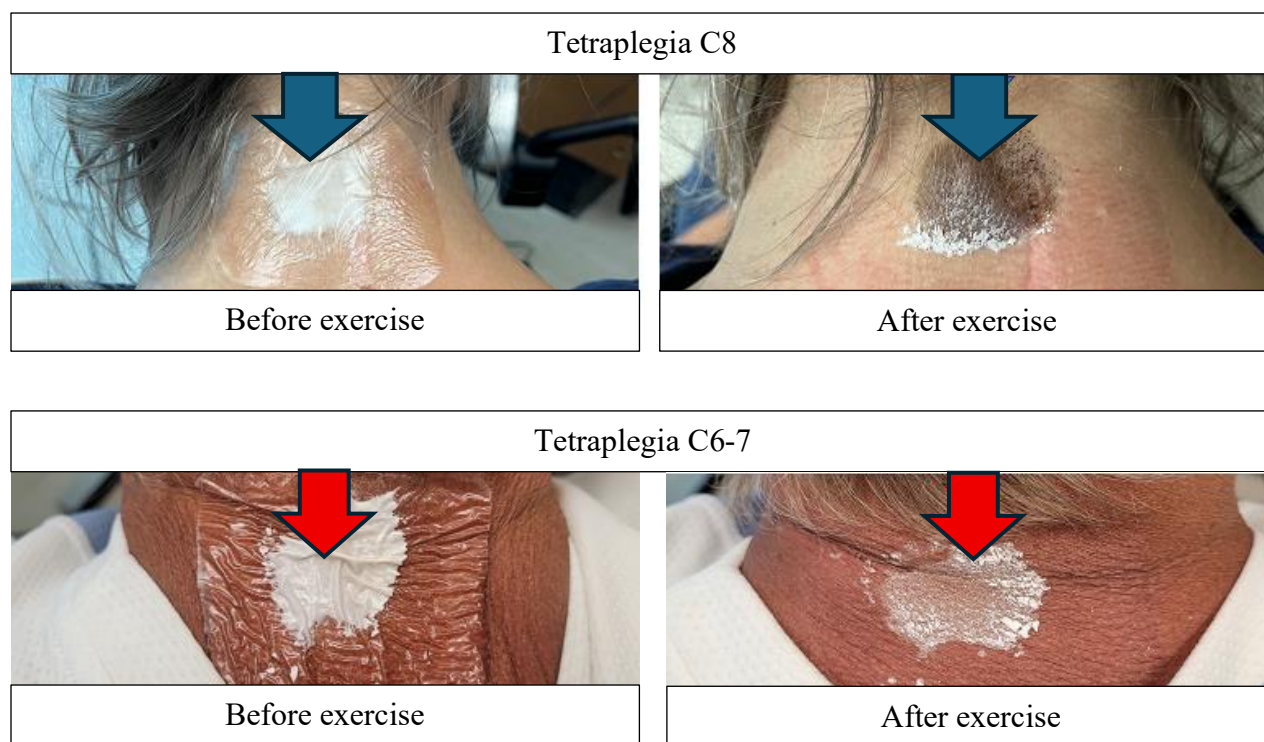


Figure 3.4 Illustration of the sweat test using the Starch-Iodine Test. Participant (top panel) showed a positive reaction (sweating) as the combination of the substances turned into dark blue/brown/black. Participant (bottom panel) showed a negative reaction (no sweating).

Visit 4: Participants arrived at the lab for their CWL exercise on an arm crank ergometer. The same pretest instructions (avoid alcohol 48 hours before test day, avoid caffeine the day of the test, and attend fasted) were given prior to arrival. When participants entered the lab, their BP (brachial and radial pressures) and temperature were taken. Muscle EMGs followed by MVC testing as described in visits 2 and 3. TSES electrodes (2 anodes on ASIS and 1 cathode on T11/T12) were applied to the skin, and the same five-minute warm-up used in visits 2 and 3 was conducted again, along with RPE on the Borg scale.

Next was the application of EKG electrodes, the NIRS device, the Garmin watch, the sweat test (for SCI participants), and the metabolic cart mask, as previously described. The exercise protocol consisted of 4 bouts of CWL exercise, each lasting 5 minutes, preceded by 3

minutes of baseline (resting) and followed by 5 minutes of recovery. Following recovery, a 7-minute break was taken to minimize carryover effects from each exercise bout. This order of events occurs four times before the test is complete. The workload for each 5-minute exercise bout was set at 40-45% of each participant's power output (PO) attained during their $\dot{V}O_2$ peak, determined in visits 2 & 3 (average PO attained during the two $\dot{V}O_2$ peak visits). Cadence was kept between 60 and 70 rpm, depending on the participant's level of injury, function, and preference.

Stimulation was randomized for each exercise bout with only two possible options, and the order was counterbalanced across participants. Option one was stim ON, OFF, ON, OFF and option two was stim OFF, ON, OFF, ON. Blood pressure (radial), aural temperature, and RPE were measured using the Borg 6-20 grade scale immediately after each exercise bout and immediately after recovery. At the end of the CWL exercise (after final recovery), notes on any adverse events, including skin redness, were documented. Additionally, participants were asked how they felt during the exercise and whether anything bothered them, to further report potential adverse events.

To minimize carry-over effects from the CPET_{peak} (visits 2 & 3), visits were booked at least 48 hours apart. Visits 3 & 4 followed the same 48-hour washout period, and peak visits (2-3) were also scheduled around the same time of day to minimize the effects of circadian rhythms. Although carryover effects between visits were a concern, they were particularly a concern during the CWL protocol in visit 4. To minimize carryover effects of the four bouts of exercise during the CWL exercise (visit 4), 7 minutes of rest between each bout was administered following the 5 minutes of recovery and preceding the 3 minutes of baseline of the next bout (Figure 3.5).

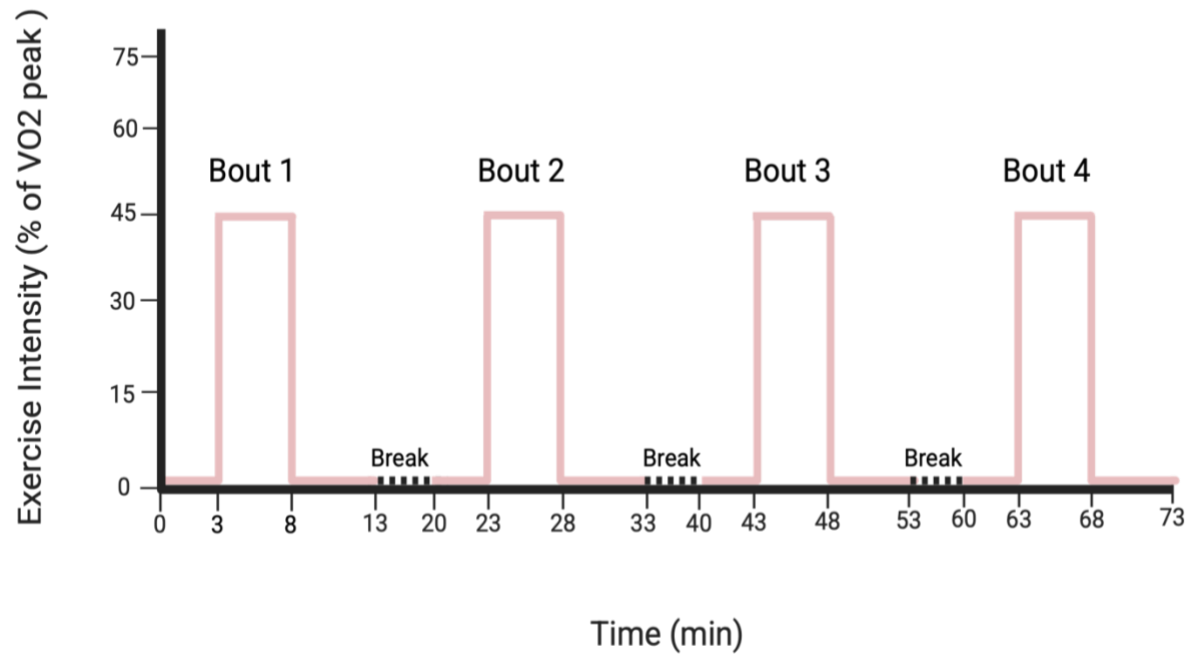


Figure 3.5 Constant workload exercise (CWL) protocol.

Data Collection

All researchers involved in data collection were trained either through lab tutorial sessions or by those with prior experience using these devices. This training was completed to ensure each researcher gained a comprehensive understanding of devices, protocols, and manuals, including potential risks (e.g., autonomic dysreflexia or a drop in BP causing syncope) that could arise during experiments. Neither participants nor researchers were blinded to the intervention due to the nature of the experiment. For example, the presence of TSES was obvious to all parties, as researchers were responsible for turning it on, and participants could generally feel when the stimulation was on. The primary study outcome was $\dot{V}O_2$ mean response time (MRT), while the secondary outcomes were time constant (τ), time delay (TD), and amplitude of the $\dot{V}O_2$ response. Specific details are provided in Chapter 5.

4. CHAPTER 4: SYSTEMATIC REVIEW

The Effects of Transcutaneous Spinal Electrostimulation on Cardiovascular and Respiratory Systems in those living with Spinal Cord Injury: A Systematic Review

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Abstract

Individuals living with spinal cord injury (SCI) experience a greater risk and earlier onset of cardiovascular disease (CVD) attributed to autonomic and cardiovascular dysfunction, and related low activity levels. Transcutaneous spinal electrostimulation (TSES) has emerged as a potential intervention to mitigate this risk; however, its effects on the cardiorespiratory system remain poorly understood. Specifically, it is unclear whether, or how, TSES affects the cardiorespiratory system; which rostro-caudal stimulation sites or parameters are most effective at mediating positive cardiovascular and respiratory responses; and whether adverse effects occur during stimulation in adults living with SCI. This systematic review aims to evaluate literature investigating the effect(s) of TSES on cardiorespiratory outcome measures and synthesize current evidence addressing these knowledge gaps. However, a meta-analysis comparing cardiorespiratory responses to TSES, epidural electrical stimulation (EES), and no stimulation across varying conditions was not feasible given the limited number of studies and their characteristics (e.g., case reports, case series). This systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Systematic searches of MEDLINE, EMBASE, CINAHL, and SCOPUS identified studies reporting cardiorespiratory responses (e.g., blood pressure, heart rate, cardiac contractility, oxygen uptake, carbon dioxide output) to postural transitions, autonomic testing, exercise, or BP stimulation mapping. Results from the systematic review showed that TSES is a relatively safe neuromodulatory strategy, and when applied to the T11-L2 region, can beneficially modulate blood pressure. Additionally, cardio-autonomic and respiratory responses to TSES appear highly individualized and further investigation is required to understand effective stimulation parameters.

Key Words: spinal cord injury; neuromodulation; spinal stimulation safety; physical activity, functional capacity

4.1 Introduction

Individuals living with SCI are at high risk for cardiovascular complications, including autonomic dysreflexia and orthostatic hypotension (Sezer et al., 2015). They also have roughly three times the risk of developing heart disease compared to the general population (Vivodtzev et al., 2021). This increased risk of CVD among the SCI population is complex and can be attributed to limited physical activity or exercise, in part due to autonomic dysfunction that limits their ability to perform exercise at sufficient intensity to confer training or health benefits (Flett et al., 2022). However, additional factors, including a sedentary lifestyle attributed to motor dysfunction, muscle weakness and paralysis, chronic inflammation, cardiovascular and pulmonary dysregulation, as well as potential deficits in muscle oxygenation, may contribute (Flett et al., 2022; Luo et al., 2024; Lagu et al., 2023). Together, these impairments lead to poor peak oxygen uptake ($\dot{V}O_2$) and cardiac output (CO), resulting in low cardiorespiratory fitness (CRF) and exercise capacity (EC) (Deley et al., 2015; Flett et al., 2022; Mercier et al., 2020), negatively affecting well-being and quality of life. Since there is currently no known cure for SCI, a reasonable alternative strategy for improving health and quality of life after injury is to understand how to enhance exercise function and capacity, including acute cardiovascular responses.

A potentially valuable research avenue for reducing the risk of CVD mortality after SCI is to investigate the capacity of spinal cord stimulation, specifically transcutaneous spinal electrostimulation (TSES), to modulate cardiovascular function (Flett et al., 2022; Law et al., 2024). TSES is a non-invasive form of neuromodulation that has been shown to elicit cardiovascular changes thought to be driven by alterations in spinal neuronal excitability (Law et al., 2024; Samejima et al., 2025). However, the effects of TSES on dynamic measures of aerobic

performance, such as $\dot{V}O_2$ kinetics, remain limited and poorly understood, warranting further investigation of TSES as a potential strategy to improve exercise tolerance and cardiovascular health after SCI.

Flett et al. (2022) conducted a comprehensive scoping review summarizing the current literature on the effects of TSES on exercise-related autonomic functions. However, respiratory outcomes, including $\dot{V}O_2$ kinetics and TSES safety were not included. Additionally, the most recent article included in this scoping review was published in 2021. Large interest in the field over the last five years has expanded the body of literature that has not yet been reviewed. However, despite growing interest in TSES and its potential effects on the cardiorespiratory system in those living with SCI, research on whether and how TSES affects the cardiorespiratory system remains emerging, and reported findings can appear contradictory. Therefore, an updated, comprehensive systematic review to identify TSES stimulation locations (mapping) that are most effective at eliciting cardiorespiratory improvements in those living with SCI is necessary to improve exercise capacity and cardiovascular health. Additionally, investigating adverse events associated with TSES will provide a more comprehensive understanding of TSES safety and efficacy for cardiorespiratory modulation. This systematic review also aims to assist researchers in developing strategies to enhance exercise capacity and cardiorespiratory fitness in individuals living with SCI, thereby supporting efforts to reduce the risk of cardiorespiratory-related mortality.

4.2 Methods

PROSPERO utilizes the PICO (Population, Intervention, Comparison, Outcome) framework (Prospero, 2018). Thus, the population of interest for this review is adults (18+) living with a SCI. The intervention was the application of TSES, compared to alternatives of

either electrical stimulation (ES) or no stimulation. Outcomes measured are described further in the Search Strategy.

Search Strategy

The PICO approach defined the search strategy: (P) Population: Adults (18+) living with SCI; (I) Intervention: spinal electrostimulation (TSES, EES, no stimulation) at rest, during autonomic testing, and/or in exercise; (C) Comparison: describe cardiovascular and respiratory responses to TSES, effective rostrocaudal stimulation sites, and parameters; (O) Outcomes: Cardiorespiratory responses (cardiac output, stroke volume, blood pressure, heart rate, oxygen uptake, minute ventilation, respiratory quotient, on or off-kinetics, and recovery times) during the application of spinal electrostimulation in adults living with SCI. Therefore, the research question is as follows: *“In people living with spinal cord injury, does transcutaneous spinal electrostimulation affect cardiovascular and respiratory responses when compared with epidural electrical stimulation or placebo?”* Adverse events were also characterized.

MEDLINE, EMBASE, CINAHL, and SCOPUS databases were systematically searched from November 2025 through January 2026. A customized search strategy was created by SP for each database (Appendix F). The search strategy included keywords such as “Transcutaneous spinal electrostimulation”, “Spinal cord stimulation”, “Non-invasive spinal cord stimulation”, “Cardiovascular neuromodulation”, “Spinal cord injury”, “Cardiovascular*”, “Respiratory*” (see Appendix F for the complete list of search strings). Boolean operators were included during the library search. No date restrictions were applied. Searches were restricted to English, peer-reviewed articles investigating cardiorespiratory outcomes. Following completion of the searches across the databases listed above, 2,396 articles were retrieved. After removal of duplicates, 1,840 articles remained, and their titles and abstracts were screened for relevance. This screening

resulted in 23 articles for eligibility assessment. During full-text screening, 15 articles were excluded for reasons outlined, leaving 8 studies for this systematic review (Figure 4.1).

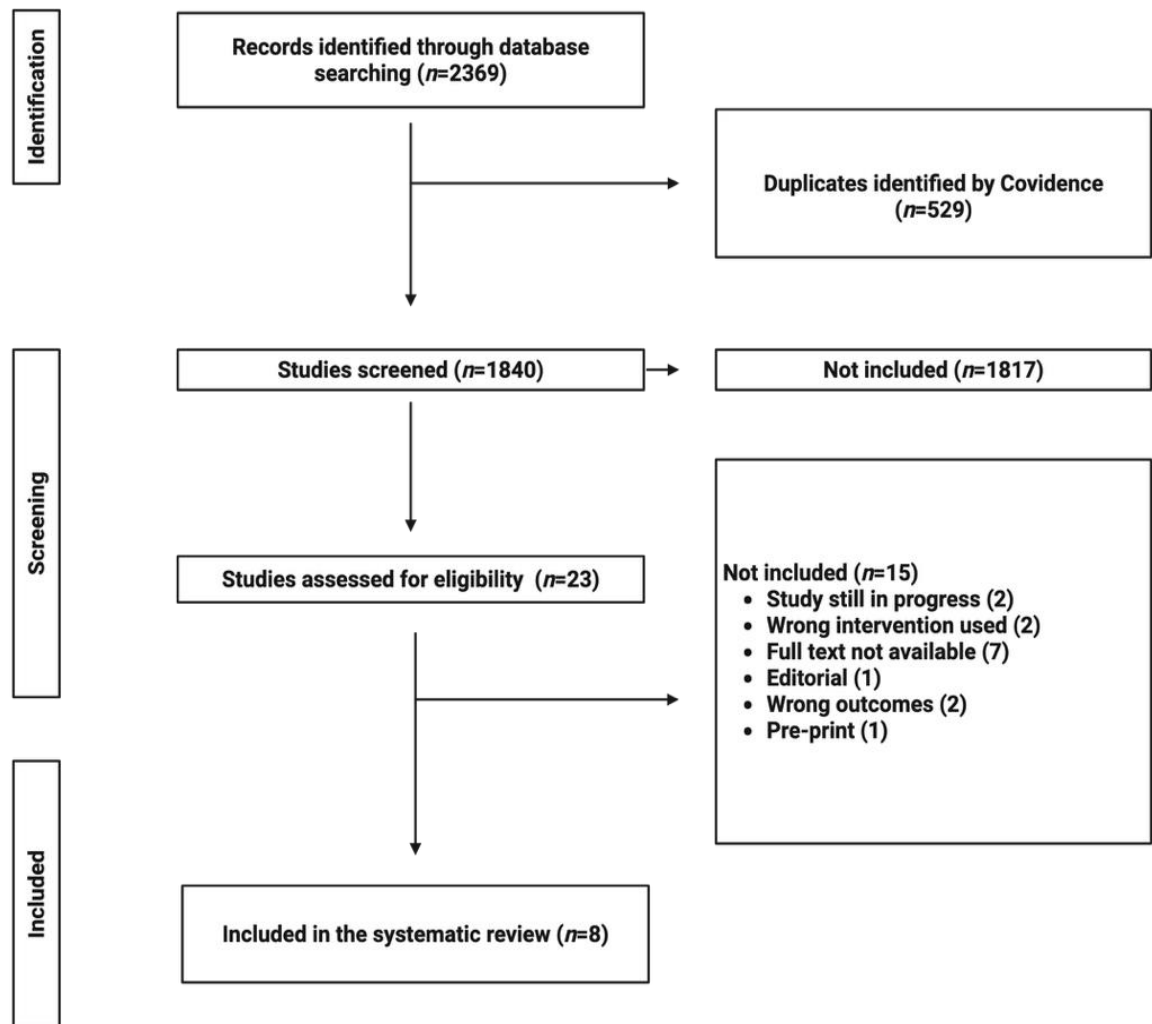


Figure 4.1 Study Identification and Screening Flow Chart.

Study Selection Criteria

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to manage articles and help streamline this systematic review. Two researchers (SP and RV) reviewed the selected manuscript titles and abstracts. Established inclusion and exclusion

criteria were used to exclude manuscripts that did not meet them. When SP and RV disagreed on a paper's eligibility, a third reviewer (KC) served as a tiebreaker to determine whether the paper should be included. The included papers were further screened, and the entire manuscript was reviewed to ensure it met the selection criteria.

Inclusion criteria were: (1) human adults (18+); (2) having sustained a traumatic or non-traumatic SCI (all AIS levels) ; (3) inclusion of at least one cardiovascular or respiratory variable of interest; (4) experimental/observational, case-control, case studies or series, cross-sectional studies, and longitudinal studies; (5) peer-reviewed articles; and (6) articles published in English. Study and report exclusion criteria were as follows: (1) abstracts, editorials, and letters to the editor; (2) participants under the age of 18; (3) studies reporting only non-cardiorespiratory outcomes; and (4) animal studies. The grey literature (e.g. studies within clinicaltrials.gov or SCITrialsfinder.net) was also assessed using a scoping review perspective. Reviews and meta-analyses were examined to inform our systematic review content, data interpretation, and alignment with conclusions drawn from our literature review, and were referenced accordingly.

Data Extraction

Data was extracted independently by two researchers (SP and RV). Variables extracted from the full text of eligible studies are listed in Table 4.1. Given the recent emergence of TSES research aimed at modifying cardiorespiratory outcomes in this population, all protocols (exercise, postural transition, autonomic function testing, cardiovascular mapping) were analyzed to achieve a comprehensive understanding of the cardiovascular and respiratory effects of TSES in those with SCI. We also searched ClinicalTrials.gov to identify any planned or ongoing studies using TSCS among the SCI population that explore cardio-autonomic and respiratory outcomes. Search terms included: “Spinal cord injuries/(SCI)”, and “Transcutaneous spinal cord

stimulation OR TSES OR Neuromodulation”, with results limited to adults. The search was conducted on June 6, 2026, and retrieved 89 results.

Table 4.1 Variables extracted from full text.

Bibliographic	Author(s) Title Journal Year of publication Country Study design Testing Setting(s) Study Objective Inclusion and exclusion criteria
Participant Characteristics	Age Sample size Sex of participants Type of spinal cord injury with corresponding ASIA score (complete vs. incomplete) Lesion level (tetraplegic vs. paraplegic) Duration of injury Presence of comorbidities Medications
Transcutaneous spinal electrostimulation parameters	Location of stimulation Frequency Pulse width and carrier frequency, if applicable Shape Amplitude Stimulator
Experimental protocol	Techniques/ devices used Questionnaires Specific task performed
Cardiovascular system	Blood pressure (systolic, diastolic, mean arterial pressure) Heart rate Heart rate variability Cardiac contractility Cardiac output Stroke volume
Respiratory system	Oxygen uptake ($\dot{V}O_2$) Minute ventilation ($\dot{V}E$) Respiratory Exchange Ratio (RER) Respiratory Quotient (RQ)
Adverse events	All reported adverse events

Study Quality and Risk of Bias Assessments

Two independent reviewers (SP and RV) assessed the quality and bias of each article using the JBI Critical Appraisal Tool (Barker et al., 2023; Barker et al., 2024; Moola et al., 2020; Munn et al., n.d.). A third reviewer (KC) resolved any disagreements if necessary. The JBI Critical Appraisal Tool was utilized because it was designed to be implemented in systematic reviews to assess the quality and bias of various study types (Barker et al., 2023; Barker et al., 2024; Moola et al., 2020; Munn et al., n.d.). See Appendix G for JBI checklists used.

Meta-analysis was planned if at least two studies met all systematic review criteria in addition to the following: 1) clearly defined neurological and/or completeness of injury (AIS scale), as these factors may impact cardiorespiratory responses; 2) reported specific TSES stimulation parameters (location of cathode(s) and anode(s), duration, frequency, intensity, pulse width) to allow for subgroup analysis or comparisons; 3) included a control group receiving sham stimulation or participants that received no stimulation; 4) reported quantitative cardiorespiratory outcomes (e.g., heart rate, blood pressure, cardiac output, stroke volume, systemic vascular resistance, heart rate variability, respiratory rate, minute ventilation, oxygen consumption, carbon dioxide output, respiratory quotient). Since none of the studies met these criteria and the majority were case reports and case series, a meta-analysis was not performed.

Data Synthesis

When available, the following data were extracted: (1) blood pressure (systolic, diastolic and mean arterial pressure), heart rate, cardiac contractility, cardiac output, stroke volume, systemic vascular resistance, and heart rate variability; (2) oxygen uptake, carbon dioxide output, minute ventilation, respiratory exchange ratio, respiratory quotient, and respiratory rate; and (3) TSES parameters (location, duration, frequency, intensity, pulse width) (Table 4.2)

4.3 Results

Characteristics of articles and participants

The use of TSCS to modulate cardiorespiratory outcomes is a relatively recent area of research, with publications ranging from 2018 to 2025. 7/8 articles were published between 2024-2026. Among the eight studies examining the effects of TSES on cardiorespiratory outcomes, there was one randomized control trial (RCT), three quasi-experimental studies, two case series, one case study, and one case report (Table 4.2).

Participants' ages ranged from 18 to 67 years, with males comprising the majority across studies (50-100%), except in one case study that was conducted on a female (Engel-Haber et al., 2025; Table 4.2). Injury levels ranged from C2 to T5. Four studies included only cervical injuries, one included only thoracic injuries, and the remaining three included those with either cervical or thoracic level injuries. All studies reported American Spinal Injury Association Impairment Scale (AIS) classifications, with five studies, including only motor complete injuries (AIS A-B). The remaining three articles included both motor complete and incomplete (AIS C-D) injuries. Injury duration varied considerably across studies, ranging from 3 months to 6 years post-injury. Four studies focused on chronic spinal cord injury, three investigated subacute SCI, and one study did not report participants' injury duration (Solinsky et al., 2024) (Table 4.2).

Table 4.2 Participant characteristics for transcutaneous spinal electrostimulation studies focusing on cardio-autonomic and respiratory outcomes.

Study	Sample Size	Sex of Participants	Age (yrs)	Injury Duration	AIS Level, n	Level of Injury	Study Type
Phillips et al., 2018	5	4 M 1 F	23-32	≥ 3 years	AIS A: 3 AIS B: 2	C5-T2	Experimental within-subject design
Engel-Haber et al., 2024	8	All M	18-67	7 months - 6 yrs	AIS A: 4 AIS B: 3 AIS C: 1	C3-C7	CSr
Hodgkiss et al., 2024	7	All M	24-59	≥1 yr post injury	AIS A: 5 AIS B: 2	C6-T4	CSr with crossover comparison
Solinsky et al., 2024	4 (2 with SCI; 2 AB control)	2 M 2 F	20-30	NR	AIS A: 2	T3-T5	Single-blinded, randomized crossover study with matched pair design
Engel-Haber et al., 2025	1	F	33	2	AIS A	C4	CS
Kumru et al., 2025	19 (15 TSCS + OT 7 OT only 4 OT only to TSES + OT)	TSCS : 14 M, 1 F CG : 9 M, 2 F	TSCS: 37.2 ± 13.5 years CG: 37.2 ± 14.6 years	TSCS: 5.7 ± 2.2 months CG: 5.5 ± 1.7 months	TSCS: AIS A: 3 AIS B: 4 AIS C: 4 AIS D: 4 CG: AIS A: 2 AIS B: 4 AIS C: 4 AIS D: 1	TSES: C3-C7 CG: C4-T1	RCT with partial crossover

Lau et al., 2026	1	M	49	3 months	AIS A	C5	CR
Samejima et al., 2025	60	50 M 10 F	42 ± 15.5 years	6.1 ± 7.5 years	AIS B: 9 AIS C: 28 AIS D: 23	C2-C7	Secondary analysis of a prospective single-arm study

All spinal levels are neurological level of injury, unless indicated otherwise with a V for vertebral. N refers to the number of persons with each American Spinal Injury Association Impairment scale (AIS) classification. OT: occupational therapy; NR: not reported; F: female; M: male; CR: case report; CS: case study; CSr: case series. TSCS: transcutaneous spinal cord stimulation; CG: control group.

Intervention characteristics

TSES parameters for eliciting cardiovascular, respiratory and autonomic outcomes varied widely, and included cervical as well as lumbar stimulation. The most frequently used stimulation sites (cathode) were T11-L2 (5/8, 63%). Additional stimulation sites included T7-T8 (2/8, 25%) and C3-T1 and S1/2 (1/8, 12.5%). Anodes were either placed at the iliac crests or on the abdomen. TSES stimulation frequency also varied widely, ranging from 30-120 Hz, with 30 Hz most common (7/8 studies, 87.5%, with only one study using 100 Hz (Lau et al., 2026). Interestingly, 6/8 studies (75%) used a carrier frequency, with 3/8 (37.5%) studies employing 5 kHz and 3/8 (37.5%) using 10 kHz. The remaining two studies (25%) did not employ a carrier frequency. Pulse width ranged from .450 to 1 ms, with 1 ms most common (6/8 studies [75%]). One study (12.5%) implemented .450 ms (Lau et al., 2026), while the other study (12.5%) did not report pulse width (Solinsky et al., 2024). A variety of stimulation amplitudes were used, with studies generally increasing intensity until either an effect was observed at a predetermined maximum or stimulation was tolerated. Stimulation waveforms varied as well; the most commonly reported was a monophasic rectangular pulse (3/8 studies [37.5%]) (Table 4.3).

Study objectives, and therefore protocols varied widely, with 2/8 studies (25%) examining the long-term effects of TSES combined with upper-extremity rehabilitation or occupational therapy designed to improve respiratory outcomes. The remaining studies (6/8 [75%]) focused on acute outcomes, with postural transition studies most common (4/8 [50%]) (Table 4.3).

Table 4.3 Transcutaneous spinal electrostimulation (TSES) using a variety of TSES parameters may improve cardiorespiratory and autonomic outcomes in the SCI population.

Study/year	Sample size (<i>n</i>)	Objective/Protocol	TSES parameters	Cardiovascular/Autonomic/ Respiratory outcomes
Phillips et al. (2018)	5	Objective: Determine if TSES can acutely restore autonomic cardiovascular function in people living with SCI during a Progressive orthostatic challenge (POC)	Location: T8 (cathode), iliac crests (anode)	*Note: Absolute values not reported* Systolic BP (SBP): POC: -37 ± 4 mmHg (absolute values not reported) POC with TSES: Restored to baseline levels (numerical values not reported)
		Protocol: POC from supine baseline rest. Upon onset of OH, TSCS was turned on and increased from 10 mA to a max of 70mA until BP was normalized for 1 minute during the orthostatic intolerance test. Test lasted 1 hr	Freq: 30 Hz Width: 1 m.s ⁻¹ Shape: Monophasic Amp: Increased from 10 mA to a max of 70 mA Stimulator: Not Reported	Diastolic BP (DBP): POC: Decreased (numerical values not reported) POC with TSES: Normalized (numerical values not reported) Mean Arterial Pressure (MAP): POC: Decreased (numerical values not reported) POC with TSES: Normalized (Numerical values not reported) Cardiac contractility (dP/dt): POC: $-52 \pm 10\%$ (decreased; absolute values not reported) POC with TSES: Restored to baseline (numerical values not reported) Stroke volume (SV): POC: Decreased (numerical values not reported)

POC with TSES: Partially restored but remained reduced (numerical values not reported)

Heart rate (HR):

POC: Increased (numerical values not reported)

With TSES: Remained elevated, did not normalize (numerical values not reported)

Cardiac output (CO):

POC: Reduced (numerical values not reported)

POC with TSES: Improved (numerical values not reported)

Middle cerebral artery velocity (MCAv):

POC: Decrease (numerical values not reported)

POC with TSES: Normalized (numerical values not reported)

Posterior cerebral artery velocity (PCAv):

POC: $-23 \pm 6\%$ (Decreased; absolute values not reported)

POC with TSES: Normalized (numerical values not reported)

Symptoms

Orthostatic intolerance symptoms (1–10 scale):

During POC: Severe ($\approx 6-9$)

POC with TSES: Almost completely abolished ($\approx 0-1$)

Engel-Haber et al., 2024	8	Objective: Identify stimulation sites that increase blood pressure in people with a chronic cervical SCI Protocol: TSCS mapping (one site at a time)	Locations: C3/4,C4/5,C5/6,C6/7,C7/T1,T11/12,L1/2 & S1/2 (cathodes), iliac crests (anode) Freq: 30 Hz, 5 kHz carrier freq. Width: 1 m.s⁻¹ Shape: Monophasic rectangular Amp: raised to a max of 120 mA in 5 mA increments Stimulator: NeoStim-5 (Cosyma Inc., Moscow Russia)	*Note: Absolute values not reported* Systolic blood pressure (mmHg): Baseline SBP: C3/C4 : 93 ± 12 C6/C7 : 93 ± 12 T1/T2 : 91 ± 14 T11/T12 : 88 ± 13* L1/L2 : 92 ± 11* <i>ANOVA: p = 0.026</i> T11/12 & L1/2: <i>p = 0.033</i> Mean ΔSBP: C3/C4 : 7 ± 5* C6/C7 : 14 ± 6 T1/T2 : 11 ± 9 T11/T12 : 40 ± 19* L1/2 : 27 ± 15 <i>ANOVA : p < 0.0001</i> C3/C4 & T11/T12 : <i>p = 0.038</i> Diastolic blood pressure (mmHg): C3/C4 : 69 ± 9 C6/C7 : 65 ± 7 T1/T2 : 66 ± 10 T11/T12 : 61 ± 9 L1/2 : 67 ± 7 <i>p = 0.007</i> Mean ΔDBP: C3/C4: 4 ± 4* C6/C7: 9 ± 5 T1/T2 : 6 ± 4 T11/T12 : 23 ± 11* L1/2 : 14 ± 10 <i>ANOVA : p = 0.0002</i>
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C3/C4 & T11/T12 : $p = 0.026$

Heart rate (bpm) :

C3/C4 : 73 ± 10

C6/C7 : 73 ± 7

T1/T2 : 83 ± 13

T11/T12 : 75 ± 10

L1/2 : 75 ± 8

$p = 0.107$

Mean Δ HR:

C3/C4: 0 ± 7

C6/C7: 0 ± 7

T1/T2: -3 ± 8

T11/T12: -16 ± 15

L1/2: -7 ± 13

$p = 0.869$

Maximum stimulation amplitude:

C3/C4: 40 ± 26

C6/C7: 48 ± 35

T1/T2: 60 ± 34

T11/T12: 85 ± 34

L1/2: 71 ± 31

$p = 0.0023$

Hodgkiss et al., 2024	Objective: Compare the acute effects of CV optimized epidural stimulation and TSCS relative to sham conditions during resting and maximal upper body exercise in people living with SCI Protocol: CV-TSCS optimization mapping session followed by a peak exercise test	Location: ESCS P1: T10-T12 ESCS P2: T11-L1 TSCS P1&P2: T11-L1(cathode), iliac crests (anode) Freq: ESCS P1: 30 Hz ESCS P2: 300 Hz TSCS P1 & P2: 30 Hz + 10 kHz carrier freq. Width: ESCS P1: 500 us ESCS P2: 380 us TSCS P1 & P2: 1 m/s Shape: Not reported Amp: ESCS P1: 6.1 mA ESCS P2: 3.6 mA TSCS P1: 39 mA TSCS P2: 78 mA Stimulator: ESCS: Verita Neuro (ESCS P1);	*Note: Quantification of absolute changes not reported except $\dot{V}E$ and $\dot{V}O_{2peak}$* *Cohen's d was reported instead of the <i>p</i>-value* Resting cardiovascular effects: CV-SCS increased resting SBP, and predicted stroke volume, cardiac contractility, and total peripheral resistance compared with SHAM-SCS. Exercise performance: Time to exhaustion increased in all participants with CV-SCS compared with SHAM-SCS Improvements were comparable between ESCS and TSCS Blood pressure: Greater increase in SBP at rest with CV-SCS than SHAM-SCS Peak oxygen pulse: Peak oxygen pulse higher with CV-SCS, suggesting increased stroke volume Heart rate: No meaningful differences between CV-SCS and SHAM-SCS Perceived exertion: RPE tended to be lower throughout exercise with CV-SCS
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Tripole™ and Proclaim elite™, Abbott (ESCS P2)].
TSCS: constant current stimulator (TESCoN, SpineX Inc., California, United States)

Muscle activation:

No meaningful increase in leg EMG activity, suggesting BP changes were not driven by skeletal muscle pump

$\dot{V}E$ (L/min):

Participant 1:TSCS = 85, Sham-SCS = 81.6, d = 0.04

Participant 2:TSCS = 38.1, Sham-SCS = 39.1, d = 0.04

$\dot{V}O_{2peak}$ (L/min):

Participant 1:TSCS = 2.13, Sham-SCS = 1.98, d = 0.14

Participant 2:TSCS = 1.17, Sham-SCS = 1.14, d = 0.14

		Note: absolute values not reported	
Solinsky et al., 2024 [§]	4	Objective: Determine if TSES improves cardiovascular autonomic regulation after SCI by comprehensively assessing sympathoexcitatory and sympathoinhibitory reflex responses at multiple stimulation frequencies Protocol: Supine resting (baseline), progressive orthostatic challenge. Application of TSCS upon OH onset. Acute physiological testing	Location: T10-T11 (cathode), bilateral iliac crests (anodes) Freq: 120Hz, 30Hz, & 30Hz + 5kHz carrier freq. Width: Not reported Shape: biphasic Amp: 80% of motor threshold Stimulator: Constant current stimulator (Digitimer DS8R) Waveform generator (RIGOL DG1022)
		Valsalva maneuver – Phase II MAP change: SCI baseline: -20.3 ± 5.5 mmHg Controls baseline: 4.9 ± 2.4 mmHg $p = 0.01$ SCI with 120 Hz TSCS: -1.1 ± 2.0 mmHg Pressure recovery time: SCI baseline: 8.7 ± 3.1 s Controls baseline: 2.2 ± 0.8 s $p = 0.009$ Increased with all stimulation frequencies in SCI Phenylephrine-induced MAP change (SCI): Baseline: 6.8 ± 1.1 mmHg With stimulation (all frequencies): 27.0 ± 2.4 mmHg $p < 0.001$ Phenylephrine-induced MAP change (controls) Baseline: 4.5 ± 1.2 mmHg With stimulation (all frequencies): 6.3 ± 0.6 mmHg $p = 0.36$ Foot cold pressor (SCI, all frequencies of TSES): ΔSBP: 27.7 ± 4.5 mmHg ΔHR: -6.3 ± 1.3 bpm Foot cold pressor (controls, all frequencies of TSES): TSES during the foot cold pressure test did not change MAP (absolute values not reported)	

Engel-
Haber et al.,
2025

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Objective: Determine if short-term repeated TSES focused on cardiovascular function produces sustained improvements in blood pressure regulation and orthostatic tolerance

Protocol: Orthostatic challenge (10 mins supine rest, tilting to 70° for 30 minutes, no stim). Intervention: six 30-min seated CV-TSCS sessions over 2 weeks

Location: T7-T8 & L1/L2 (cathodes), iliac crests (anode)

Freq: 30 Hz + 5 kHz carrier freq.

Width: 1 m.s⁻¹

Shape: monophasic rectangular

Amp: up to 80 mA (thoracic) & up to 150 mA (lumbar)

Stimulator: NeoStim-5 (Cosyma Inc., Moscow, Russia)

Baseline

SBP: 112 ± 4 (supine) → Tilt: 69 ± 10 (Δ -43)

DBP: 74 ± 4 (supine) → Tilt: 46 ± 6 (Δ -28)

HR: 68 ± 5 (supine) → Tilt: 102 ± 7 (Δ +34)

Duration of 70° tilt: 3.3 min

Max symptoms total: 13

1 day post-intervention

SBP: 124 ± 3 → Tilt: 88 ± 11 (Δ -36)

DBP: 84 ± 2 → Tilt: 61 ± 9 (Δ -23)

HR: 74 ± 3 → Tilt: 100 ± 11 (Δ +26)

Duration of 70° tilt: 30.5 min

Max symptoms total: 4 (0*)

At 20 min: fatigue 3/10 + faint 1/10; resolved, and she completed the test.

6 weeks post-intervention

SBP: 121 ± 3 → Tilt: 69 ± 14 (Δ -52)

DBP: 82 ± 3 → Tilt: 41 ± 17 (Δ -41)

HR: 74 ± 4 → Tilt: 105 ± 4 (Δ +31)

Duration of 70° tilt: 4.2 min

Max symptoms total: 12

Kumru et al., 2025	19	Objective: Determine if cervical TSES during occupational therapy (OT) improves respiratory muscle strength and pulmonary function in people living with cervical SCI better than OT alone Protocol: TSCS during OT for improving respiratory function vs. traditional OT. Each intervention being 2 weeks long	Location: C3/C4 & C6/C7 (cathodes) iliac crests (anode) Freq: 30 Hz + 10 kHz carrier freq. Width: 1 m.s⁻¹ Shape: biphasic, charge-balanced rectangular (anodic first) Amp: 90% of RMT of ABP muscle Stimulator: BioStim-5 (Cosyma Inc., Moscow, Russia)	*Note: absolute values not reported except FVC* MIP (cmH₂O): TSCS: 9.5 (9.1) Controls: 0.7(12.1), $p = 0.008$ MIP%: TSCS: 10.1% (16.4) Controls: 0.8% (10.7), $p = 0.01$ MEP (cmH₂O): TSCS: 10.1(16.4) Controls: 0.8(10.7), $p = 0.01$ MEP%: TSCS: 6.1% (6.1) Controls: 0.5% (4.1), $p = 0.01$ FVC(L): Pre-tSCS: 2.5 ± 0.9 vs. Post-tSCS: 2.7 ± 1.0, $p = 0.01$ Pre-control: 2.1 ± 0.5 vs. 2.2 ± 0.6, $p = 0.46$ Other spirometry variables: no significant changes
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Samejima et al., 2025	60	Objective: Determine if cervical TSES in combination with upper extremity rehabilitation alters cardiovascular regulation in people with a chronic cervical SCI Protocol: 2 phase study: Phase 1: upper extremity rehab alone Phase 2: TSCS + upper extremity rehab	Location: one segment above & one segment below NLI (cervical level; cathode), iliac crests (anode) Freq: 30 Hz burst + 10 kHz carrier freq. Width: 1 m.s⁻¹ Shape: biphasic (83% of sessions) or monophasic Amp: 52.4 +/-31.0 mA (biphasic), 39.3+/- 25.5 mA (monophasic) Stimulator: ARCEX Therapy system (ONWARD Medical; earlier generation)	Systolic Blood Pressure (mmHg) Rehab only: Pre: 112.7 ± 17.8 Mid: 110.7 ± 18.0 Post: 112.2 ± 19.0 TSCS + rehab: Pre: 111.5 ± 17.7 Mid: 112.1 ± 18.6 Post: 113.2 ± 19.8 No effect seen in SBP, $p = 0.088$ Diastolic Blood Pressure (mmHg) Rehab only: Pre: 68.9 ± 11.6 Mid: 68.3 ± 11.3 Post: 69.3 ± 11.6 TSCS + rehab: Pre: 68.2 ± 10.7 Mid: 69.0 ± 11.1 Post: 69.5 ± 11.8 No effect seen in DBP, $p = 0.112$ Heart Rate (bpm) Rehab only: Pre: 71.2 ± 11.2 Mid: 71.2 ± 11.3 Post: 69.0 ± 10.6
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			TSCS + rehab: Pre: 71.6 ± 11.3 Mid: 70.1 ± 11.7 Post: 68.8 ± 11.1
			No effect seen in HR, $p = 0.259$
Lau et al., 2026	1	Objective: Describe the feasibility and effectiveness of a commercially available NMES device adapted for TSES to manage orthostatic hypotension in a patient with complete SCI Protocol: Participant was seated in an upright position (90°) Stimulation was initiated when BP fell below 90/60mmHg with symptoms of OH. 30 min sessions for a total of 9 sessions Location: T8 & L1 (cathodes), umbilical region (anode) Freq: 100 Hz Width: 450 us Shape: NR Amp: started at 10 mA and increased up to 90 mA (until a SBP of 100-110 was reached) Stimulator: NeuroTrac MultiTENS (commercial NMES device)	*Values reported as median* Supine (pre-stimulation): SBP: 107 mmHg (IQR 92.0–113.5) DBP: 68 mmHg (IQR 56.5–82.0) HR: 61 bpm (IQR 59.0–62.5) Sitting (pre-stimulation): SBP: 77 mmHg (IQR 69.5–84.0) DBP: 46 mmHg (IQR 42.0–53.0) HR: 72 bpm (IQR 65.0–75.0) 1 min after stimulation: SBP: 102 mmHg (IQR 96.5–108.5) DBP: 64 mmHg (IQR 60.5–68.0) HR: 63 bpm (IQR 61.0–67.0) End of stimulation: SBP: 80 mmHg (IQR 67.0–84.5) DBP: 47 mmHg (IQR 38.0–51.5) HR: 69 bpm (IQR 63.0–75) Median values of SBP, DBP, & HR during supine, sitting, 1 minute after stimulation, and end of stimulation were statistically significant; $p = 0.001$

ABP: abductor pollicis brevis; BFV_{MCA} : blood flow velocity in the middle cerebral artery; BFV_{PCA} : blood flow velocity in the posterior cerebral artery; CV-TSCS: cardiovascular optimized transcutaneous spinal cord stimulation; CO: cardiac output; DBP: diastolic blood pressure; HR: heart rate; MAP: mean arterial pressure; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; NMES: neuromuscular electrical stimulation; POC: progressive orthostatic challenge; OH: orthostatic hypotension; OT: occupational therapy; RER: respiratory exchange ratio; RMT: resting motor threshold; RPE: rating of perceived exertion; SBP: systolic blood pressure; SV: stroke volume; $\dot{V}E$: minute ventilation; $\dot{V}O_2$ peak: peak oxygen consumption. [§]In this study, the able-bodied (control group) was age and sex matched to SCI participants.

Effects of TSES on cardiovascular, respiratory, & autonomic outcomes

The eight studies that met the inclusion criteria examined the effects of TSES on a wide range of cardio-autonomic variables. Two studies (25%) (Engel-Haber et al., 2024; Samejima et al., 2025) examined the effects of TSES on resting cardiovascular function. A single study (12.5%) (Hodgkiss et al., 2024) examined peak exercise performance, including respiratory variables (e.g., maximal oxygen uptake, minute ventilation), while another study (12.5%) (Kumru et al., 2025) focused on resting respiratory function. Four of the eight studies (50%) (Engel-Haber et al., 2025; Lau et al., 2026; Phillips et al., 2018; Solinsky et al., 2024) focused on responses to autonomic reflex challenges, including orthostatic challenge. However, Solinsky et al. (2024) also conducted cold pressor and Valsalva maneuver tests. Considerable heterogeneity was observed across experimental objectives and protocols, including postural transitions, cardiovascular-optimized TSES mapping, exercise testing, and long-term rehabilitation interventions. Findings across studies were variable, with generally consistent findings of improved blood pressure regulation (mitigation of hypotension), but greater heterogeneity among HR and other cardiovascular outcomes.

Systolic Blood Pressure, diastolic blood pressure, and mean arterial pressure outcomes

Findings regarding SBP were consistent in 5/7 studies (71%), such that TSES increased resting SBP significantly (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Hodgkiss et al., 2024; Lau et al., 2026; Phillips et al., 2018), which was regarded as beneficial since the participants had resting hypotension. In contrast, one study (14%) reported no effect of TSES on SBP during an upper extremity rehabilitation program (Samejima et al., 2025). An additional study (14%) reported substantial increases in SBP in all participants ($n = 2$), sufficient enough to classify them as bouts of AD, when TSES was administered during a foot cold pressor test

(Solinsky et al., 2024). Phillips et al. (2018) and Hodgkiss et al. (2024) did not report numerical values, limiting interpretation of the magnitude of change.

Findings for the effect(s) of TSES on DBP were also consistent across studies such that 4/5 studies (80%) (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Lau et al., 2025; Phillips et al., 2018) reported that TSES either stabilized or improved DBP. Samejima et al. (2025) reported no effect of TSES on DBP. Phillips et al. (2018) did not report absolute values for observed changes but reported resting BP and that TSES normalized MAP (reduced orthostatic hypotension) during progressive orthostatic challenge (POC).

Limited information on the effect(s) of stimulation on MAP was reported. One study obtained baseline MAP measurements that were not reported, followed by a battery of autonomic tests that showed mixed findings (Solinsky et al., 2025). At least three supine Valsalva maneuvers were performed during which TSES was not observed to affect MAP during phase 2. The supine hand cold pressure test was also performed, and no meaningful differences were observed compared with TSES. However, when phenylephrine was combined with TSES in the supine position, those living with SCI experienced a substantial increase in MAP across all stimulation frequencies, with no effect observed in controls. A supine foot cold pressor test in 0°C water was the final autonomic assessment. During this test, MAP reached thresholds classifiable for AD every time TSES was applied; however, only the change in MAP was reported, therefore limiting interpretation.

Heart Rate

Findings regarding the effect(s) of TSES on HR were mixed. Four studies (50%) (Engel-Haber et al., 2024; Hodgkiss et al., 2024; Phillips et al., 2018; Samejima et al., 2025) found no effect of TSES on HR during rest, orthostatic challenge, CPET_{max} testing, or two weeks post-

TSES upper-extremity rehabilitation. Absolute numerical values were not reported by Phillips et al. (2018) or Hodgkiss et al. (2024) (25%) and were expressed as proportional changes from baseline, limiting interpretation. Two studies (25%) (Lau et al., 2026; Engel-Haber et al., 2025) reported improvements in HR responses during postural transitions. Lau et al. (2026) observed that 1 minute after stimulation while seated, HR improved (reduced tachycardic response), returning HR to resting supine levels. These effects appeared transient, diminishing after stimulation was complete. Long-term effects were limited, as HR responses returned to baseline within 6 weeks.

Cardiac function and additional hemodynamic variables

Evidence for SV, CO, cardiac contractility, and TPR was limited across the eight included studies. Based on monitoring the resting effects of TSES, Hodgkiss et al. (2024) reported that TSES should improve predicted SV, cardiac contractility, total peripheral resistance (TPR), and peak oxygen pulse, suggesting improved cardiovascular performance during exercise. During exercise, observations of an increase in time to exhaustion in their study ($n=2$) was reported (Hodgkiss et al., 2024). Phillips et al. (2018) conducted supine-to-sit maneuvers and reported no effect on SV, with improvements in CO and cardiac contractility (restoration to baseline levels when supine). Neither study (Hodgkiss et al., 2024; Phillips et al., 2018) reported absolute values, indicating only proportional changes from baseline, therefore limiting interpretation of these findings. Cerebral artery blood flow velocity was assessed using a transcranial Doppler in one study (Phillips et al., 2018) where TSES was reported to normalize MCAv and PCAv during a tilt test, but absolute values were not reported.

Orthostatic intolerance and exercise performance

Two studies tested the effects of TSES on blood pressure regulation during postural transitions (Phillips et al., 2018; Engel-Haber et al., 2025). Results from these studies show that both acute (Phillips et al., 2018) and long-term (Engel-Haber et al., 2025) TSES improved symptoms of OI and increased the duration of upright positioning tolerance. Acute TSES (one session) nearly eliminated symptoms during sitting, while longer-term stimulation (six sessions over 2 weeks) reduced symptom burden and improved tilt duration, allowing the participant to complete the tilt test (30 mins) up to one day after the intervention was discontinued (Engel-Haber et al., 2025). These effects were not sustained long-term, with symptoms and tilt tolerance returning to baseline levels 6 weeks post-intervention (Engel-Haber et al., 2025). Aside from orthostatic outcomes, Hodgkiss et al. (2024) reported a prolonged time to exhaustion during steady-state exercise and reduced ratings of perceived exertion during cardiovascular optimized transcutaneous spinal cord stimulation (CV-SCS) compared with sham spinal cord stimulation (sham-SCS).

Respiratory outcomes

Research investigating respiratory outcomes was limited, with only two studies examining respiratory outcome measures. Hodgkiss et al. (2024) reported that TSES had no effect on minute ventilation and peak oxygen uptake during incremental tests to exhaustion. Kumru et al. (2025) examined the effects of a two-week TSES occupational therapy (OT) program and reported significant improvements in maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), percentage of maximal inspiratory pressure (MIP%), percentage of maximal expiratory pressure (MEP%) and forced vital capacity (FVC). Other spirometry measures, including forced expiratory volume in one second (FEV1), peak expiratory flow

(PEF), and forced expiratory flow (FEF) at 25%, 50%, and 75% of exhaled volume, were not improved with TSES (Kumru et al., 2025).

Adverse effects

Two out of eight articles (25%) (Phillips et al., 2018; Engel-Haber et al., 2024) did not comment on any TSES-related adverse events. Another two studies (25%) reported no adverse events related to TSES (Hodgkiss et al., 2024; Kumru et al., 2025). The remaining four articles (50%) reported minor adverse events such as mild AD (not requiring medical intervention), back muscle spasms, and redness at the TSES stimulation site (Table 4.4).

Table 4.4 Adverse events reported in the current body of TSES literature, looking at cardiorespiratory and autonomic outcomes.

Study/year	Sample size	AIS Classification, <i>n</i>	Level of Injury	TSES Parameters	Adverse Events
Phillips et al., 2018	5	AIS A: 3 AIS B: 2	C5-T2	Location: T8 Freq: 30 Hz Width: 1 ms Shape: Monophasic Amp: Increased from 10 mA to a max of 70 mA Stimulator: Not reported	None reported
Engel-Haber et al., 2024	8	AIS A: 4 AIS B: 3 AIS C: 1	C3-C7	Locations: C3/4, C4/5, C5/6, C6/7, C7/T1, T11/12, L1/2 & S1/2 Freq: 30 Hz, 5 kHz carrier freq. Width: 1 ms Shape: Monophasic rectangular Amp: raised to a max of 120 mA in 5 mA increments Stimulator: NeoStim-5 (Cosyma Inc., Moscow Russia)	None reported
Hodgkiss et al., 2024	7	AIS A: 5 AIS B: 2	C6-T4	Location: ESCS P1: T10-T12 ESCS P2: T11-L1 TSCS P1&P2: T11-L1(cathode), iliac crests (anodes) Freq: ESCS P1: 30 Hz ESCS P2: 300 Hz TSCS P1 & P2: 30 Hz + 10 kHz carrier freq. Width:	No adverse events related to the exercise protocol, ESCS or TSCS. (One skin lesion due to wheelchair friction unrelated to intervention)

				ESCS P1: 500 us ESCS P2: 380 us TSCS P1 & P2: 1 ms Shape: Charged-balanced monophasic rectangular waveform Amp: ESCS P1: 6.1 mA ESCS P2: 3.6 mA TSCS P1: 39 mA TSCS P2: 78 mA Stimulator: ESCS: Verita Neuro (ESCS P1); Tripole™ and Proclaim elite™, Abbott (ESCS P2)]. TSCS: constant current stimulator (TESCoN, SpineX Inc., California, United States)	
Solinsky et al., 2024	4 (2 with SCI, 2 AB controls)	AIS A:2	T3-T5	Location: T10-T11 (cathode), bilateral iliac crests (anodes) Freq: 120 Hz, 30 Hz, & 30 Hz with a 5 kHz carrier freq. Width: NR* Shape: biphasic Amp: 80% of motor threshold Stimulator: Constant current stimulator (Digitimer DS8R) Waveform generator (RIGOL DG1022)	AD was reported to have occurred in every SCI participant during the foot cold pressure test with TSES. No severe or medically emergent events reported

Engel-Haber et al., 2025	1	AIS A	C4	Location: T7-T8 & L1/L2 Freq: 30 Hz with a 5 kHz carrier freq. Width: 1 ms Shape: monophasic rectangular Amp: up to 80 mA (thoracic) & up to 150 mA (lumbar) Stimulator: NeoStim-5 (Cosyma Inc., Moscow, Russia)	Redness at the TSES stimulation and EMG sites (expected by researchers)
Kumru et al., 2025	19	AIS A: 4 AIS B: 5 AIS C: 5 AIS D: 5	C3-T1	Location: C3/C4 & C6/C7 Freq: 30 Hz with a 10 kHz carrier waveform. Width: 1 ms Shape: biphasic, charge-balanced rectangular (anodic first) Amp: 90% of RMT of ABP muscle Stimulator: BioStim-5 (Cosyma Inc., Moscow, Russia)	No TSES related adverse events
Samejima et al., 2025	60	AIS B: 9 AIS C: 28 AIS D: 23	C2-C7	Location: one segment above & one segment below NLI (cervical) Freq: 30 Hz burst with a 10 kHz carrier freq. Width: 1 ms Shape: biphasic (83% of sessions) or monophasic Amp: 52.4 +/-31.0 mA (biphasic), 39.3+/- 25.5 mA (monophasic) Stimulator: ARCEX Therapy system (ONWARD Medical; earlier generation)	4 incidents of AD in 2 participants, all mild. Only 2 possibly related to TSCS No severe cardiovascular adverse events.

Lau et al., 2026	1	AIS A	C5	Location: T8 & L1 (cathode), umbilical region (anode) Freq: 100 Hz Width: 450 us Shape: NR Amp: started at 10 mA and increased up to 90 mA (until a SBP of 100-110 was reached) Stimulator: NeuroTrac MultiTENS (commercial NMES device)	Patient reported occasional self- limiting back muscle spasms (resolved without any intervention) No other adverse events occurred
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AIS: American spinal injury association impairment scale; TSES: transcutaneous spinal electrostimulation; freq: frequency; Amp: amplitude; NR: not reported; ESCS: epidural spinal cord stimulation; TSCS: transcutaneous spinal cord stimulation; AD: autonomic dysreflexia; EMG: electromyography.

Risk of bias assessment

The risk of bias varied across studies, reflecting differences in study designs, and concerns regarding internal validity were identified in 5/8 studies (62.5%). Limitations related to internal validity and bias regarding study blinding, and selection and allocation of participants was identified in the randomized control trials (RCT's) and quasi-experimental studies. It was unclear whether the case studies used consecutive recruitment (continuous recruitment in a set time frame) or completed testing of all enrolled participants (complete inclusion).

Table 4.5 Quality Assessment score of JBI Risk Assessment among TSES studies assessing cardio, autonomic and respiratory outcomes.

Study/Year	Study Type	JBI Critical Appraisal	Quality of Bias
		Tool used	Assessment Score
Phillips et al., 2018	Experimental within-subject design	JBI Checklist for Quasi-Experimental Studies (2023)	7/9
Engel-Haber et al., 2024	CSr	JBI Checklist for Case Series (2023)	8/10
Hodgkiss et al., 2024	CSr with crossover comparison	JBI Checklist for Case Series (2023)	7/10
Solinsky et al., 2024	Single-blinded randomized crossover study	JBI Checklist for Quasi-Experimental Studies (2023)	9/9

with matched pair design			
Engel-Haber et al., 2025	CS	JBI Checklist for Case Reports (2020)	8/8
JBI Critical Appraisal Tool			
Kumru et al., 2025	RCT with partial crossover design	for Assessment of Risk of Bias for Randomized Controlled Trials (2023)	10/13
Lau et al., 2026	CR	JBI Checklist for Case Reports (2020)	8/8
JBI Checklist for Quasi-			
Samejima et al., 2025	Secondary analysis of a prospective single-arm study	Experimental Studies (2023)	8/9

CR: case report; CS: case study; CSr: case series

4.4 Discussion

This systematic review aimed to i) provide an updated and comprehensive synthesis of the current literature regarding cardio-autonomic and respiratory effects of TSES in individuals living with SCI; ii) compile and report the documented adverse events within the current body of literature examining cardio-autonomic and respiratory parameters; and iii) assist researchers by synthesizing knowledge that may be used develop strategies aimed at enhancing exercise capacity and cardiorespiratory fitness in individuals living with SCI. Overall, findings from 5/8 studies, involving 22 participants, suggest that TSES could normalize blood pressure regulation, particularly in those with impaired BP regulation and injury above T5. However, findings related

to the effects of TSES on respiratory outcomes, HR, and other cardiovascular outcomes remain inconsistent.

Initially, the focus of TSES was on the management of spasticity (Hofstoetter et al., 2014), motor control to improve arm and hand function (Freyvert et al., 2018), and lower-limb function and gait (Gerasimenko et al., 2015). More recently, researchers have been testing whether TSES can also be used to alter autonomic and cardiorespiratory functions, including cardiorespiratory fitness (CRF) and exercise capacity (EC). The earliest study investigating the effect(s) of TSES on these outcomes was published in 2018 (Phillips et al., 2018), and since then, five research groups have published seven articles, each with different protocols (all eight of these studies have been included in this review). However, the current body of literature is quite small and limited to case reports, case studies, case series, and pilot studies, which often rely on anecdotal evidence and use small sample sizes.

In all studies, research samples were small and predominantly male, limiting the generalizability of findings. Although these samples likely reflect the higher prevalence of males in the SCI population, future research should include more female participants to diversify samples. It is well understood that research in the SCI population is often limited in sample size due to many factors (e.g. difficulty recruiting, drop out due to health concerns, physical limitations, lack of interest). Sample sizes may be further reduced by additional exclusion criteria (e.g. requiring an injury duration of at least one year, or medical stability). Injury severity and neurological level of injury may also further restrict the ability of participants to complete the required protocol (physical limitations), which could further limit participant diversity.

Blood pressure modulation

Currently, it is unknown what TSES parameters are effective for improving autonomic function as it pertains to cardiorespiratory outcomes. During rest, CV-TSCS mapping, PTs and exercise, several studies (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Hodgkiss et al., 2024; Lau et al., 2026; Phillips et al., 2018) reported improvements in SBP, suggesting that TSES may improve blood pressure regulation. However, one study (Solinsky et al., 2024) compared increases in SBP in response to autonomic reflex testing (foot cold pressor test) during TSES in controls and two participants with SCI and reported greater increases in SBP in those with SCI, concluding that their exaggerated responses were a form of autonomic dysreflexia (AD). While reports of increased SBP in the SCI group were much larger than their neurologically intact controls (change of 27.7 ± 4.5 mmHg), and consistent with AD thresholds, changes in SBP were dependent on stimulation frequency, with 120 Hz showing the greatest change, whereas 30 Hz, with a 5 KHz elicited similar responses in both groups. Furthermore, given the small sample size ($n = 2$), these findings should be interpreted with caution. An additional study (Samejima et al., 2025) found no effect on DBP. Samejima et al. (2025) applied stimulation in the cervical vertebral region, which has not yet been shown as effective in modulating SBP. Perhaps stimulation at more caudal regions that target the lumbar enlargement (as seen in other studies) would elicit a response by potentially activating V3 neurons eliciting a sympathetic spinally mediated reflex response to increase DBP via vasoconstriction.

Findings for DBP were consistent across studies, as 4/5 studies that investigated DBP reported normalization of DBP responses. One study (Samejima et al., 2025) found no effect on DBP; however, this is likely attributed to the stimulation location selected being too high on the vertebral column. Two studies (Phillips et al., 2018; Solinsky et al., 2024) looked at MAP,

however, the results were mixed, which may be attributed to the variation in participant characteristics and/or stimulation parameters as well as the variability in experimental protocols as Phillips (2018) conducted a progressive orthostatic challenge (POC) and Solinsky et al. (2024) conducted autonomic testing (Valsalva maneuver, hand and foot cold pressure tests).

Additional hemodynamic variables

HR findings were heterogeneous as short-term normalization of tachycardia was observed in two studies (Engel-Haber et al., 2025; Lau et al., 2026). However, four additional studies with varying protocols observed no effect on HR (Engel-Haber et al., 2024; Hodgkiss et al., 2024; Phillips et al., 2018; Samejima et al., 2025). Samejima et al. (2025) tested cervical stimulation, which did not alter any cardiovascular variable. Phillips et al. (2018) utilized a more caudal location of T8, where observations of restored CO and cardiac contractility were noted. SV appears to have remained diminished with TSES. Therefore, it may be possible that the decreased SV increased the need for a compensatory HR response (elevated HR), which is why HR was increased upon TSES. This relationship may also explain why Hodgkiss et al. (2024) observed no effect on HR with increased peak O₂ pulse (an indication of improved SV). Engel-Haber et al. (2024) did not explicitly measure SV or systemic vascular resistance (SVR), and no effect on HR was observed. It is plausible to speculate that TSES either increased SV or SVR or maybe both to achieve the observed increases in SBP and DBP. Unfortunately, since these measures were not taken, there is no evidence to explain why HR was not affected or how blood pressure improved within this sample.

Autonomic function

TSES appears to improve orthostatic intolerance (OI), particularly in short-term symptomology, where acute improvements were consistently reported. Improvements were

maintained up to one day post-intervention (six, 30-minute seated CV-TSES sessions; Engel-Haber et al., 2025). However, long-term effects are limited as effects were abolished by the 6-week follow-up. TSES would therefore need to be applied intermittently to maintain any positive effects. Evidence regarding exercise performance is limited but promising, as a single study conducted by Hodgkiss et al. (2024) observed improvements in time to exhaustion and RPE. These findings are consistent with case reports from epidural stimulation studies, which demonstrated safe and effective improvements in exercise capacity in a participant with motor complete tetraplegia (Nightingale et al., 2019).

Respiratory function

Evidence supporting the use of TSES for improving respiratory outcomes remains limited, with only two studies and mixed results. A single study examined improvements in respiratory outcomes such as MIP, MEP, and FVC, only when TSES was combined with OT (Kumru et al., 2025). No effects of TSES were reported regarding respiratory outcomes such as forced expiratory flow at 25% exhaled volume (FEF25) and forced expiratory flow at 50% exhaled volume (FEF50) (Kumru et al., 2025). An additional study (Hodgkiss et al., 2024), found no effect of TSES on $\dot{V}E$ or $\dot{V}O_2$ peak; however, these findings should be interpreted with caution due to the small sample size ($n = 2$), limiting statistical power and the ability to detect significant changes in the data.

Reported adverse events

Our findings suggest that TSES appears to be well tolerated, with most studies reporting minimal or no serious adverse events. Reported adverse events were generally mild and transient in nature, including skin irritation, muscle spasticity and AD that all resolved on their own. However, reporting of adverse events was inconsistent, as two studies did not report any adverse

events, and the remaining studies did not describe monitoring procedures or the documentation process, raising concerns of possible underreporting. Additionally, 7/8 studies (87.5%) reviewed had small sample sizes, which limits our understanding of TSES safety. Long-term consequences of TSES also remain unknown, as there is currently no literature looking at long-term use of TSES.

Proposed physiological mechanisms

Studies reporting a beneficial effect of TSES on hemodynamic variables (SBP, DBP, MAP, HR, SV), orthostatic intolerance, and exercise performance most commonly applied stimulation at T11-L2, which coincides with the lumbar enlargement. The precise mechanism of action is currently unknown. However, researchers have generated hypotheses regarding the potential mechanism of action. One proposed mechanism is that TSES increases the excitability (i.e. increases resting membrane potential) of intact lower motor neurons (LMNs) at and below the level of injury, thereby allowing previously ineffective descending signals to activate these LMNs and elicit autonomic responses that had been absent (Smith et al., 2020; Taylor et al., 2021; Tefertiller et al., 2022). Alternatively, it has been suggested that TSES may act by enhancing the excitability in dorsal root afferents, spinal interneurons, and, in some cases, motoneurons below the lesion, thereby facilitating either reflex afferent-evoked or weak descending command signal-evoked responses that are otherwise absent without spinal stimulation (Angeli et al., 2014; Flett et al., 2022; Hofstoetter et al., 2018; West et al., 2018). Stimulation of spinal afferents may activate a reflexive release of catecholamines via the adrenal gland, causing vasoconstriction and potentially increasing cardiac preload. Increased cardiac preload may increase stroke volume (Frank-Starling mechanism) and therefore CO. Consequently, blood pressure may be increased, and greater oxygenation of working tissues and

the brain could be achieved, delaying fatigue during exercise and mitigating orthostatic intolerance symptoms during POC.

4.5 Strengths and limitations

To the best of our knowledge, this is the first systematic review to synthesize the current literature on TSES and its effects on cardio-autonomic and respiratory function in those living with SCI. Cardio-autonomic and respiratory outcomes were chosen as our area of focus, as there is limited research on these outcomes as it pertains to TSES, making this review a relevant tool for understanding the current state of findings. Our inclusion criteria allowed for the inclusion of diverse protocols (postural transitions, blood pressure mapping, exercise, autonomic testing) and study designs, enhancing the breadth of knowledge across a variety of testing approaches and characterizing the level of rigour currently present in the existing literature. Additionally, we included a rigorous methodology by following the PRISMA guidelines and conducting quality assessments using the JBI Critical Appraisal Tool to convey our findings with the utmost certainty. However, limitations should be considered. This review was restricted to cardiorespiratory outcomes and, therefore, does not capture the physiological effects of other bodily systems. The exclusion of studies not published in English may introduce language bias, while omitting those involving individuals under 18 years of age limits the generalizability of the findings to pediatric populations. Furthermore, the exclusion of animal models may have limited our understanding of emerging mechanistic insights that have not yet been studied in humans.

4.6 Recommendations for future research and the clinical implications of TSES

Future research should address several key gaps in the current body of literature. A greater inclusion of female participants is needed to improve the generalizability of findings, as existing studies are predominantly conducted in male populations. Additionally, improved

reporting practices are needed, with studies providing both baseline and post-intervention absolute numerical values in tables rather than only reporting change scores or graphs. This will enhance transparency of findings and assist with improving comprehension of changes. Standardization of TSES parameters and adverse events should be implemented to better characterize the efficacy and safety of TSES. Additionally, the use of more rigorous study designs, such as RCTs, would strengthen findings.

High-quality research in this area has important implications for clinical practice, particularly in the development of evidence-based guidelines for health professionals, including clinicians, physiotherapists, and exercise physiologists (health professionals who work with clinical populations to improve exercise outcomes and prevent secondary health complications via exercise). These clinical guidelines could assist these professionals in identifying those with SCI most likely to benefit from TSES. Additionally, these guidelines could assist with treatment parameters by identifying effective stimulation sites and parameters for modifying cardiorespiratory outcomes. Emerging evidence may also support a more individualized approach, where guidelines serve as a foundation that can be adapted based on individual responses. Advancement of evidence-based clinical practice regarding TSES is needed so clinicians may work with people living with SCI to tackle improving cardiovascular health and reduce the risk for adverse cardiac events, such as heart attacks or ischemic strokes, often seen in this population. Additionally, exercise professionals (e.g. kinesiologists and exercise physiologists) could use TSES as a tool to assist those living with SCI to improve their exercise capacity and cardiorespiratory fitness by optimizing training effects.

4.5 Conclusions

This systematic review synthesizes the current literature examining the effects of TSES on cardio-autonomic and respiratory function, highlighting the most effective stimulation parameters, as well as reported adverse events. While current research has shown normalization of cardiovascular variables and improvements in respiratory outcomes that assist researchers in understanding how to develop strategies to enhance exercise capacity and cardiorespiratory fitness, these findings should be interpreted with caution. Studies reviewed in this systematic review used small, predominantly male samples, with heterogeneous protocols and methodological limitations, including the predominance of case reports/studies, case series, and pilot studies, as well as insufficient reporting of TSES parameters and associated adverse events, limiting generalizability.

Currently, much of the research in this area is exploratory. Future research requires analysis of potential mechanisms of action, standardization of protocols and outcome reporting, increased inclusion of female participants, and the conduction of stronger study designs (e.g. randomized control trials) to synthesize a high-quality body of evidence. High-quality research is critical for informing clinical guidelines and supporting clinicians, physiotherapists, exercise physiologists, kinesiologists and other health professionals in identifying optimal stimulation parameters to modify cardiorespiratory outcomes, as well as the individuals most likely to benefit from these interventions.

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5. CHAPTER 5: EXPERIMENTAL STUDY

Effects of Transcutaneous Spinal Electrostimulation on Exercise Capacity and Oxygen Uptake

Kinetics in People Living With Spinal Cord Injury

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Abstract

Background. Autonomic and cardiovascular dysfunction, sedentary behavior, chronic inflammation and deficits in oxygen delivery increase cardiovascular disease (CVD) risk after SCI. However, autonomic dysregulation caused by inadequate or inappropriate activation of spinal neural regulatory circuitry is the primary cause of increased CVD risk rather than physical inactivity. Transcutaneous spinal electrostimulation (TSES) is a non-invasive intervention that may improve cardioautonomic regulation by modulating acute spinally mediated cardiovascular responses. Currently, the effects of TSES on cardiorespiratory function and dynamic measures of aerobic performance such as $\dot{V}O_2$ on-kinetics remain poorly understood. **Objectives.** To compare the effects of TSES versus no TSES on $\dot{V}O_2$ on-kinetics during constant workload exercise (CWL). **Methods.** Fourteen individuals with SCI were recruited (7 tetraplegic, 7 paraplegic, with SCI at or below C4/5, aged 18-75 y, and ≥ 1 -year post-SCI) plus seven healthy, age-, sex-, and height-matched neurologically intact (NI) references, to the tetraplegic group. Participants performed two $\dot{V}O_2$ peak tests and one CWL test with at least 48 hours between each test to prevent carryover effects. The two peak tests determined each participant's power output (PO) for the CWL exercise test (40-45% of the PO at peak $\dot{V}O_2$), and consisted of four bouts of exercise, each 5 minutes long (two bouts with TSES, and two without TSES). $\dot{V}O_2$ on-kinetics, consisting of the primary variable mean response time (MRT), and secondary variables time constant (τ), time delay (TD), and amplitude, were measured. **Results.** Findings revealed that when TSES is applied at T12 using 20 Hz, 900 μ s and an intensity around motor threshold, $\dot{V}O_2$ on-kinetics was not significantly altered in those living with SCI or their NI references. Although TSES was well tolerated, an individualized approach may be required to optimize autonomic and cardiorespiratory outcomes in those living with SCI.

Keywords: spinal cord injury, transcutaneous spinal electrostimulation, oxygen uptake kinetics, exercise capacity, cardiorespiratory fitness, tetraplegia, paraplegia, able-bodied.

5.1 Introduction

Individuals with a SCI have roughly three times the prevalence of heart disease and around six times the prevalence of stroke compared to the general population (Cragg et al., 2013). This increased risk for CVD and stroke is not only attributed to a sedentary lifestyle or muscle paralysis, but to autonomic dysfunction, cardiovascular and pulmonary dysregulation, as well as inadequate oxygen delivery (Flett et al., 2022). These impairments contribute to slowed $\dot{V}O_2$ kinetics (Gollie et al., 2017), resulting in low cardiorespiratory fitness (CRF) and exercise capacity (EC) (Deley et al., 2015; Mercier et al., 2020).

There is emerging evidence that electrical stimulation (ES), including transcutaneous spinal electrostimulation (TSES), may improve cardio-autonomic function in those with SCI and ultimately CRF (Harkema et al., 2018; Hodgkiss et al., 2024; Phillips et al., 2018). TSES is a non-invasive neuromodulatory device used to modulate spinal circuitry via increasing excitability in dorsal root afferents, spinal interneurons and, in some cases, motoneurons below the injury site, thereby facilitating either reflex afferent-evoked or weak descending command signal-evoked responses that are absent without spinal stimulation (Angeli et al., 2014; Flett et al., 2022; Hofstoetter et al., 2018). When applied at the level of the lumbar enlargement (~T12-L1), whole-body metabolic substrate use is altered, and ratings of perceived exertion during exercise are reduced in people with SCI (Carhart et al., 2004; Ganley et al., 2005; Herman et al., 2002). Other studies have shown that TSES can increase resting blood pressure (BP) without inducing leg muscle activity during exercise (Hodgkiss et al., 2024; Phillips et al., 2018). These findings suggest that the rise in BP may be mediated by spinal cord effects that increase sympathetic outflow, increase vasomotor tone, and promote vasoconstriction, thereby improving venous return (cardiac preload) and thus BP (Hodgkiss et al., 2024; Phillips et al., 2018).

Therefore, TSES may improve cardiorespiratory outcomes by increasing cardiac output (CO), leading to greater $\dot{V}O_2$ as per their relationship ($\dot{V}O_2 = CO \times [a-vO_2 \text{ difference}]$) (Magder, 2021).

Although the use of epidural spinal stimulation to improve exercise-related functions has been reported since the early 2000's (Carhart et al., 2004), the application of TSES for improving cardio-autonomic function after SCI is relatively new, with Phillips et al. (2018) being one of the first to investigate this relationship. Most studies to date have focused on lower extremity, upper extremity and trunk motor function, bladder function, spasticity, and neuropathic pain (Laskin et al., 2022) rather than CRF, EC, or $\dot{V}O_2$ kinetics. Existing literature investigating the effects of spinal stimulation on cardiorespiratory variables consists mainly of case reports, case series, or pilot studies that report anecdotal evidence or provide findings based on small sample sizes (Flett et al., 2022). Of these studies, only two (Hodgkiss et al., 2024; Kumru et al., 2025) examined the effects on respiratory outcomes, with neither exploring the effect on $\dot{V}O_2$ on-kinetics.

Additionally, most of these studies do not fully report their TSES stimulation parameters, and those that do often lack a clear rationale for parameter selection (Law et al., 2024). There is a substantial gap in the literature regarding the risks and safety associated with TSES applications, as no original studies on TSES have examined safety as a primary outcome (Laskin et al., 2022). Taken together, these limitations highlight the need for well-designed studies that investigate cardiovascular and cardiorespiratory responses using transparent, reproducible protocols.

To address these gaps, the primary aim of this study is to determine if TSES can improve $\dot{V}O_2$ on-kinetics during constant workload (CWL) arm crank exercise. A secondary aim is to compare $\dot{V}O_2$ on-kinetic parameters between individuals living with tetraplegia, paraplegia and those who are neurologically intact. A final aim is to characterize the safety of TSES. It is hypothesized that the application of lumbar TSES will result in shorter mean response time

(MRT), time constant (τ), and time delay (TD). A secondary hypothesis is that the use of TSES will be associated with a larger amplitude of $\dot{V}O_2$ response compared to the condition without TSES in people with tetraplegia. It is also hypothesized that individuals with tetraplegia will show longer mean response time (MRT), time constant (τ), and time delay (TD), as well as a smaller $\dot{V}O_2$ amplitude response when compared to age-, sex-, and height-matched neurologically intact controls, as well as those living with paraplegia. Additionally, the paraplegic group may demonstrate shorter mean response time (MRT), time constant (τ), and time delay (TD), compared to the neurologically intact participants, due to their familiarity with upper extremity exercise. Lastly, we hypothesize that TSES will be a safe neuromodulatory tool for those living with SCI.

5.2 Methods

Study Design

This study implemented a randomized, repeated measures, crossover design that followed the Consolidated Standards of Reporting Trials Statement (CONSORT 2010 statement: Extension to randomized crossover trials for randomized crossover design, Appendix B) (Dwan et al., 2019), as well as the Consensus on Exercise Reporting Template (CERT) for exercise intervention (Slade et al., 2016) (Appendix C) and the Sex and Gender Equity in Research Guidelines (SAGER, Appendix D) (Heidari et al., 2016). Considering the variability among participants with SCI (level of injury, AIS scale), a within-subject design was appropriate to determine individual responses to arm-crank exercise performed with or without TSES. In this design, stimulation condition (TSES vs. no stimulation) served as the within-subject factor, and group (tetraplegic, paraplegic, neurologically intact) served as the between-subject factor.

Settings

This study was conducted at the Spinal Cord Research Centre (SCRC) Human Lab in the Department of Physiology and Pathophysiology, located in the Basic Medical Science Building, Bannatyne Campus at the University of Manitoba, from January 2024 to April 2026. The laboratory temperature was controlled ($\sim 22^{\circ}\text{C}$), and humidity and barometric pressure were left ambient. Testing sessions were scheduled at similar times of day for each participant to minimize potential circadian cycle influences on physiological responses. This study was approved by the Health Research Ethics Board, Bannatyne Campus, at the University of Manitoba (approval # HS22987-H2019:279). All participants provided written informed consent prior to participation.

Participants

Participants were recruited through mailed invitations sent to clients of Spinal Cord Injury Manitoba (Inc.). Individuals who were interested in participating contacted our research team by email or phone. Following this initial contact, our research team conducted telephone screening to determine eligibility. Participants were included if they were between 18 and 75 years of age, at least 1-year post-injury (SCI participants) with an injury level of C5 or below, accompanied by an AIS classification of A-D, and were medically stable and sufficiently healthy to engage and complete protocol requirements. Participants were excluded if they had one or more ongoing serious upper-body injuries, pressure ulcer(s) that affect their ability to perform exercise tests, uncontrolled persistent hypertension ($> 140/90\text{mmHg}$) (i.e., not due to an acute bout of autonomic dysreflexia [AD]), known cardiovascular disease or an implanted electronic cardiac device (e.g., pacemaker, defibrillator), were classified as morbidly obese, were known to have thyroid dysfunction, were actively diagnosed with cancer, had uncontrolled epilepsy, had a history of deep vein thrombosis (DVT), were ventilator-dependent, had a cognitive impairment,

or if the SCI Fit arm crank ergometer was not accessible from their wheelchair. Fifty-eight participants were contacted by the researchers, of whom 32 were not included. Twenty-six participants were enrolled in the study, of whom 21 completed it (tetraplegic group [TP, $n = 7$], paraplegic group [PP, $n = 7$], and neurologically intact reference group [NI, $n = 7$]). Eight participants were not included due to their inability to exercise on the arm crank ergometer ($n = 3$), failure to pass health screening ($n = 1$), or participant withdrawal ($n = 1$) (Figure 5.1).

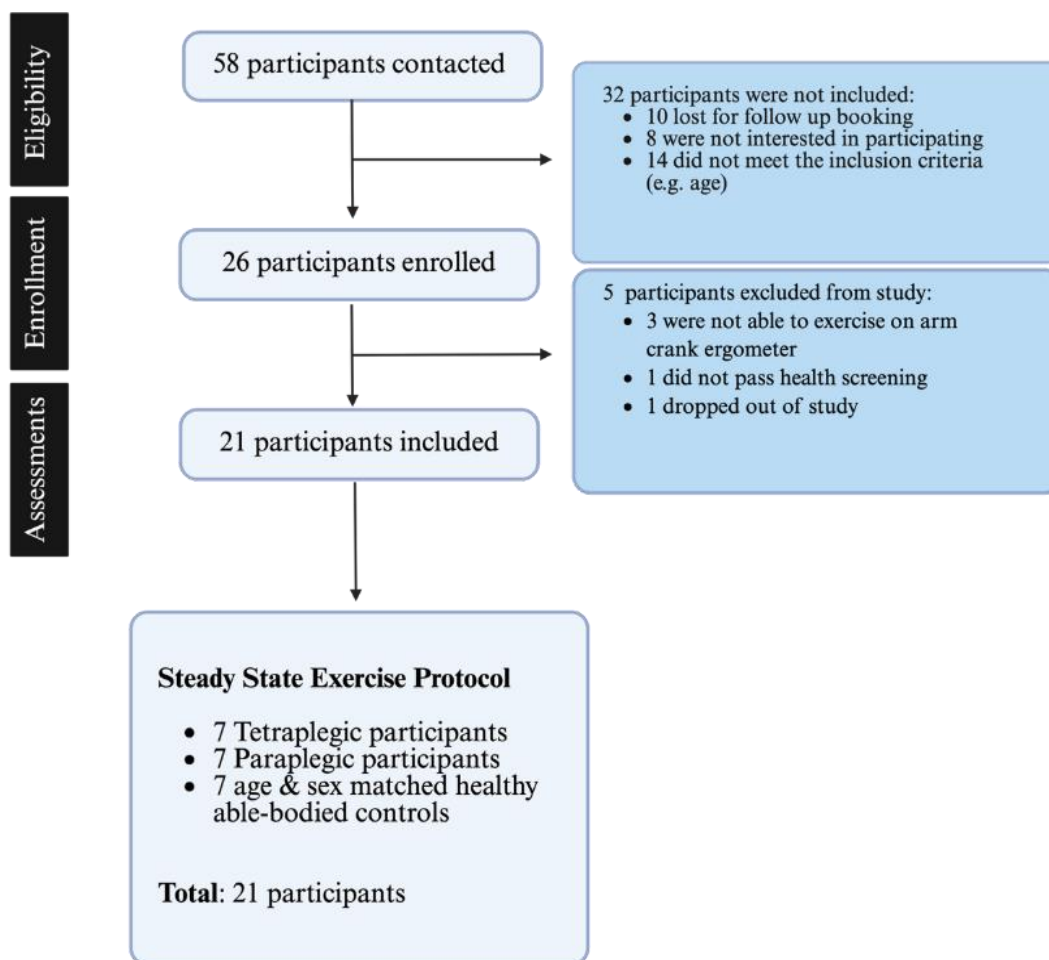


Figure 5.1 Participant Recruitment Flow Chart.

Participants visited the laboratory four times. In Visit 1, we confirmed inclusion criteria, obtained informed consent, collected personal information and anthropometric measurements, performed preliminary exercise tests, and conducted a sweat test. During visits 2 and 3, participants completed a maximal cardiopulmonary exercise test (CPET_{max}) either with TSES or without stimulation, with at least a 48-hour break between these visits. The order in which tests were completed with stimulation was randomized and counterbalanced. The CPET_{max} protocol consisted of an incremental exercise test to volitional exhaustion (~6-10 minutes total duration) on an arm-crank ergometer (SCI-FIT) at 60-70 rpm. The fourth and final visit was a constant workload exercise protocol (CWL), where participants completed four identical bouts, each bout lasting 5 minutes, with an intensity of 40-45% of the power output (W) at $\dot{V}O_2$ peak. Two of the four bouts were with TSES, and two were without stimulation (Figure 5.2, bottom panel). Stimulation was randomized for each exercise bout and counterbalanced using only two possible options (1: ON, OFF, ON, OFF; 2: OFF, ON, OFF, ON).

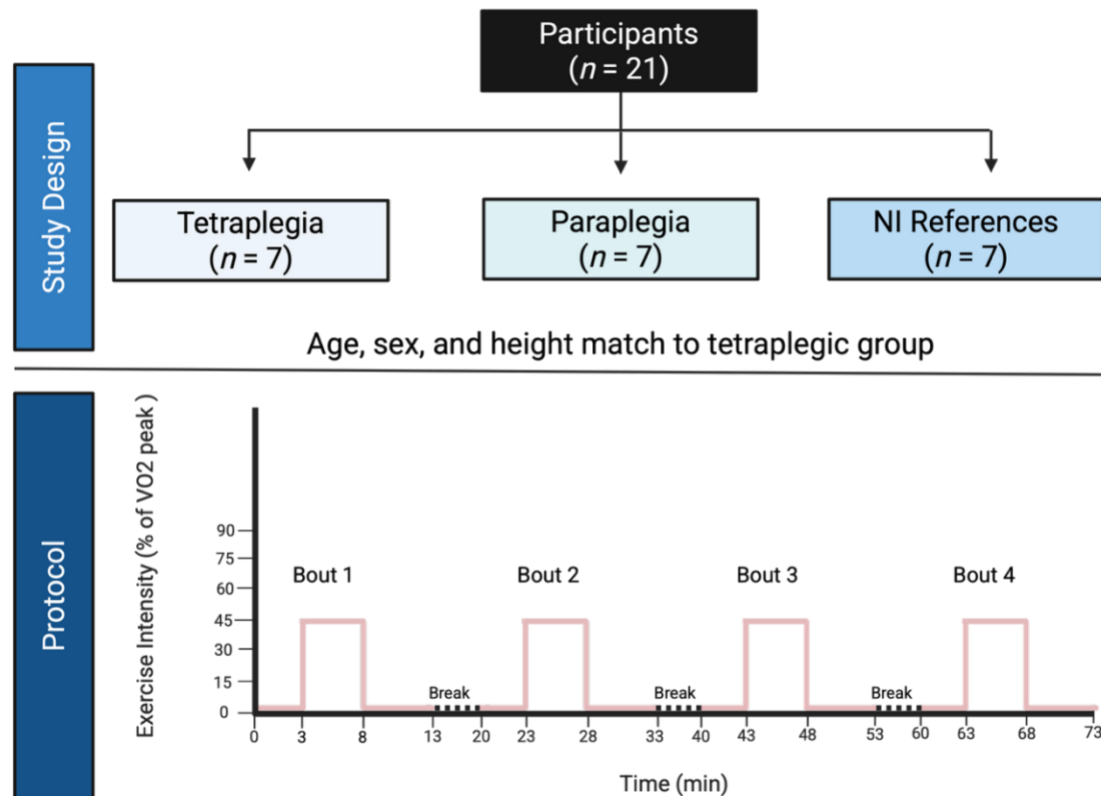


Figure 5.2 Study design (top panel) and protocol (bottom panel).

Data Acquisition

Researchers involved in data collection received standardized training before recruitment started. Due to the nature of the intervention, neither participants nor researchers were blinded to the conditions (TSES; without stimulation). The primary outcome measure was the mean response time (MRT) of pulmonary $\dot{V}O_2$ during the on-transient phase of CWL arm-crank exercise. Secondary outcome measures included the $\dot{V}O_2$ time constant (τ), time delay (TD), and amplitude (Amp) of the $\dot{V}O_2$ response.

Assessment of the Oxygen Uptake Kinetics

Breath-by-breath measurements of $\dot{V}O_2$ were recorded using a metabolic cart (Quark Cardiopulmonary exercise testing [CPET], COSMED, Rome, Italy). Before calibrating and operating the CPET system, the metabolic cart was turned on for ~20 minutes to equilibrate with

room conditions. The system was then calibrated according to the manufacturer's instructions for gas analyzers and flow measurements (COSMED, 2022).

Following calibration, participants' information, such as name, age, sex assigned at birth, race, body mass, and height, was saved in the database. An appropriately sized mask and head strap were selected and fitted to the participant's face. The facemask was tightened to form an airtight seal while ensuring it was comfortable enough for the participant. To assess whether an airtight seal was formed, participants or a member of our team (depending on functional capabilities) would cover the turbine opening with the palm of their hand and have the participant exhale forcefully. If no air leaked out the side of the facemask, an airtight seal was formed, and the two-way valve and turbine flowmeter were connected to the mask. This allowed the participants' breathing to be continuously monitored with the metabolic cart for subsequent data collection.

Transcutaneous Spinal Electrostimulation Parameters

TSES was applied rostro-caudally at T12 (vertebral level) unless otherwise indicated using a DS8R bipolar constant current stimulator with a biphasic waveform. Stimulation amplitude was set around motor threshold based on tolerance of stimulation, with a frequency of 20 Hz, and a pulse width of 900 μ s (Table 5.1), consistent with early work from Carhart et al. (2004) and Ganley et al. (2005). Stimulation was turned on at the start of each five-minute CWL exercise bout and was turned off after its completion.

Table 5.1 Transcutaneous Spinal Electrostimulation Parameters and associated Exercise Intensity.

Participant	(NLI)	Stim Parameters				
		AIS	Stim	[intensity (mA)/	PO	rpm
		Classification	Location	frequency (Hz)/pulse	(W)	
width (µs)]						
Participants Living with Tetraplegia						
01	C8	B	Rostral @T12	20 mA/ 20 Hz/ 900 µs	20	70
02	C5/6	C	Rostral @T12	12.5 mA/ 20 Hz/ 900 us	7	50
05	C7	B	Rostral @T12	10 mA/ 20 Hz/ 900 µs	30	70
08	C6/7	B	Rostral @T12	15 mA/ 20 Hz/ 900 µs	40	70
09	C6/7	A	Rostral @T12	35 mA/ 20 Hz/ 900 µs	20	70
13	Cervical injury (NLI unknown)	C	Rostral @T12	17 mA/ 20 Hz/ 900 µs	19	60
14	C5/6	C	Rostral @T12	27 mA/ 20 Hz/ 900 µs	30	70

Participant	(NLI)	Stim Parameters				
		AIS	Stim	[intensity (mA)/	PO	rpm
		Classification	Location	frequency (Hz)/pulse width (μs)]	(W)	
Participants Living with Paraplegia						
03	T1	C	Rostral @T12	20 mA/ 20 Hz/ 900 μs	10	70
04	T3	A	Rostral @T12	35 mA/ 20 Hz/ 900 μs	40	70
06	T12	B	Rostral @T11	10 mA/ 20 Hz/ 900 μs	18	60
07	T7	A	Rostral @T12	25 mA/ 20 Hz/ 900 μs	20	70
10	T12	D	Rostral @T10	25 mA/ 20 Hz/ 900 μs	30	70
11	L1-L3	D	Rostral @T11	15 mA/ 20 Hz/ 900 μs	45	70
12	L2-S1	D	Rostral @T12	10 mA/ 20 Hz/ 900 μs	25	70

Participant	(NLI)	AIS Classification	Stim Location	Stim Parameters		
				[intensity (mA)/ frequency (Hz)/pulse width (μs)]	PO (W)	rpm
				Age, Sex, and Height Matched Neurologically Intact Controls		
C01	-	-	Rostral @ T12	15 mA/ 20 Hz/ 900 us	30	70
C02	-	-	Rostral @ T12	10 mA/ 20 Hz/ 900 us	45	70
C05	-	-	Rostral @ T12	7.5 mA/ 20 Hz/ 900 us	45	70
C08	-	-	Rostral @ T12	15 mA/ 20 Hz/ 900 us	75	70
C09	-	-	Rostral @ T12	7.5 mA/ 20 Hz/ 900 us	40	70
C13	-	-	Rostral @ T12	15 mA/ 20 Hz/ 900 us	50	70
C14	-	-	Rostral @ T12	12.5 mA/ 20 Hz/ 900 us	60	70

Sample Size

Using GPower V3.0.10 (Dusseldorf, Germany), considering a medium effect size of 0.5, and repeated measures ANOVA with 95% power, and an alpha of 0.05, a total sample size of 21 (7 tetraplegic participants, 7 paraplegic participants, and 7 neurologically intact control participants) is needed to detect differences among the three groups exercising with or without stimulation. This is the assumed effect size, since the question addressed in this study is novel, but it will be sufficient to evaluate the needed group sizes and determine the effect size for future experiments using data compiled from this research study.

Data Analysis

Raw breath-by-breath $\dot{V}O_2$ data was exported from the metabolic cart and analyzed using a customized LabVIEW software (LabView v20.0.01, National Instruments Corp, United States) developed specifically for on-kinetics analysis of several exercise bouts. This program fits the data using a non-linear curve-fitting function that minimizes the sum of squared errors via a standard Levenberg-Marquardt algorithm, commonly used to solve non-linear least squares problems. The fittings considered the preceding 120s of the rest phase as the baseline, where a straight line was fitted to the data. Additionally, in this program, outlier data located 4 standard deviations (SD) or more from the mean were removed, following standard practice (Hesse et al., 2025). For instance, non-linear least-squares regression methods were used, with the baseline and on-transient phases fitted to a linear function (slope equal to zero, baseline) and a mono-exponential function (on) (Keir et al., 2014). Following this step, a second-by-second linear interpolation and time alignment of the data was performed to ensure the transition from baseline to exercise happens at time zero (0s) (Murias et al., 2010).

Data from two of the four bouts conducted under TSES and two performed without stimulation were ensemble-averaged within each condition. The resulting mean responses for each participant were used to compare the on-kinetics of arm-cranking with and without TSES. This transition was further time-averaged into 5-s bins to obtain a single time-averaged response (George et al., 2018; Murias et al., 2010). For on-kinetics fitting, the first 20 seconds of the $\dot{V}O_2$ data was not included in the fitting of phase II of the $\dot{V}O_2$ response to minimize the effects of phase I (cardiogenic) responses, as previously recommended (George et al., 2018; Murias et al., 2011) and seen in other research in the SCI population (Fukuoka et al., 2002; Fukuoka et al., 2009). Therefore, the data was modelled using a mono-exponential function, as described in the equation below, from the beginning of phase II to the end of the constant workload (CWL) exercise, to characterize the primary component of pulmonary oxygen consumption ($\dot{V}O_{2p}$):

$$\dot{V}O_{2p}(t) = \dot{V}O_{2b} + \dot{V}O_{2amp} * (1 - e^{-(t - TD_{\dot{V}O_2})/\tau_{\dot{V}O_2}})$$

Where $\dot{V}O_{2p}(t)$ represents the $\dot{V}O_2$ changes over time (t); $\dot{V}O_{2b}$ is the baseline value of $\dot{V}O_2$ at rest; $\dot{V}O_{2amp}$ represents the amplitude from baseline to steady-state increase; $TD_{\dot{V}O_2}$ is the time delay of the function (such that the model is not constrained to pass through the origin); and $\tau_{\dot{V}O_2}$ represents the time taken to achieve 63% of the steady state. Similarly, the mean response time (MRT) was computed as the sum of $\tau_{\dot{V}O_2}$ and $TD_{\dot{V}O_2}$.

Statistical Analysis

Normality was assessed using the Shapiro-Wilk normality test, and homogeneity of variance with Levene's test. $\dot{V}O_2$ kinetic parameters (MRT, τ , TD, and amplitude) were analyzed using a two-way repeated measures ANOVA with group (tetraplegic, paraplegic, neurologically

intact reference) as the between-subject factor and condition (TSES *vs.* without TSES) as the within-subject factor. Two-way repeated measures ANOVA was followed by post-hoc t-tests (Tukey HSD). Sphericity and homogeneity of variance were not violated ($p \geq 0.05$).

The **primary outcome**, MRT, was analyzed at an α level of 0.05 because MRT was the sole primary outcome; no adjustment for multiple primary outcomes was required. When the two-way repeated measures ANOVA indicated significant effects, Tukey's multiple comparisons test with a single pooled variance was performed to account for multiple comparisons. The **secondary outcomes** (τ , TD, and amplitude) were considered exploratory. For each outcome, *post hoc* pairwise comparisons were adjusted for multiple testing using Tukey's HSD to control the family-wise error rate within that outcome. Effect sizes were reported as Cohen's d (small effect [0-.20], medium effect [.21-.50], large effect [.51-.80]) (Cohen, 1992) for pairwise comparisons, with a 95% confidence interval. Analyses were performed using GraphPad Prism computer software (version 11, GraphPad Software, San Diego, California, USA), and data are presented as mean $\pm$ SD.

5.3 Results

Participant Characteristics and Study Participation

Participant ages ranged from 25-65 years (48.9 ± 12.6 years), with a mean injury duration of 14.1 ± 13 years (2-41 years). Injury levels ranged from C5/6 to S1, with 12 requiring full-time use of a wheelchair (10 MWC, 2 PWC, none used both). Seven of the fourteen participants were motor complete (4 males, 3 females), and the remaining 7 were motor incomplete (4 participants able to walk full-time or while in their homes) (Table 5.2). Overall, 14 participants living with SCI completed the CWL exercise on the arm crank ergometer. Two participants in the tetraplegia group were excluded from the analysis (one was removed due to their inability to complete

exercise protocol requirements and the other was removed for being an outlier), as well as their respective controls.

Table 5.2 Characteristics of participants living with SCI.

ID #	Age (Years)	Sex M/F	Body Mass (kg)	Height (cm)	Duration of injury (years)	Neurological level of injury/ TP & PP	Motor C/I	Ambulation mode
01	57	F	57.8	170	37	C8 (TP)	MC	MWC
02	35	F	49.6	171	6	C5/6 (TP)	MI	MWC
05	34	M	63.8	181	15	C7 (TP)	MC	MWC
08	25	M	75.1	185	6	C6/7 (TP)	MC	MWC
09	52	M	73.9	170	32	C6/7 (TP)	MC	MWC
13	65	M	102.4	183	6	Participant is unsure (TP)	MI	PWC (walks with walker very short distances)
14	57	M	110.8	180	41	C5/6 (TP)	MI	PWC
03	41	F	75.7	163	2	T1 (PP)	MI	MWC
04	37	M	104.5	180	7	T3 (PP)	MC	MWC
06	53	F	48.7	163	8	T12 (PP)	MC	MWC
07	49	F	88	177	18	T7 (PP)	MC	MWC
10	65	M	95.1	173	4	T12 (PP)	MI	MWC (also uses a walker for shorter distances)
11	50	M	107.0	193	11	L1-L3 (PP)	MI	WFT
12	64	F	103.6	176.5	5	L2-S1 (PP)	MI	WFT
Mean ± SD	48.9 ±12.6	-	82.6 ± 21.9	176.1 ± 8.4	14.1 ± 13	-	-	-
Range	25-65	-	48.7-110.8	163-193	2-41	-	-	-

Mean and range are shown at the bottom, where appropriate. C, cervical level; T, thoracic level; TP, participant living with tetraplegia; PP, participant living with paraplegia; MI, motor incomplete; MC, motor complete; WFT, walks full time; WB, weight bearing; MWC, manual wheelchair; PWC, power wheelchair; F, female; M, male.

The control group consisted of age-, sex- and height-matched neurologically intact (NI) references to those living with tetraplegia selected from the general population (Table 5.3).

Table 5.3 Characteristics of neurologically intact control participants.

ID#	SCI	Age	Sex	Body mass	Height
	Matched Pair	(years)	(M/F)	(Kg)	(cm)
C01	01	56	F	78	167.6
C02	02	37	F	68.8	167.6
C05	05	37	M	88.5	180.7
C08	08	24	M	78	190.5
C09	09	51	M	62.4	170
C13	13	63	M	78.2	177
C14	14	57	M	76.6	178
Mean ± SD	-	48 ± 14	-	77.0 ± 8.2	177.3 ± 8.3
Range	-	24-63	-	62.4-88.5	167.7-190.5

Mean ± SD and range are shown at the bottom, where appropriate. Participants were age-, sex-, and height-matched to participants living with tetraplegia.

Effects of TSES on $\dot{V}O_2$ on-kinetic parameters and $\dot{V}O_2$ amplitude during Constant Workload

Arm Ergometry Exercise

Table 5.4 displays the $\dot{V}O_2$ on-kinetic parameters (MRT, τ and TD), resting $\dot{V}O_2$, and $\dot{V}O_2$ amplitude during CWL for the participants living with tetraplegia, paraplegia, and neurologically intact reference during TSES off and on. It can be observed a variability in the responses to TSES, where some participants showed improvements, others remained the same, and others demonstrated worse responses.

Table 5.4 $\dot{V}O_2$ on-kinetic parameters, resting $\dot{V}O_2$, and $\dot{V}O_2$ amplitude during constant workload exercise during TSES off and on conditions.

Participant	MRT		Tau (τ)		TD		Resting $\dot{V}O_2$		$\dot{V}O_2$ Amplitude	
	(s)		(s)		(s)		(mL.min ⁻¹)		during exercise (mL.min ⁻¹)	
Participants Living with Tetraplegia										
01	236	227	55	49	181	179	243	234	390	365
05	241	211	54	22	187	189	302	303	424	451
08	228	233	43	57	185	176	351	347	577	613
09	211	231	42	64	169	167	248	265	359	437
14	226	227	32	46	194	181	310	283	578	617
Participants Living with Paraplegia										
03	231	243	72	79	160	164	232	237	447	415
04	218	221	38	40	180	180	360	332	676	730
06	230	231	64	92	166	139	232	198	328	388
07	246	240	41	56	205	184	293	273	390	391
10	249	230	102	80	147	150	343	305	558	582
11	249	241	73	63	176	178	308	307	879	896
12	232	229	52	53	180	176	287	306	511	510

Neurologically Intact Reference Controls										
C01	243	261	58	75	185	186	279	258	493	532
C05	239	243	54	61	185	182	368	380	806	795
C08	233	229	38	43	195	186	427	437	1232	1224
C09	208	215	36	42	173	173	234	240	744	787
C14	234	229	59	59	175	170	321	329	933	903

MRT: mean response time; TD: time delay; $\dot{V}O_2$: oxygen uptake; Grey bolded values represent the off-condition; Black bolded values represent the on-condition.

There were no statistically significant differences in baseline $\dot{V}O_2$ values within (off vs. on) or between groups (tetraplegic, paraplegic, or the neurologically intact controls) (all $p > 0.05$). (Figure 5.3).

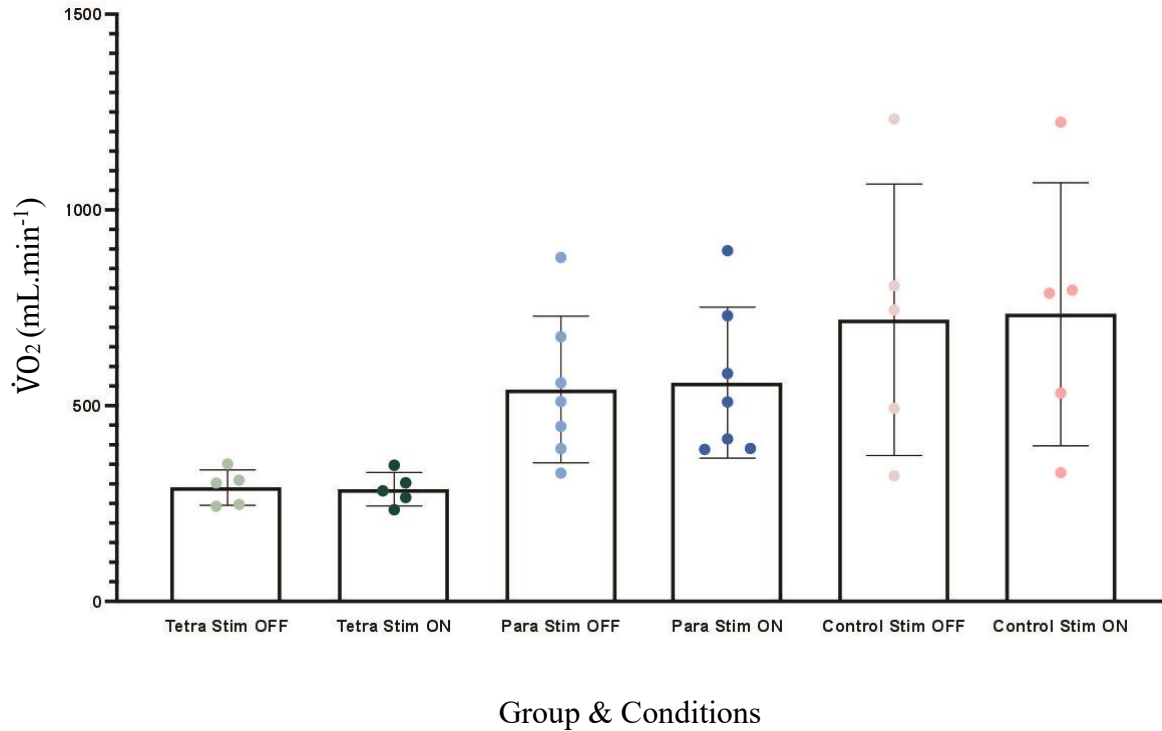


Figure 5.3 Baseline $\dot{V}O_2$ values between groups. $\dot{V}O_2$: oxygen consumption; TP: tetraplegia; PP: paraplegia; light green = stimulation off for people living with tetraplegia; dark green = stimulation on for people living with tetraplegia; light purple = stimulation off for people living with paraplegia; dark purple = stimulation on for people living with paraplegia; light pink = stimulation off for neurologically intact controls; dark pink = stimulation on for neurologically intact controls.

No statistically significant differences were observed in $\dot{V}O_2$ amplitude values during CWL between groups (TP, PP, or NI references) when comparing TSES and no-TSES conditions (Figure 5.4). However, $\dot{V}O_2$ amplitude values were statistically significant different between participants living with tetraplegia and their matched neurologically intact reference in both the TSES ($p = 0.02$; $d = -1.81$) and no-TSES ($p = 0.03$; $d = -1.83$) conditions. This finding

was expected, as absolute power output (PO) differed significantly between these groups ($p < 0.0022$) (Figure 5.4).

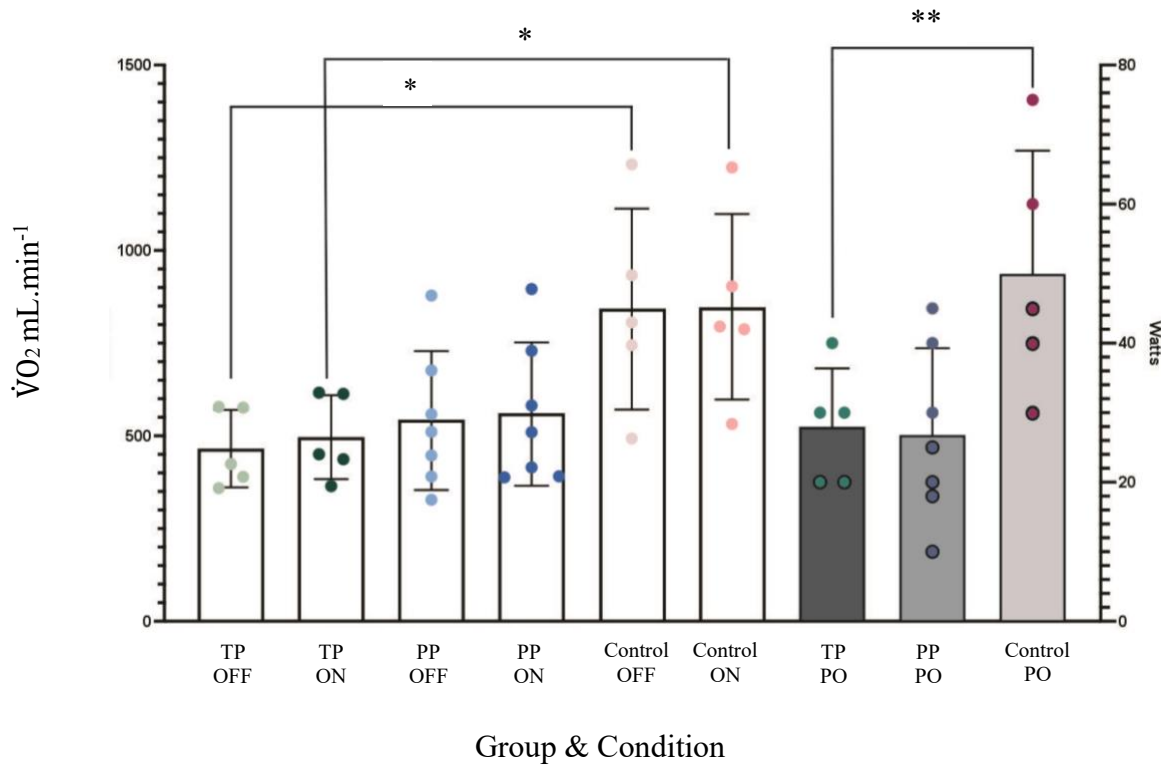


Figure 5.4 Effect of TSES on $\dot{V}O_2$ amplitude values during constant workload exercise within the ON and OFF conditions and between groups. Oxygen consumption ($\dot{V}O_2$) during constant workload exercise is depicted on the graph above. TP: tetraplegia; PP: paraplegia; PO: power output. Light green = stimulation off; dark green = stimulation on for people living with tetraplegia; Light blue = stimulation off; dark blue = stimulation on for people living with paraplegia; Light pink = stimulation off; dark pink = stimulation on for neurologically intact controls.

No significant differences were observed in mean response time (MRT) values within (stim on vs. stim off) or between groups (TP, PP, or NI references). Figure 5.5 highlights the

mean, SD, and variability in individual responses of MRT among participants, where 7 individuals had faster MRT's, 7 had slower MRT's, and 3 had similar MRT's between TSES and no-TSES. In the TP group, 2/5 participants had faster MRT's, 2/5 individuals took slightly longer when stimulation was applied, and 1/5 showed similar MRT's between stimulation and no stimulation. In the PP group, 3/7 participants had a faster MRT, 2/7 showed slightly slower MRT's, and 2/7 showed no change between TSES and no-TSES. In the NI reference group, 2/5 people had a slightly faster MRT, and 3/5 slowed down slightly.

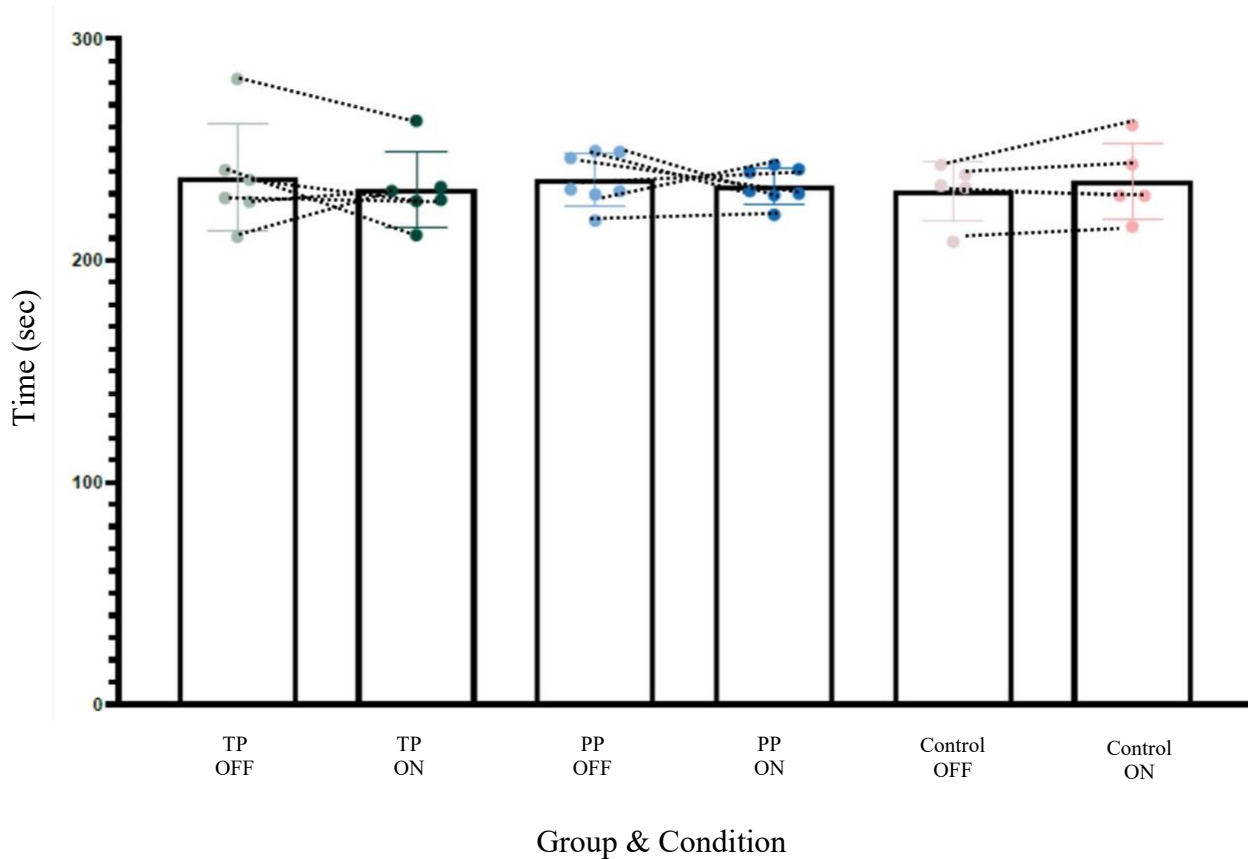


Figure 5.5 Effect of TSES on mean response time (MRT) values within and between groups.

The time it took to reach the steady-state exercise is shown in the graph above. TP: tetraplegia; PP: paraplegia; Light green = stimulation off; dark green = stimulation on for people living with

tetraplegia; Light blue = stimulation off; dark blue = stimulation on for people living with paraplegia; Light pink = stimulation off; dark pink = stimulation on for neurologically intact controls.

Statistically significant differences were not found for time constant (τ) between groups or within participants (Figure 5.6). Figure 5.6 highlights the mean, SD, and variability in individual responses of τ among participants, where 2/5 individuals in the TP group had a faster τ , and 3/5 individuals took slightly longer when stimulation was applied. In the PP group, 2/7 participants had a faster τ , 3/7 showed slightly slower τ , and 2/7 showed no change between TSES and no-TSES. In the NI reference group, 4/5 people had slightly slower τ responses, and 1/5 showed no change.

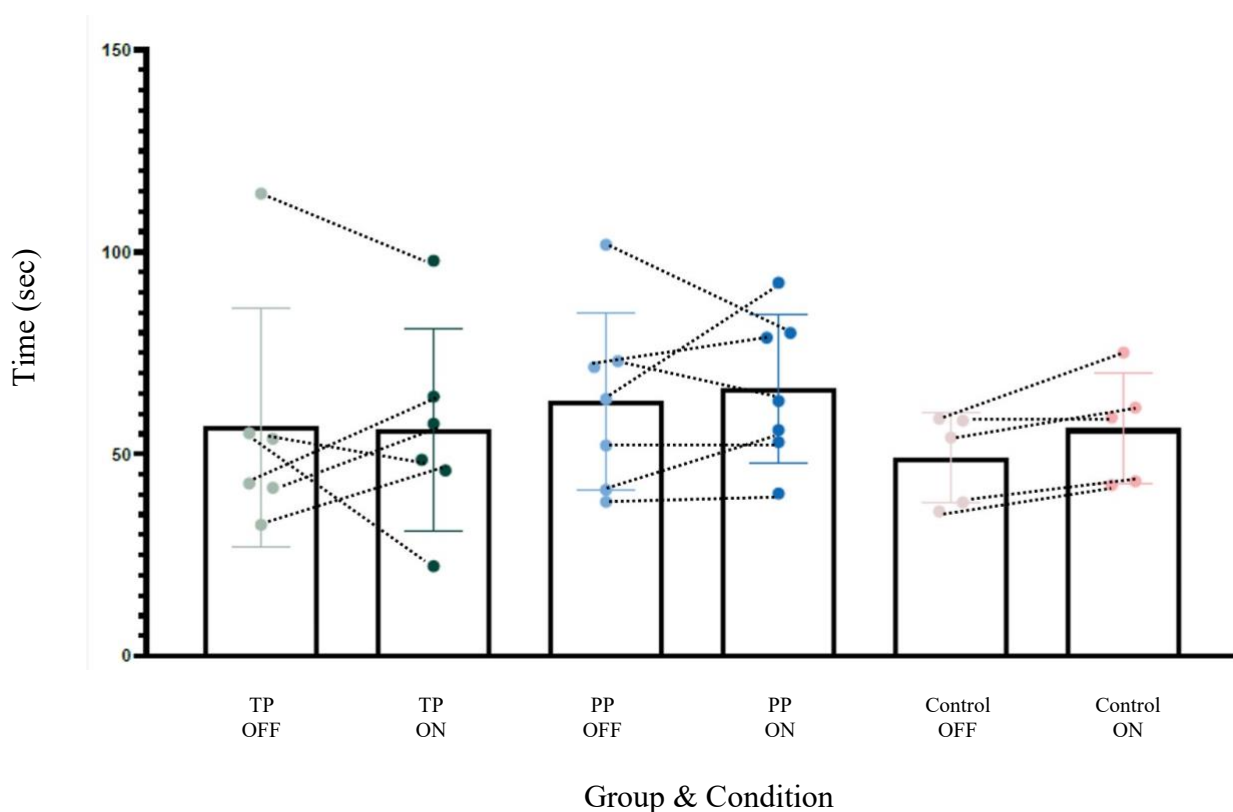


Figure 5.6 Effect of TSES on τ values within and between groups. The time to reach 63% of the steady-state exercise response is shown in the graph above. TP: tetraplegia; PP: paraplegia; Light green = stimulation off; dark green = stimulation on for people living with tetraplegia; Light blue = stimulation off; dark blue = stimulation on for people living with paraplegia; Light pink = stimulation off; dark pink = stimulation on for neurologically intact references.

Statistically significant differences were not found for time delay (TD) between groups or within participants (Figure 5.7). Figure 5.7 highlights the mean, SD, and variability in individual responses of TD among participants, where 2/5 individuals in the TP group had a smaller TD, 1/5 individuals took slightly longer when stimulation was applied, and 2/5 showed a similar response between stimulation and no stimulation. In the PP group, 2/7 participants had a shorter TD, 2/7 showed a slightly longer TD, and 3/7 showed no change between TSES and no-TSES. In the NI reference group, 2/5 people had slightly faster TD, 1/5 slowed down slightly and 2/5 showed no change.

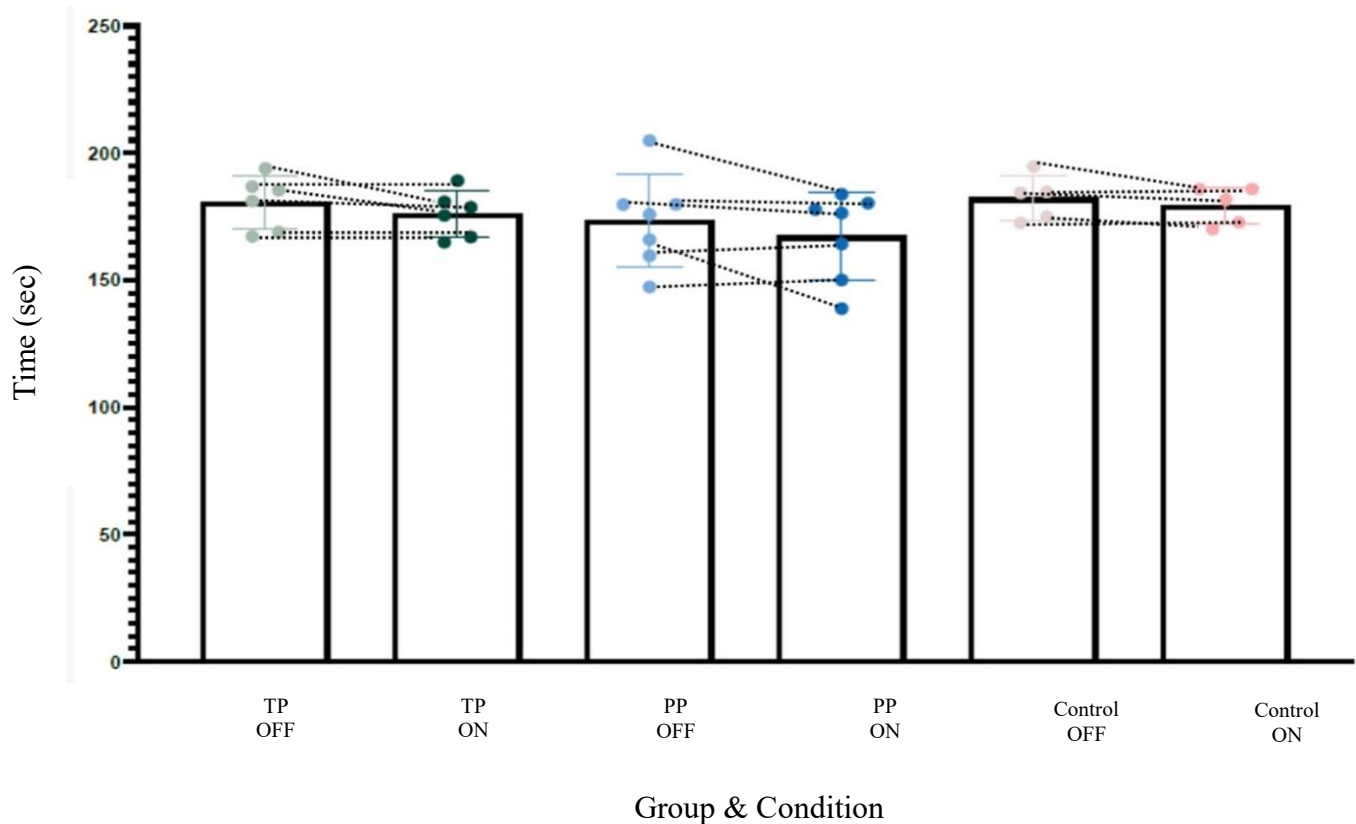


Figure 5.7 Effect of TSES on time delay (TD) values within and between groups. The time delay, the time between the start of exercise/workload transition and the beginning of the modeled exponential rise in $\dot{V}O_2$ is shown in the graph above. TP: tetraplegia; PP: paraplegia; Light green = stimulation off; dark green = stimulation on for people living with tetraplegia; Light blue = stimulation off; dark blue = stimulation on for people living with paraplegia; Light pink = stimulation off; dark pink = stimulation on for neurologically intact controls.

Adverse events associated with transcutaneous spinal electrical stimulation (TSES)

Seven of the thirteen participants (54%) living with SCI and five of the six neurologically intact controls (83%) had minimal redness at the stimulation electrode site (Table 5.5). This was expected, as increased heat at the electrode contact site may increase local blood flow, the electrode adhesive may cause mild skin irritation and contact or friction between participants and their chair may contribute to redness. No other adverse events were reported.

Table 5.5 Transcutaneous spinal electrostimulation parameters and related adverse events.

Participant	Stim Location	Stim Parameters [intensity (mA)/ frequency (Hz)/pulse width (μ s)]	Adverse Events
Participants living with SCI			
01	Rostral @T12	20 mA/20 Hz/900 μ s	Redness at the stimulation site
02	Rostral @T12	12.5 mA/20 Hz/900 μ s	Brief muscle spasm in the back
03	Rostral @T12	20 mA/20 Hz/900 μ s	None
04	Rostral @T12	35 mA/20 Hz/900 μ s	None
05	Rostral @T12	10 mA/20 Hz/900 μ s	Redness on the back where the tape was placed to secure the electrode
06	Rostral @T11	10 mA/20 Hz/900 μ s	None
07	Rostral @T12	25 mA/20 Hz/900 μ s	None
08	Rostral @T12	15 mA/20 Hz/900 μ s	None
09	Rostral @T12	35 mA/20 Hz/900 μ s	Redness at the stimulation site
10	Rostral @T10	25 mA/20 Hz/900 μ s	Redness at the stimulation site
11	Rostral @T11	15 mA/20 Hz/900 μ s	Redness at the stimulation site
12	Rostral @T12	10 mA/20 Hz/900 μ s	Redness at the stimulation site
13	Rostral @T12	17 mA/20 Hz/900 μ s	Redness at the stimulation site
14	Rostral @T12	27 mA/20 Hz/900 μ s	None
Neurologically Intact Controls			
C01	Rostral @ T12	15 mA/20 Hz/900 us	Redness at the stimulation site
C05	Rostral @ T12	7.5 mA/20 Hz/900 us	Redness at the stimulation site
C08	Rostral @ T12	15 mA/20 Hz/900 us	None
C09	Rostral @ T12	7.5 mA/20 Hz/900 us	Redness at the stimulation site

C13	Rostral @ T12	15 mA/20 Hz/900 us	Redness at the stimulation site
C14	Rostral @ T12	12.5 mA/20 Hz/900 us	Redness at the stimulation site

5.4 Discussion

To the best of our knowledge, this is the first study to examine the effect of TSES on $\dot{V}O_2$ on-kinetics during rest-to-exercise transitions, and among only a few studies examining cardiorespiratory outcomes in the SCI population when TSES is used as an intervention. Findings from this study show that TSES had no effect on $\dot{V}O_2$ amplitude, τ , TD, and MRT within or between groups. However, PO and associated $\dot{V}O_2$ consumption during constant workload testing differed between the group with tetraplegia and their neurologically intact, age-, sex-, and height-matched references. This was expected as those living with tetraplegia were working at a lower absolute workload than those who were neurologically intact (Figure 5.3). Furthermore, TSES appeared to be a safe intervention as some participants only experienced minimal redness at the stimulation electrode site. However, our hypothesis (TSES would improve MRT during constant workload exercise on an arm-crank ergometer in those living with tetraplegia) was rejected for the following reasons (1) O_2 extraction may have been the limiting factor that needed to be addressed rather than O_2 delivery, (2) exercise training and/or a longitudinal TSES study may be necessary to see differences rather than an acute intervention, (3) injury level, completeness of injury and stimulation parameters could have played a role in why significant effect(s) of TSES on $\dot{V}O_2$ on-kinetics were not seen.

The role of cardiovascular-autonomic control, O_2 delivery, and O_2 extraction on $\dot{V}O_2$ kinetics

Recently, there has been emerging physiological evidence and acute data suggesting that TSES has the potential to alter cardiovascular/autonomic control and O_2 delivery during

movement and exercise. For example, TSES may increase BP in those living with SCI (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Hodgkiss et al., 2024; Kumru et al., 2025; Lau et al., 2026; Phillips et al., 2018; Samejima et al., 2025; Solinsky et al., 2024), which would therefore be expected to directly impact $\dot{V}O_2$ kinetics.

Multiple spinal reflex mechanisms may be triggered by TSES during exercise, many of which have not been systematically examined. To date, the main focus has been on alteration of BP, although no one has continuously measured BP during upper body exercise with TSES, and improvements in exercise performance have been attributed to increased BP, based upon observing increases in BP during TSES applied at rest. TSES may alter other exercise-related ‘descending command’ reflex functions. For example, perhaps spinal afferents responsible for innervation of the adrenal gland were activated, resulting in the release of catecholamines. Circulating catecholamines mediate an increase in HR, cardiac contractility, and vasoconstriction (Bolli et al., 1987). An increase in vasoconstriction results in increased systemic vascular resistance and therefore blood pressure (DeLong & Sharma, 2023). As blood pressure increases, venous return might increase, improving cardiac preload and consequently increasing SV and CO, allowing for an increased delivery of oxygen-rich blood to working tissues.

Despite a potential increase in BP, the contribution of increased O_2 delivery to the working muscles may have been too small to meaningfully accelerate $\dot{V}O_2$ on-kinetics in the current study, given that they were only working at 40-45% peak oxygen uptake. Early work (Hagberg et al., 1980) in the neurologically intact population postulated that $\dot{V}O_2$ on-kinetics improved through two mechanisms: increased O_2 delivery to and increased O_2 extraction in the working muscle. Studies have shown that during steady-state exercise at moderate intensity (below lactate threshold), the increase in $\dot{V}O_2$ reflects O_2 utilization (Whipp & Wasserman, 1972;

Whipp & Ward, 1990). However, it is important to note that the accumulation of metabolites at the site of the muscle (e.g. accumulation of H^+ ions, lactate, inorganic phosphate, and reactive oxidative species (ROS) all contribute to muscle fatigue, and adequate oxygen delivery is needed to remove these by-products and prolong fatigue (Wan et al., 2017).

Literature from the SCI population suggests that improvements in $\dot{V}O_2$ on-kinetics may be driven more by adaptations in oxygen utilization rather than oxygen delivery. Fukuoka et al. (2009) reported improvements in $\dot{V}O_2$ on-kinetics, specifically, a faster τ was seen after only 1 week (3 sessions) of a wheelchair training program (Fukuoka et al., 2009). The authors indicated that since improvements in $\dot{V}O_2$ on-kinetics were observed so quickly, they postulated that any direct contribution of improved O_2 delivery to working muscles would be relatively too small to account for such improvements in $\dot{V}O_2$ on-kinetics (Fukuoka et al., 2009) and suggested rather that improvements were due to an increase in O_2 utilization specifically a reduction in metabolic inertia (reliance on anaerobic metabolism at the start of exercise).

Earlier work by Fukuoka et al. (2002) reported greater reliance on oxygen extraction in trained participants with SCI, who exhibited lower CO (calculated via the Fick equation: $\dot{V}O_2 = CO \times a-vO_2$ difference) compared to their sedentary neurologically intact control group. $\dot{V}O_2$ peak was not significantly different between the groups, which suggests that the trained SCI participants' compensatory response was characterized by a greater reliance on oxygen extraction in the working muscle. Findings from Gollie et al. (2017) demonstrated that phase 2 on-kinetics during self-selected treadmill walking was prolonged in incomplete SCI (iSCI) participants despite a slower walking speed compared with the neurologically intact reference group. Gollie et al. (2017) also observed that those living with iSCI demonstrated slower τ and slower resting

(during arterial occlusion in the gastrocnemius) change in muscle deoxygenation capacity $\frac{1}{2}$ time, suggesting limitations in oxygen delivery and/or utilization at the tissue.

The role of training and muscle fatigue on $\dot{V}O_2$ On-Kinetics

Our participants did not use an arm crank regularly; however, some may do other physical activity/sports (e.g. rugby), which could have led to some variability. This suggests that arm cranking is not regularly performed, contributing to slower $\dot{V}O_2$ kinetics. Much of our sample are manual wheelchair users; however, a lack of familiarity with the arm crank means a lack of training specificity, which could lead to slower $\dot{V}O_2$ kinetics when compared to those who have trained their muscles using the arm crank ergometer. This is because muscles that are trained gain an increase in oxidative capacity, allowing for more efficient utilization of substrates in the presence of oxygen, reducing lactate production during submaximal exercise (Gollnick et al., 1972). Therefore, it is possible that TSES did not alter $\dot{V}O_2$ on-kinetics to a significant degree in many participants because the lack of training outweighed the benefits of TSES.

Early work showed positive effects of specificity of training on $\dot{V}O_2$ on-kinetics (Cerretelli et al., 1979). Trained muscles were observed to have a faster $\dot{V}O_2$ on-kinetic response and smaller changes in blood lactate accumulation/production (Cerretelli et al., 1979). Exercise on an arm ergometer has been associated with lower blood lactate levels compared to FES leg exercise in those with paraplegia (T4-T12) (Barstow et al., 2000). MRT was also deemed to be in the expected range during arm-crank exercise in those living with paraplegia, compared with data previously collected in the neurologically intact population (Barstow et al., 2000). Additionally, studies focusing on the neurologically intact population observed that $\dot{V}O_2$ kinetics were slower during arm exercise than leg exercise; therefore, it was thought that conditioning of

the limbs exercised played a role in $\dot{V}O_2$ kinetics (Barstow et al., 2000; Casaburi et al., 1992; Cerretelli et al., 1977; Cerretelli et al., 1979).

Potential contributions of variation in stimulation parameters, injury level, & completeness of injury on the effect(s) of TSES on $\dot{V}O_2$ on-kinetics

To date, it is unclear which stimulation parameters are most effective for improving cardiorespiratory responses since research is still in the exploratory stage and only eight studies have examined the effect(s) of TSES on cardiorespiratory measures. Cardiorespiratory measures include systolic blood pressure, diastolic blood pressure, heart rate, minute ventilation, peak oxygen uptake and related variables (e.g. peak oxygen pulse, stroke volume). Currently, only two studies (Hodgkiss et al., 2024; Kumru et al., 2025) examined respiratory variables (e.g. minute ventilation, peak oxygen uptake, maximal inspiratory pressure, maximal expiratory pressure), with neither investigating the effects on $\dot{V}O_2$ on-kinetics; thus, the parameters considered effective for modulating $\dot{V}O_2$ on-kinetics are currently unknown.

We examined whether TSES at a frequency of 20 Hz, pulse width of 900 μ s, and an amplitude around motor threshold at T12-L1(spinal) would improve acute exercise responses based on studies in the early 2000s (Carhart et al., 2004; Ganley et al., 2005) that showed improvements in whole body metabolic substrate use, walking function, speed and ratings of perceived exertion, and possibly increased BP during exercise. Increasing BP has the potential to improve exercise responses by increasing venous return and consequently CO, therefore increasing O_2 delivery to the working muscle (Guyton & Hall, 1986) and accelerating $\dot{V}O_2$ on-kinetics per their relationship observed in the Fick equation (Gazibarich, 2019). Findings from 27 participants across several studies suggest that short pulse widths (less than approximately 1 ms) reduce BP, whereas longer pulse widths (greater than approximately 1 ms) increase BP (Law

et al., 2024). Our pulse width was on the shorter side at 900 μ s, which may not have been high enough to elicit changes in BP for everyone, which could have contributed to the individualized findings.

Mechanistically speaking, it is proposed that preferential recruitment of large diameter fibers of dorsal roots is activated and elicits a somatoautonomic reflex that causes modulation of blood pressure by either excitation (increase in BP) or inhibition (decrease in BP) of sympathetic preganglionic neurons (Samejima et al., 2023; Law et al., 2024; Grill et al., 1995).

Half of the participants included in our sample were living with incomplete injuries, and seven of the thirteen participants were living with paraplegia. Law et al. (2024) reported that the effectiveness of TSES is dependent on cardiovascular dysfunction, such that AD and OH can be mitigated. However, those without cardiovascular dysfunction experience mixed effects on HR and BP. It is possible that the variability of the responses in our sample led to no statistically significant findings. In support of this, only five of our study participants had motor complete injuries above T5, which has been identified as the population most likely to show increased BP in response to electrical spinal stimulation. Therefore, it is possible if the greatest improvement elicited by TSES during exercise is related to the increase in BP, only these five would be expected to show an improvement. This remains to be analysed.

Limitations and Future Directions

This study has limitations that need to be acknowledged. For example, due to the nature of the intervention, blinding of participants and researchers was not feasible, because many participants could feel when the stimulation occurred, and because researchers had to manually turn on the stimulator. However, whether this knowledge affected participants' exercise responses during this protocol was not analyzed. Seven of twelve participants living with SCI

(58%) were on a variety of different prescribed medications, which could affect their responses to exercise. Despite documentation of medications, medication use was not included as a covariate. Exercise was conducted on an arm-crank ergometer, which limited continuous measurements of cardiovascular variables using photoplethysmography (e.g., blood pressure, stroke volume, cardiac output), due to noise and movement artifacts compromising data quality and accurate interpretation of these physiological responses. Lastly, following removal of outliers and unsuitable data sets, only five participants were left in each of the TP and NI reference groups and seven in the PP group, limiting statistical power, confidence in the findings, and generalizability.

Results from our study showed that amplitude of the $\dot{V}O_2$ response during exercise was significantly smaller in those living with tetraplegia than their NI references, when differences in MRT were not observed. Therefore, future studies should examine relative measures of $\dot{V}O_2$ on-kinetics (e.g. MRT: $\dot{V}O_2$ amplitude) in the SCI population. Furthermore, studies analyzing underlying mechanisms through which TSES might influence exercise function and cardiorespiratory variables would help support development of TSES as a potential therapeutic intervention for those living with SCI. Perhaps implementation of continuous measurements of cardiac output, heart rate, systemic vascular resistance, blood pressure and muscle oxygenation may help identify potential mechanisms. Future studies should also investigate the effects of TSES on off-kinetics (recovery) to better understand the oxygen debt accumulated during exercise and whether TSES improves oxygen recovery after exercise. Specifically, by investigating changes in RQ and substrate utilization (% fats, % carbs) attributed to TSES, researchers may further understand the mechanism by which TSES works, as well as understand its benefits surrounding exercise recovery.

5.5 Conclusion

This is the first study to investigate the effects of TSES on $\dot{V}O_2$ on-kinetics in the SCI population. Although TSES could facilitate faster on-kinetic responses in some participants during constant workload exercise testing, under these experimental conditions, we did not observe statistically significant differences in $\dot{V}O_2$ on-kinetic responses with or without TSES at the individual or group level. Furthermore, this study demonstrates individualized responses to TSES, suggesting that an individualized approach is needed to understand its effects better. Slight redness at the stimulation site was the only adverse effect of TSES, suggesting that its application is safe. This study contributes to the literature as foundational work providing preliminary evidence on the effects of TSES in people living with SCI, particularly in relation to $\dot{V}O_2$ kinetics.

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6. CHAPTER 6: GENERAL DISCUSSION

As a result of SCI, descending control of sympathetic function is compromised and autonomic dysfunction occurs, affecting the cardiorespiratory system (Myers et al., 2007). Consequently, activities of daily living become increasingly difficult, and health is negatively impacted as blood pressure instability becomes typical, with bouts of chronic hypotension interspersed with bouts of autonomic dysreflexia (Carlozzi et al., 2013), as discussed in chapter 4 (systematic review). Chronic hypotension may leave individuals experiencing extreme dizziness and/or loss of consciousness (Carlozzi et al., 2013). Resting hypotension can be further exacerbated by postural transitions (e.g., getting up from bed in the morning and transferring to a wheelchair) or following meals (Carlozzi et al., 2013; Moura et al., 2024), increasing the risk of fainting and further injury.

Autonomic dysreflexia (AD) primarily affects those with complete injuries above T6 due to disruption of supraspinal regulatory control of spinal sympathetic regulatory regions that are responsible for cardiovascular function (e.g. mediating blood pressure responses) (Cowley, 2018; Hopman et al., 1993; Wulf & Tom, 2023). AD is induced by any noxious stimuli (e.g. full bladder) causing a sudden substantial increase in blood pressure (Cowan et al., 2020), which may reach severe thresholds placing individuals at risk for cerebrovascular and cardiovascular complications (Eltorai et al., 1992; Groah et al., 2001; Ho & Krassioukov, 2010; Pan et al., 2005; West et al., 2016). In addition to autonomic dysfunction, modifiable cardiovascular disease (CVD) risk factors such as poor exercise capacity (EC) and cardiorespiratory fitness (CRF) (Ross et al., 2016) are prevalent among individuals living with SCI and may contribute to an increased risk of premature mortality.

In addition to the rationale associated with exercise-related health benefits, exercise performance could potentially be improved for Paralympic athletes using TSES as well. Tetraplegic athletes, who lack the ability to activate any of the descending exercise commands that support movement and exercise (e.g., increases in HR, BP, catecholamine release, and glucose and fatty acid mobilization), have reported that ~90-100% of them ‘boost’ (Wheeler et al., 1994). ‘Boosting’ involves intentionally inducing AD for competition to try and increase blood pressure (and any other factors, such as increasing release of catecholamines) with the hope of enhancing exercise performance (Wheeler et al., 1994). Some athletes go as far as clamping their indwelling catheter to obstruct the flow of urine and cause bladder distension (Wheeler et al., 1994), which in turn will cause an increase in discharge from nociceptive bladder afferents that will trigger AD. However, the intensity and duration of boosting are unpredictable, depending on how it is induced (Wheeler et al., 1994). Indeed, purposeful boosting has been banned since 1994 in Paralympic sport because of the concern for hypertension-related risk of injury (Bhambhani et al., 2009).

While boosting may represent an unsafe method of enhancing exercise performance, there is a need for safe therapeutic strategies for improving blood pressure regulation and exercise capacity in people living with SCI. Given the prevalence and consequence of chronic hypotension following SCI, there is a need for non-invasive neuromodulation strategies targeted at improving blood pressure and exercise responses. Transcutaneous spinal electrostimulation (TSES) has gained attention as a potential non-invasive neuromodulation strategy aimed at modifying cardiorespiratory variables. Although evidence remains limited mainly to case studies or case series reports (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Hodgkiss et al., 2024; Kumru et al., 2025; Lau et al., 2025; Phillips et al., 2018; Samejima et al., 2025; Solinsky et al.,

2024), it is hypothesized that TSES can improve cardio-autonomic and respiratory responses in those living with SCI.

Both sedentary individuals and Paralympic athletes living with SCI may benefit from TSES, which has the potential to increase exercise capacity. Emerging evidence suggests that TSES can be effective in increasing BP, which may result in an increase in venous return and thus CO, allowing for greater oxygen delivery to working tissues, increasing $\dot{V}O_2$ peak, $\dot{V}O_2$ on-kinetics, delaying fatigue, and improving EC. Improved EC would lead to improved CRF long-term, mitigating modifiable risk factors for CVD (e.g. low CRF).

Overview of findings

This thesis was designed to assess whether stimulation of spinal neurons via TSES would beneficially affect spinal autonomic systems during exercise by interpreting evidence from a systematic review and performing an experimental study. The overarching goal was to identify if there were TSES parameters deemed effective at positively modulating the cardio-autonomic system within the research literature, and to generate novel findings on whether TSES can alter cardio-respiratory variables such as $\dot{V}O_2$ on-kinetics in the SCI population. Our particular area of interest was those with motor complete tetraplegia, as this sub-population with SCI is known to experience the greatest levels of autonomic instability, and reduced ability to exercise, which corresponds to the highest incidence and earliest onset of sedentary-related diseases such as obesity (Gorgey & Gater, 2007), cardiovascular disease (Cragg et al., 2013a), type II diabetes (Cragg et al., 2013b) and early mortality (Gorgey & Gater, 2007).

The systematic review identified significant limitations in the current literature (Engel-Haber et al., 2024; Engel-Haber et al., 2025; Hodgkiss et al., 2024; Kumru et al., 2025; Lau et al., 2025; Phillips et al., 2018; Samejima et al., 2025; Solinsky et al., 2024), particularly as it

pertains to a lack of analysis on respiratory variables and weak reporting practices. The majority of existing studies focused on cardiovascular variables, with the two studies on respiratory variables focusing on maximal inspiratory and expiratory pressure and $\dot{V}O_2$ max. Studies often did not report absolute numerical values for baseline measurements, limiting data interpretation and a real-world understanding of the effect(s) of their experimental manipulations. Additionally, it was unclear whether the safety of TSES was of concern, as adverse events were not always reported. However, it is also possible that no adverse events were seen, and this is why none were reported. Lastly, a large limitation in the literature is that the majority of findings come from case studies, case reports, and case series, thus, the rigor behind findings is reduced. This thesis aimed to address these gaps by analyzing the effects of TSES on $\dot{V}O_2$ on-kinetics and by complete reporting of all data values measured as it pertained to $\dot{V}O_2$ on-kinetics and related adverse events.

The experimental data of this thesis contributed novel findings to the literature, as our initial analysis suggests variability among individualized responses to TSES, reflecting differences in injury severity, preserved autonomic pathways, stimulation tolerance, or responsiveness to neuromodulation; however, this requires quantitative analysis. Additionally, our findings show that TSES did not have a statistically significant effect on $\dot{V}O_2$ on-kinetics between groups. However, there were significant findings between those living with tetraplegia and their neurologically intact controls regardless of stimulation condition due to significant differences in power output. Our findings suggest that standardized TSES protocols may not be adequately fit to each person living with SCI, and that TSES may only be helpful to a specific subset of those with SCI. In particular, those with higher level (T6 or above), motor complete SCI. To our knowledge, this is the first study to assess the effects of TSES on $\dot{V}O_2$ on-kinetics in

the SCI population, providing preliminary evidence to support future investigations into $\dot{V}O_2$ on-kinetics. Collectively, the findings from both studies suggest that more research on TSES and its effects on cardio-autonomic and respiratory variables are needed in individuals living with SCI.

From a clinical implications standpoint, these findings support the need for an individualized prescription of TSES that can benefit the more sedentary population and Paralympic athletes. TSES has the potential to improve exercise performance in a safer way for Paralympic athletes, as well as help others manage their chronic hypotension sufficiently to complete activities of daily living independently.

Strengths and limitations

Despite the strengths of this thesis, several limitations are acknowledged. One limitation relates to the systematic review, in which all studies, regardless of protocol (e.g. progressive orthostatic challenge, blood pressure mapping at rest, and exercise), were included, making it difficult to draw definitive conclusions on cardiorespiratory variables during exercise since the body of literature is so variable and repeatability of findings for a single protocol is limited. Another limitation was that, during application of TSES in the experimental study, slight variations in stimulation parameters were used based on tolerance to stimulation and neurological level of injury, which may have contributed to more distinct responses and the lack of statistical significance in the findings. This is because some participants may have received stimulation above motor threshold, which may have been sufficient to observe slight improvements in $\dot{V}O_2$ on-kinetics while others were only stimulated below motor threshold, which may not have been enough of a stimulus and may help explain why some participants presented no change. Additionally, many participants were taking anti-spasticity medication (e.g. baclofen) and medications for pain management (e.g. morphine, gabapentin), which may directly

influence cardio-autonomic variables such as heart rate and blood pressure, potentially confounding the interpretation of physiological responses to exercise and TSES (Chahl & Walker, 1980; Watso et al., 2022; Pendyala et al., 2023). However, given that pain and spasticity are secondary outcomes of SCI, it would be unethical to have participants stop treating their conditions for the purpose of this study. Furthermore, including medicated participants reflects real-world clinical conditions, enhancing the ecological validity and applicability of findings to many people living with SCI. To minimize this limitation in future work, stratified analysis by medication type could improve physiological interpretation and help better distinguish the intervention effects from pharmacological influences. Our sample was too small to permit this type of subgroup analysis, which is itself a limitation. However, seven of the eight studies in the systematic review had sample sizes smaller than those of the present study, highlighting the challenges of collecting larger samples in this population, particularly in the short term. Lastly, there is a lack of exploration and understanding of the underlying mechanisms of action behind TSES. Exploration of the mechanism of action is beyond the scope of this thesis; however, several possibilities have been discussed in Flett et al. (2022).

Despite these limitations, this thesis provides important preliminary evidence regarding cardiorespiratory effects of TSES in individuals living with SCI. This thesis's findings contribute to a growing body of literature that supports the potential of neuromodulation strategies to improve autonomic function, while also highlighting the need for individualized stimulation approaches and further investigations into cardio-autonomic and respiratory outcomes, particularly during exercise.

Future directions

Preliminary data on acute respiratory quotient (RQ) responses showed that during bouts of constant workload with stimulation on, RQ was lower during recovery than in bouts without stimulation. When RQ is lower, there is a higher reliance on the percentage of fats being utilized as an energy substrate compared to carbohydrates (Peronnet & Massicotte 1991), suggesting an easier recovery as participants have faster regulation of post-exercise metabolism (Short & Sedlock, 1997) (Figure 6.1). Additionally, lipid oxidation during long-term recovery may improve weight management (Houmard et al., 2008; Marra et al., 1998; Marra et al., 2004; Seidell et al., 1992; Zurlo et al., 1990), decreasing the risk of obesity and potentially ameliorating CVD risk factors. Our study findings are intriguing, and more research is needed to confirm this RQ response.

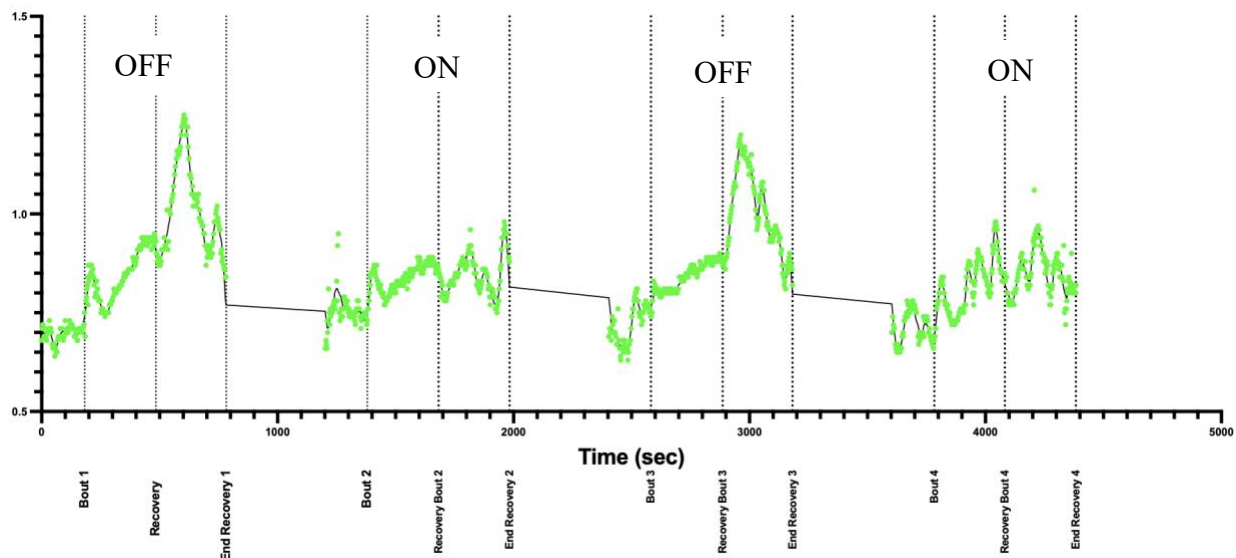


Figure 6.6 Example of a smoothed and second-by-second linearly interpolated data sample of RQ during constant workload exercise (off and on) for participant 09 living with tetraplegia.

To advance the field of TSES as it pertains to autonomic function and cardiorespiratory variables, recovery kinetics should be analyzed. This will allow researchers to better understand

post-exercise metabolism in people living with SCI. In Figure. 6.1, RQ appears to be altered for the better when stimulation is applied. If TSES is altering RQ so that a greater percentage of fats is used as an energy substrate during recovery, and recovery kinetics are improved (i.e., faster), the mechanism underlying this should be explored. Furthermore, the mechanism of TSES and how it improves $\dot{V}O_2$ kinetics in some participants and not others should also be investigated.

To address these mechanistic questions, it would be useful to conduct an exercise test and measure catecholamines. If catecholamines increase during/after exercise, it could indicate that stimulation enhances activity in sympathetic efferents innervating the adrenal gland, causing release of catecholamines. Those living with SCI, especially with higher levels of injury, do not increase release or only release small amounts of catecholamines during exercise (Schmid et al., 1998). Circulating catecholamines support several functions, including acting on cardiac receptors to increase HR and cardiac contractility, as well as acting on lipid stores, causing lipids to be used as an energy substrate. Furthermore, catecholamines cause vasoconstriction (Bolli et al., 1987), increasing systemic vascular resistance, thus increasing blood pressure and mitigating hypotension, allowing for improved CO and O₂ delivery and potentially better oxygen uptake.

Variability in stimulation site and intensity was also a limitation of the experimental study, as stimulation amplitude was set around motor threshold based on participant tolerance. Therefore, some participants were stimulated at, below, or above the motor threshold. Further, for those with injury at T12, TSES was applied more rostrally, at T10, since one would anticipate no TSES response at T12 in those whose primary damage occurs at T12. It would therefore be of interest to perform a secondary analysis of stimulation amplitude and location to determine whether any differences were observed by stimulation intensity or site.

Conclusion

This thesis contributes the first systematic review comprehensively examining the role of TSES on cardiorespiratory variables, alongside the first experimental study exploring the effects of TSES on $\dot{V}O_2$ on-kinetics in people living with SCI. Taken together, the findings of this thesis advance the current understanding of exercise-related physiological responses in people living with SCI and provide preliminary insight into the potential role of TSES in autonomic regulation during exercise.

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APPENDICES

Appendix A. International Standards for Neurological Classification of Spinal Cord Injury.

**INTERNATIONAL STANDARDS FOR NEUROLOGICAL
CLASSIFICATION OF SPINAL CORD INJURY
(ISNCSCI)**

Patient Name _____ Date/Time of Exam _____

Examiner Name _____ Signature _____

RIGHT

MOTOR KEY MUSCLES

Elbow flexors C5
Wrist extensors C6
Elbow extensors C7
Finger flexors C8
Finger abductors (little finger) T1

UER (Upper Extremity Right)

Comments (Non-key Muscle? Reason for NT? Pain? Non-SCI condition?):

Hip flexors L2
Knee extensors L3
Ankle dorsiflexors L4
Long toe extensors L5
Ankle plantar flexors S1

LER (Lower Extremity Right)

(VAC) Voluntary Anal Contraction (Yes/No) ☐

RIGHT TOTALS (MAXIMUM)

(50) (56) (56)

• Key Sensory Points

LEFT

MOTOR KEY MUSCLES

Elbow flexors C5
Wrist extensors C6
Elbow extensors C7
Finger flexors C8
Finger abductors (little finger) T1

UEL (Upper Extremity Left)

MOTOR (SCORING ON REVERSE SIDE)

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, gravity eliminated
3 = Active movement, against gravity
4 = Active movement, against some resistance
5 = Active movement, against full resistance
NT = Not testable
0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present

SENSORY (SCORING ON REVERSE SIDE)

0 = Absent
1 = Altered
2 = Normal
NT = Not testable
0*, 1*, NT* = Non-SCI condition present

Hip flexors L2
Knee extensors L3
Ankle dorsiflexors L4
Long toe extensors L5
Ankle plantar flexors S1

LEL (Lower Extremity Left)

(DAP) Deep Anal Pressure (Yes/No) ☐

LEFT TOTALS (MAXIMUM)

(56) (56) (50)

MOTOR SUBSCORES

UER + UEL = UEMS TOTAL (50) (25)

LER + LEL = LEMS TOTAL (50) (25)

SENSORY SUBSCORES

LTR + LTL = LT TOTAL (56) (56)

PPR + PPL = PP TOTAL (56) (56)

NEUROLOGICAL LEVELS

1. SENSORY R L

2. MOTOR R L

3. NEUROLOGICAL LEVEL OF INJURY (NLI)

4. COMPLETE OR INCOMPLETE? (In injuries with absent motor OR sensory function in S4-5 only)

5. ASIA IMPAIRMENT SCALE (AIS)

6. ZONE OF PARTIAL PRESERVATION R L

7. ASIA IMPAIRMENT SCALE (AIS)

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Muscle Function Grading

- 0 = Total paralysis
 1 = Palpable or visible contraction
 2 = Active movement, full range of motion (ROM) with gravity eliminated
 3 = Active movement, full ROM against gravity
 4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position
 5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person
 NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)
 0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present *

Sensory Grading

- 0 = Absent 1 = Altered, either decreased/impaired sensation or hypersensitivity
 2 = Normal NT = Not testable

0*, 1*, NT* = Non-SCI condition present *

Note: Abnormal motor and sensory scores should be tagged with a "" to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation	C5
Elbow: Supination	
Elbow: Pronation	
Wrist: Flexion	C6
Finger: Flexion at proximal joint	
Thumb: Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint	
Thumb: Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation	
Knee: Flexion	
Ankle: Inversion and eversion	L4
Toe: MP and IP extension	
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3 .

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3 .

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.



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Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.

The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.

Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).

Note: In regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).

This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.

The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.

(i.e. absence or presence of sacral sparing)

If voluntary anal contraction = No AND all S4-5 sensory scores = 0 AND deep anal pressure = No, then injury is Complete.

Otherwise, injury is Incomplete.

5. Determine ASIA Impairment Scale (AIS) Grade.

Is injury Complete? If YES, AIS=A

NO ↓

Is injury Motor Complete? If YES, AIS=B

NO ↓

(No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓

AIS=C

YES ↓

AIS=D

If sensation and motor function is normal in all segments, AIS=E

Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).

The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Appendix B. CONSORT checklist of information to include when reporting randomized crossover trials.

Section/Topic	Item No	Checklist item	Reported on page No 107
Title and abstract			
	1a	Identification as a randomized crossover trial in the title	_____
	1b	Specify a crossover design and report all information outlined in table 2	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	_____
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect	_____
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	_____
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	_____
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	_____
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined, accounting for within participant variability	_____

	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison)	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period	
	13b	No of participants excluded at each stage, with reasons, separately for each sequence and period	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	

Baseline data	15	A table showing baseline demographic and clinical characteristics by sequence and period
Numbers analysed	16	Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons. In addition, results for each intervention in each period are recommended
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	Describe all important harms or untended effects in a way that accounts for the design (for specific guidance, see CONSORT for harms ³²)
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

Appendix C. Consensus on Exercise Reporting Template (CERT) —Checklist of items that should be included in reports of exercise intervention.

Item Category	Item No	Abbreviated Item Description	Reported on page No 107
WHAT: materials			
	1	Type of exercise equipment	
WHO: provider			
	2	Qualifications, teaching/supervising expertise, and/or training of the exercise instructor	
HOW: delivery			
	3a	Whether exercises are performed individually or in a group	_____
	3b	Whether exercises are supervised or unsupervised	_____
	3c	Measurement and reporting of adherence to exercise	_____
	3d	Details of motivation strategies	_____
	3e	Decision rules for progressing the exercise program	_____
	3f	Each exercise is described so that it can be replicated (e.g., illustrations, photographs)	_____
	3g	Content of any home program component	_____
	3h	Nonexercise components	_____
	3i	How adverse events that occur during exercise are documented and managed	_____
Where: location	1	Setting in which exercises are performed	
WHEN, HOW MUCH: dosage	1	Detailed description of the exercises (e.g. sets, repetitions, durations, intensity)	_____
TAILORING: what, how	1a	Whether exercises are generic (“one size fits all”) or tailored to the individual	
	1b	Decision rule that determines the starting level for exercise	_____
HOW WELL: planned, actual	1a	Whether the exercise intervention is delivered and performed as planned	_____

Citation: Slade, S. C., Dionne, C. E., Underwood, M., Buchbinder, R., Beck, B., Bennell, K., Brosseau, L., Costa, L., Cramp, F., Cup, E., Feehan, L., Ferreira, M., Forbes, S., Glasziou, P., Habets, B., Harris, S., Hay-Smith, J., Hillier, S., Hinman, R., Holland, A., White, C. (2016). Consensus on Exercise Reporting Template (CERT): Modified Delphi Study. *Physical therapy*, 96(10), 1514–1524. <https://doi.org/10.2522/ptj.20150668>

Appendix D. Sex and Gender Equity in Research Guidelines (SAGER) Guidelines. Checklist of items that should be included in reports of sex equity in research.

Section/topic	Item No	Checklist item	Reported on page No 107
General	1	The terms sex/gender used appropriately	
Title	2	Title specific the sex/gender of participants if only one included	
Abstract	3a	Abstract specifics the sex/gender of participants if only one included	
	3b	Study population described with sex/gender breakdown*	
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	
	4c	The demographics of the study population with regard to sex/gender (e.g., disease prevalence among male/female study participants) are outlined	
Methods	5a	Method of definition of sex/gender (e.g., self-report, genetic testing)	
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (e.g., mandating contraception for women) * Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required	
Results	6a	Study population description with complete gender/sex breakdown for all categories considered*	
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	

- 6c Sex-and gender-based analysis reported regardless of outcome (in main paper if pre-specified; otherwise in appendix) *
- 6d For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix) *
- 6f For epidemiological studies, the effects of other exposure on health problems examined for all genders and analysed critically from a gender perspective
- 6g Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected*

Adapted from SAGER guidelines. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review 1, Article number: 2 (2016) <https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6>. * These points extend beyond the original SAGER table.

Appendix E. Preferred Reporting Items for Systematic Review and Meta-Analysis

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications

Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Appendix F. Search Strategy

MEDLINE Search Strategy		
	Search String	Results
1	(Spinal cord injury or SCI).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	<i>n</i> =359
2	Spinal Cord Injuries/	<i>n</i> =308
3	1 or 2	<i>n</i> =379
4	(Transcutaneous spinal stimulation or transcutaneous spinal electrostimulation or spinal stimulation).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	<i>n</i> =0
5	3 and 4	<i>n</i> =0
6	(oxygen uptake or oxygen uptake kinetics or oxygen consumption).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	<i>n</i> =41
7	5 and 6	<i>n</i> =0
8	(Fatigability, oxygen uptake kinetics and muscle deoxygenation in incomplete spinal cord injury during treadmill walking).m_titl.	<i>n</i> =0
9	find similar to Fatigability, oxygen uptake kinetics and muscle deoxygenation in incomplete spinal cord injury during treadmill walking.	<i>n</i> =0
10	7 and 8	<i>n</i> =0
11	(Gollie adj34 "Fatigability, oxygen uptake kinetics and muscle deoxygenation in incomplete spinal cord injury during treadmill walking.").rf.	<i>n</i> =0
12	(VO2 peak or VO2 max or maximal oxygen uptake or peak oxygen uptake or maximal oxygen consumption or peak oxygen consumption).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	<i>n</i> =9
13	6 or 12	<i>n</i> =43
14	5 and 13	<i>n</i> =0
EMBASE Search Strategy		
	Search String	Results
1	exp spinal cord injury/	<i>n</i> =104,126
2	Spinal cord injury*.tw,kf.	<i>n</i> =73,095
3	1 or 2	<i>n</i> =113,567
4	exp spinal cord stimulation/	<i>n</i> =11,958
5	(transcutaneous spinal electrostimulation or transcutaneous stimulation or transcutaneous spinal stimulation or spinal cord stimulation or cardiovascular neuromodulation or non-invasive spinal cord stimulation or noninvasive spinal cord stimulation or spinal cord electrostimulation).tw,kf.	<i>n</i> =10,815
6	4 or 5	<i>n</i> =13,629
7	3 and 6	<i>n</i> =1,622
8	Limit 7 to human	<i>n</i> =1,300

9	Limit 7 to (human and English language)	<i>n</i> =1,265
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CINAHL Search Strategy

Search String	Results
(spinal cord injury or sci or spinal injury) AND ("transcutaneous electrical stimulation" OR "spinal cord stimulation" OR "transcutaneous spinal electrostimulation" OR "non-invasive spinal cord stimulation" OR "noninvasive spinal cord stimulation" OR "cardiovascular neuromodulation" OR "transcutaneous spinal electro stimulation" OR "transcutaneous spinal stimulation" OR "transcutaneous stimulation")	<i>n</i> =213

SCOPUS Search Strategy

Search String	Results
(TITLE-ABS-KEY(Spinal cord injury*) AND TITLE-ABS-KEY(Transcutaneous spinal electrostimulation) OR TITLE-ABS-KEY(Transcutaneous spinal electro stimulation) OR TITLE-ABS-KEY(spinal cord stimulation) OR TITLE-ABS-KEY(Transcutaneous spinal stimulation) OR TITLE-ABS-KEY(Transcutaneous stimulation) OR TITLE-ABS-KEY(noninvasive spinal cord stimulation) OR TITLE-ABS-KEY(non-invasive spinal cord stimulation) AND TITLE-ABS-KEY(VO2 peak) OR TITLE-ABS-KEY(peak oxygen consumption) OR TITLE-ABS-KEY(peak oxygen uptake) OR TITLE-ABS-KEY(VO2 max) OR TITLE-ABS-KEY(maximal oxygen uptake) OR TITLE-ABS-KEY(maximal oxygen consumption) OR TITLE-ABS-KEY(oxygen uptake kinetics))	<i>n</i> =102

Appendix G: Quality of Bias Assessment Tools (JBI checklists)

JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Reviewer _____

Date _____

Author _____ Year _____

Number _____

Record

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☐	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☐	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☐	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☐	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	☐	☐	☐
8. Does the case report provide takeaway lessons?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

EXPLANATION OF CASE REPORTS CRITICAL APPRAISAL

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from <https://synthesismanual.jbi.global>

Case Reports Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. *Were patient's demographic characteristics clearly described?*

Does the case report clearly describe patient's age, sex, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications? The setting and context may also be described.

2. *Was the patient's history clearly described and presented as a timeline?*

A good case report will clearly describe the history of the patient, their medical, family and psychosocial history including relevant genetic information, as well as relevant past interventions and their outcomes. (CARE Checklist 2013)

3. *Was the current clinical condition of the patient on presentation clearly described?*

The current clinical condition of the patient should be described in detail including the uniqueness of the condition/disease, symptoms, frequency and severity. The case report should also be able to present whether differential diagnoses was considered.

4. *Were diagnostic tests or methods and the results clearly described?*

A reader of the case report should be provided sufficient information to understand how the patient was assessed. It is important that all appropriate tests are ordered to confirm a diagnosis and therefore the case report should provide a clear description of various diagnostic tests used (whether a gold standard or alternative diagnostic tests).

Photographs or illustrations of diagnostic procedures, radiographs, or treatment procedures are usually presented when appropriate to convey a clear message to readers.

5. *Was the intervention(s) or treatment procedure(s) clearly described?*

It is important to clearly describe treatment or intervention procedures as other clinicians will be reading the paper and therefore may enable clear understanding of the treatment protocol. The report should describe the treatment/intervention protocol in detail; for e.g. in pharmacological management of dental anxiety - the type of drug, route of administration, drug dosage and frequency, and any side effects.

6. *Was the post-intervention clinical condition clearly described?*

A good case report should clearly describe the clinical condition post-intervention in terms of the presence or lack thereof symptoms. The outcomes of management/treatment when presented as images or figures would help in conveying the information to the reader/clinician.

7. *Were adverse events (harms) or unanticipated events identified and described?*

With any treatment/intervention/drug, there are bound to be some adverse events and in some cases, they may be severe. It is important that adverse events are clearly documented and described, particularly when a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

8. *Does the case report provide takeaway lessons?*

Case reports should summarize key lessons learned from a case in terms of the background of the condition/disease and clinical practice guidance for clinicians when presented with similar cases.

REFERENCES:

Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, CARE Group. The CARE Guidelines: Consensus-Based Clinical Case Reporting Guideline Development. *Headache: The Journal of Head and Face Pain*, 2013;53(10):1541-1547.

JBI Critical Appraisal Checklist for Case Series

Reviewer_____

Date_____

Author_____Year_____

Record

Number_____

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
Did the case series have complete inclusion of participants?	☐	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

TOOL GUIDANCE

Answers: Yes, No, Unclear or Not/Applicable

1. Were there clear criteria for inclusion in the case series?

The authors should provide clear inclusion (and exclusion criteria where appropriate) for the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. *Was the condition measured in a standard, reliable way for all participants included in the case series?*

The study should clearly describe the method of measurement of the condition. This should be done in a standard (i.e. same way for all patients) and reliable (i.e. repeatable and reproducible results) way.

3. *Were valid methods used for identification of the condition for all participants included in the case series?*

Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

4. *Did the case series have consecutive inclusion of participants?*

Studies that indicate a consecutive inclusion are more reliable than those that do not. For example, a case series that states ‘we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006’ is more reliable than a study that simply states ‘we report a case series of 24 people with osteosarcoma.’

5. *Did the case series have complete inclusion of participants?*

The completeness of a case series contributes to its reliability (1). Studies that indicate a complete inclusion are more reliable than those that do not. As stated above, a case series that states ‘we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006’ is more reliable than a study that simply states ‘we report a case series of 24 people with osteosarcoma.’

6. *Was there clear reporting of the demographics of the participants in the study?*

The case series should clearly describe relevant participant’s demographics such as the following information where relevant: participant’s age, sex, education, geographic region, ethnicity, time period, education.

7. *Was there clear reporting of clinical information of the participants?*

There should be clear reporting of clinical information of the participants such as the following information where relevant: disease status, comorbidities, stage of disease, previous interventions/treatment, results of diagnostic tests, etc.

8. *Were the outcomes or follow-up results of cases clearly reported?*

The results of any intervention or treatment should be clearly reported in the case series. A good case study should clearly describe the clinical condition post-intervention in terms of the presence or lack of symptoms. The outcomes of management/treatment when presented as images or figures can help in conveying the information to the reader/clinician. It is important that adverse events are clearly documented and described, particularly a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

9. *Was there clear reporting of the presenting site(s)/clinic(s) demographic information?*

Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. women vs. men, sociodemographic variables between countries). The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them.

10. *Was statistical analysis appropriate?*

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of studies should be detailed enough for reviewers to identify which analytical techniques were used and whether these were suitable.

REFERENCES

Appendix 1: Case series definitions:

‘A report on a series of patients with an outcome of interest. No control group is involved.’() (p 279)

‘A case series is a descriptive study involving a group of patients who all have the same disease or condition: the aim is to describe common and differing characteristics of a particular group of individuals’ (Oxford Handbook of medical statistics)

‘A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment.’ Law K, Howick J. OCEBM Table of Evidence Glossary. 2013 [cited 2014 10th January]; Available from:

<http://www.cebm.net/index.aspx?o=1116>

‘A **case series** (also known as a clinical **series**) is a type of medical research study that tracks subjects with a known exposure, such as patients who have received a similar treatment, or examines their medical records for exposure and outcome.’ Wikipedia

‘A study which makes observations on a series of individuals, usually all receiving the same intervention, with no control group. Comments: At this stage it is unclear whether case series should be included in Cochrane systematic reviews, but we have left them in the list so that working groups can consider whether there are circumstances in which it would be appropriate to include them, and to assess risk of bias. A particular reason for including case series might be where they provide evidence relating to adverse effects of an intervention. Potential examples of risk of bias might be that if a case series does not [attempt to] recruit consecutive participants, this might introduce a risk of selection bias, while some case series could be at risk of detection bias, if the circumstances in which adverse effects are reported (or elicited) are not standardised.’

<http://bmg.cochrane.org/research-projectscochrane-risk-bias-tool>

JBI CRITICAL APPRAISAL TOOL

JBI CHECKLIST FOR QUASI-EXPERIMENTAL STUDIES

2023

INTRODUCTION

JBİ is a global organization promoting and supporting evidence-based decisions that improve health and health service delivery. JBİ offers a unique range of solutions to access, appraise and apply the best available evidence, servicing over 90 countries. Working with 80+ universities, hospitals and NGOs from across the globe through the JBİ Collaboration, JBİ is a recognized global leader in evidence-based health care.

JBİ Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available evidence and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. JBİ takes a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, JBİ has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. Guidance now exists for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBİ systematic reviews can be found in the JBİ Manual for Evidence Synthesis.

JBİ Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal for quantitative evidence is to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. Although designed for use in systematic reviews, JBİ critical appraisal tools can also be used when creating Critically Appraised Topics, in journal clubs and as an educational tool.

How were these tools developed?

JBİ critical appraisal tools have been developed by JBİ and collaborators. The particular iteration of this tool was developed by the JBİ Effectiveness Methodology Group following oversight by the JBİ Scientific Committee.

Like the previous versions of these tools, this version presents signaling questions to prompt reviewers to identify whether certain safeguards of bias have been met, in the primary literature under review. However, unlike previous iterations of this tool, this version has separated questions into whether they provide an answer relating to internal, external or statistical conclusion validity. For questions related to internal validity, these have been further separated to identify what domain of bias they are referring. Finally, this tool has also been structured to facilitate judgments related to bias at different levels (e.g. bias at the outcome level or bias at the result level) where appropriate.

These tools have been approved following extensive peer review by the JBİ Scientific Committee.

How to cite

Please use the following when citing this tool: Barker TH, Habibi N, Aromataris E, Stone JC, Leonardi-Bee J, Sears K, et al. The revised JBİ critical appraisal tool for the assessment of risk of bias quasi-experimental studies. JBİ Evid Synth. 2024;22(3):378-88.

RoB Assessor:	Date of Appraisal:	Record Number:
Study Author:	Study Title:	Study Year:

Internal Validity	Choice - Comments/Justification	Yes	No	Unclear	N/A
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Bias related to temporal precedence

1	Is it clear in the study what is the “cause” and what is the “effect” (i.e. there is no confusion about which variable comes first)?		☐	☐	☐	☐
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Bias related to selection and allocation

2	Was there a control group?		☐	☐	☐	☐
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Bias related to confounding factors

3	Were participants included in any comparisons similar?		☐	☐	☐	☐
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Bias related to administration of intervention/exposure

4	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?		☐	☐	☐	☐
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Bias related to assessment, detection and measurement of the outcome

5	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐

Outcome 6		☐	☐	☐	☐
Outcome 7		☐	☐	☐	☐

6	Were the outcomes of participants included in any comparisons measured in the same way?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

7	Were outcomes measured in a reliable way?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

8	Was follow-up complete and if not, were differences between groups in terms of		
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their follow-up adequately described and analyzed?					
Outcome 1		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐

Result 3		☐	☐	☐	☐
Outcome 7		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

9	Was appropriate statistical analysis used?				
Outcome 1		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		Yes	No	Unclear	N/A

Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Overall
appraisal:

Include:
☐

Exclude: ☐

Seek Further Info: ☐

Comments:

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JBI CRITICAL APPRAISAL TOOL FOR assessment of risk of bias for randomized controlled trials

2023

INTRODUCTION

JBI is a global organisation promoting and supporting evidence-based decisions that improve health and health service delivery.

JB

I offers a unique range of solutions to access, appraise and apply the best available evidence.

JB

I's approach to evidence-based healthcare is unique. JBI considers evidence-based healthcare as decision making that considers the feasibility, appropriateness, meaningfulness and effectiveness (FAME) of healthcare practice.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available evidence and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. JB

I take a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, JBI has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. Guidance now exists for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Manual for Evidence Synthesis.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal for quantitative evidence is to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. Although designed for use in systematic reviews, JB

I critical appraisal tools can also be used when creating Critically Appraised Topics (CATs), in journal clubs and as an educational tool.

How were these tools developed?

JB

I critical appraisal tools have been developed by JBI and collaborators. The particular iteration of this tool was developed by the JBI Effectiveness Methods Group following oversight by the JBI Scientific Committee.

Like the previous versions of these tools, this version presents signalling questions to prompt reviewers to identify whether certain safeguards of bias have been met, in the primary literature under review. However, unlike previous iterations of this tool, this version has separated questions into whether they provide an answer relating to internal, external or statistical conclusion validity. For questions related to internal validity, these have been further separated to identify what domain of bias they are referring. Finally, this tool has also been structured to facilitate judgments related to bias at different levels (e.g. bias at the outcome level or bias at the result level) where appropriate.

These tools have been approved following extensive peer review by the JB

I Scientific Committee.

How to cite: Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, Aromataris E, Munn Z. The revised JB

I critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI Evidence Synthesis. 2023;21(3):494-506

Assessor:	Date of Appraisal:	Record Number:
Study Author:	Study Title:	Study Year:

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?		☐	☐	☐	☐
2	Was allocation to treatment groups concealed?		☐	☐	☐	☐
3	Were treatment groups similar at the baseline?		☐	☐	☐	☐
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?		☐	☐	☐	☐
5	Were those delivering the treatment blind to treatment assignment?		☐	☐	☐	☐
6	Were treatment groups treated identically other than the intervention of interest?		☐	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐

Outcome 5		☐	☐	☐	☐
Outcome 6		☐	☐	☐	☐
Outcome 7		☐	☐	☐	☐

8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	Were outcomes measured in a reliable way		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐

Outcome 6		☐	☐	☐	☐
Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10

Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?

Outcome 1

Result 1

Result 2

Result 3

Outcome 2

Result 1

Result 2

Result 3

Outcome 3

Result 1

Result 2

Result 3

Outcome 4

Yes **No** **Unclear** **N/A**

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

Yes **No** **Unclear** **N/A**

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

Yes **No** **Unclear** **N/A**

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

☐ ☐ ☐ ☐

Yes **No** **Unclear** **N/A**

Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	Were participants analysed in the groups to which they were randomized?				
	Outcome 1		Yes	No	Unclear N/A

Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Outcome 6		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

12

Was appropriate statistical analysis used?					
Outcome 1		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 2		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 3		Yes	No	Unclear	N/A

Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 4		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		Yes	No	Unclear	N/A
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

		Yes	No	Unclear	N/A
13 Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		☐	☐	☐	☐

Overall appraisal:

Include: ☐
Exclude: ☐

Seek Further Info: ☐

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

QUESTION GUIDANCE

How to use the JBI Tools for the Assessment of Risk of Bias

Each question presented in a JBI tool for the assessment of risk of bias for quantitative study designs answers a question related to certain *categories of validity* and *domains of bias*. The concept of validity is often used when referring to the soundness or rigour in which a study was conducted, and whether the results of the study are likely to be true and generalizable. At JBI we have broken this down to include three separate categories that constitute *validity*, these include internal validity, external validity, statistical conclusion validity. In addition, we have also included comprehensiveness of reporting.

Questions categorised as “Internal Validity” are then further organised to specific domains of bias in which they relate. The domains of bias that are used as an indicator of internal validity include bias related to selection and allocation, bias related to administration of the intervention/exposure, bias related to assessment, detection and measurement of the outcome, bias related to participant retention, bias related to temporal precedence, bias related to classification of the exposure, bias related to confounding factors and bias related to selective reporting and/or publication bias.

For more information, please see [Barker et al. 2022](#)

Question 1: Was true randomization used for assignment of participants to treatment groups?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

If participants are not allocated to treatment and control groups by random assignment there is a risk that this assignment to groups can be influenced by the known characteristics of the participants themselves. These known characteristics of the participants may distort the comparability of the groups (i.e. does the intervention group contain more people over the age of 65 as compared to the control?). A true random assignment of participants to the groups means that a procedure is used that allocates the participants to groups purely based on chance, not influenced by any known characteristics of the participants. Reviewers should check the details about the randomization procedure used for allocation of the participants to study groups. Was a true chance (random) procedure used? For example, was a list of random numbers used? Was a computer-generated list of random numbers used? Was a statistician, external to the research team consulted for the randomization sequence generation? Additionally, reviewers should check that the authors are not stating they have used random approaches when they have instead used systematic approaches (such as allocating by days of the week).

Question 2: Was allocation to groups concealed?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

If those allocating participants to the compared groups are aware of which group is next in the allocation process, (i.e., the treatment or control group) there is a risk that they may deliberately and purposefully intervene in the allocation of patients. This may result in the preferential allocation of patients to the treatment group or to the control group. This may directly distort the

results of the study, as participants no longer have an equal and random chance to belong to each group compared. Concealment of allocation refers to procedures that prevent those allocating patients from knowing before allocation which treatment or control is next in the allocation process. Reviewers should check the details about the procedure used for allocation concealment. Was an appropriate allocation concealment procedure used? For example, was central randomization used? Were sequentially numbered, opaque and sealed envelopes used? Were coded drug packs used?

Question 3: Were treatment groups similar at the baseline?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

As with question 1, any differences between the known characteristics of participants included in compared groups constitutes a threat to internal validity. If differences in these characteristics do exist, then there is potential that the ‘effect’ cannot be attributed to the potential ‘cause’ (the examined intervention or treatment). This is because the ‘effect’ may be explained by the differences between participant characteristics and not due to the intervention/treatment of interest. Reviewers should check the characteristics reported for participants. Are the participants from the compared groups similar with regards to the characteristics that may explain the effect even in the absence of the ‘cause’, for example, age, severity of the disease, stage of the disease, co-existing conditions and so on? Reviewers should check the proportions of participants with specific relevant characteristics in the compared groups. [Note: **Do NOT** only consider the P-value for the statistical testing of the differences between groups with regards to the baseline characteristics.]

Question 4: Were participants blind to treatment assignment?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

Participants that are aware of their allocation to either the treatment or the control may behave, respond, or react differently to their assigned treatment (or control) than compared to participants that remain unaware of their allocation. Blinding of participants is a technique used to minimize this risk. Blinding refers to procedures that prevent participants from knowing which group they are allocated. If blinding has been followed, participants are not aware if they are in the group receiving the treatment of interest or if they are in any other group receiving the control interventions. Reviewers should check the details reported in the article about the blinding of participants with regards to treatment assignment. Was an appropriate blinding procedure used? For example, were identical capsules or syringes used? Were identical devices used? Be aware of different terms used, blinding is sometimes also called masking.

Question 5: Were those delivering the treatment blind to treatment assignment?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

Like question 4, those delivering the treatment that are aware of participant allocation to either treatment or control, may treat participants differently than compared to those that remain

unaware of participant allocation. There is the risk that any potential change in behaviour may influence the implementation of the compared treatments and the results of the study may be distorted. Blinding of those delivering treatment is used to minimize this risk. When this level of blinding has been achieved, those delivering the treatment are not aware if they are treating the group receiving the treatment of interest or if they are treating any other group receiving the control interventions. Reviewers should check the details reported in the article about the blinding of those delivering treatment with regards to treatment assignment. Is there any information in the article about those delivering the treatment? Were those delivering the treatment unaware of the assignments of participants to the compared groups?

Question 6: Were treatment groups treated identically other than the intervention of interest?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

To attribute the ‘effect’ to the ‘cause’, (assuming no bias related to selection and allocation) there should be no other difference between the groups in terms of treatment or care received, other than the treatment or intervention controlled by the researchers. If there are other exposures or treatments occurring at the same time with the ‘cause’ (the treatment or intervention of interest), then the ‘effect’ can potentially not be attributed to the examined ‘cause’ (the investigated treatment). This is because it is plausible that the ‘effect’ may be explained by these other exposures or treatments that occurred at the same time with the ‘cause’. Reviewers should check the reported exposures or interventions received by the compared groups. Are there other exposures or treatments occurring at the same time with the ‘cause’? Is it plausible that the ‘effect’ may be explained by other exposures or treatments occurring at the same time with the ‘cause’? Is it clear that there is no other difference between the groups in terms of treatment or care received, other than the treatment or intervention of interest?

Question 7: Were outcome assessors blind to treatment assignment?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

Like question 4 and 5, those assessing the outcomes that are aware of participant allocation to either treatment or control, may treat participants differently than compared to those that remain unaware of participant allocation. Therefore, there is a risk that the measurement of the outcomes between groups may be distorted, and the results of the study may themselves be distorted. Blinding of outcomes assessors is used in order to minimize this risk. Reviewers should check the details reported in the article about the blinding of outcomes assessors with regards to treatment assignment. Is there any information in the article about outcomes assessors? Were those assessing the treatment’s effects on outcomes unaware of the assignments of participants to the compared groups?

Question 8: Were outcomes measured in the same way for treatment groups?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

If the outcome is not measured in the same way in the compared groups, there is a threat to the internal validity of a study. Any differences in outcome measurements may be due to the method of measurement employed between the two groups, and not due to the intervention/treatment of interest. Reviewers should check if the outcomes were measured in the same way. Same instrument or scale used? Same measurement timing? Same measurement procedures and instructions?

Question 9: Were outcomes measured in a reliable way?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

Unreliability of outcome measurements is one threat that weakens the validity of inferences about the statistical relationship between the ‘cause’ and the ‘effect’ estimated in a study exploring causal effects. Unreliability of outcome measurements is one of the different plausible explanations for errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment (‘cause’). Reviewers should check the details about the reliability of the measurement used, such as the number of raters, training of raters, the intra-rater and the inter-raters reliability within the study (not as reported in external sources). This question is about the reliability of the measurement performed in the study, it is not about the validity of the measurement instruments/scales used in the study. Finally, some outcomes may not rely on instruments or scales (e.g. death) and reliability of the measurements may need to be assessed in the context of the study being reviewed. [Note: Two other important threats that weaken the validity of inferences about the statistical relationship between the ‘cause’ and the ‘effect’ are low statistical power and the violation of the assumptions of statistical tests. These other two threats are explored within Question 12).]

Question 10: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?

Category: Internal validity

Domain: Bias related to participant retention

Appraisal: Result level

For this question, follow up refers to the period from the moment of randomization to any point in which the groups are compared during the trial. This question asks if there is complete knowledge (measurements, observations etc.) for the entire duration of the trial for all randomly allocated participants. If there is incomplete follow up from all randomly allocated participants, this is known as post-assignment attrition. As RCTs are not perfect, there is almost always post-assignment attrition, and the focus of this question is on the appropriate exploration of post-assignment attrition. If differences do exist with regards to the post-assignment attrition between the compared groups of an RCT, then there is a threat to the internal validity of that study. This is because these differences may provide a plausible alternative explanation for the observed ‘effect’ even in the absence of the ‘cause’ (the treatment or intervention of interest). It is important to note that with regards post-assignment attrition, it is not enough to know the number of participants and the proportions of participants with incomplete data; the reasons for loss to follow up are essential in the analysis of risk of bias.

Reviewers should check if there were differences with regards to the loss to follow up between the compared groups. If follow up was incomplete (incomplete information on all participants),

examine the reported details about the strategies used to address incomplete follow up. This can include descriptions of loss to follow up (absolute numbers; proportions; reasons for loss to follow up) and impact analyses (the analyses of the impact of loss to follow up on results). Was there a description of the incomplete follow up including the number of participants and the specific reasons for loss to follow up? Even if follow up was incomplete, but balanced between groups, if the reasons for loss to follow up are different (e.g., side effects caused by the intervention of interest), these may impose a risk of bias if not appropriately explored in the analysis. If there are differences between groups with regards to the loss to follow up (numbers/proportions and reasons), was there an analysis of patterns of loss to follow up? If there are differences between the groups with regards to the loss to follow up, was there an analysis of the impact of the loss to follow up on the results? [Note: Question 10 is NOT about intention-to-treat (ITT) analysis; question 11 is about ITT analysis.]

Question 11: Were participants analysed in the groups to which they were randomized?

Category: Statistical conclusion validity

Appraisal: Result level

This question is about the intention-to-treat (ITT) analysis. There are different statistical analysis strategies available for the analysis of data from RCTs, such as intention-to-treat analysis (known also as intent to treat; abbreviated, ITT), per-protocol analysis, and as-treated analysis. In the ITT analysis the participants are analysed in the groups to which they were randomized. This means that regardless of whether participants received the intervention or control as assigned, were compliant with their planned assignment or participated for the entire study duration, they are still included in the analysis. The ITT analysis compares the outcomes for participants from the initial groups created by the initial random allocation of participants to those groups. Reviewers should check if an ITT analysis was reported; check the details of the ITT. Were participants analysed in the groups to which they were initially randomized, regardless of whether they participated in those groups, and regardless of whether they received the planned interventions? [Note: The ITT analysis is a type of statistical analysis recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement on best practices in trials reporting, and it is considered a marker of good methodological quality of the analysis of results of a randomized trial. The ITT is estimating the effect of offering the intervention, that is, the effect of instructing the participants to use or take the intervention; the ITT it is not estimating the effect of receiving the intervention of interest.]

Question 12: Was appropriate statistical analysis used?

Category: Statistical conclusion validity

Appraisal: Result level

Inappropriate statistical analysis may cause errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment ('cause'). Low statistical power and the violation of the assumptions of statistical tests are two important threats that weaken the validity of inferences about the statistical relationship between the 'cause' and the 'effect'. Reviewers should check the following aspects: were the assumptions of the statistical tests were respected; if appropriate statistical power analysis was performed; if appropriate effect sizes were used; if appropriate statistical methods were used given the nature of the data and the objectives of statistical analysis (association between variables; prediction; survival analysis etc.).

Question 13: Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Category: Statistical conclusion validity

Appraisal: Study level

The typical, parallel group RCT may not always be appropriate depending on the nature of the question being asked. Therefore, some additional RCT designs may have been employed that each come with their own additional considerations.

Crossover trials should only be conducted in people with a chronic, stable condition, where the intervention produces a short-term effect (i.e. relief in symptoms). Crossover trials should ensure there is an appropriate period of washout between treatments. This may also be considered under question 6.

Cluster RCTs randomize groups individuals or groups (e.g. communities, wards etc.) , forming ‘clusters.’ When we are assessing outcomes on an individual level in cluster trials, there are unit-of-analysis issues, as individuals within a cluster are correlated. This should be considered by the study authors when conducting analysis, and ideally authors will report the intra-cluster correlation coefficient. This may also be considered under question 12.

Stepped wedge RCTs may be appropriate to establish when and how a beneficial intervention may be best implemented within a defined setting, or due to logistical, practical, or financial considerations in the roll out of a new treatment/intervention. Data analysis in these trials should be conducted appropriately, considering the effects of time. This may also be considered under question 12.