Chapter 12
Methods to Enhance the Beneficial Effects of Exercise in Individuals with Spinal Cord Injuries

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Abstract Physical deconditioning commonly occurs following spinal cord injury (SCI) due to loss of voluntary functional movement and resultant increased sedentary behavior. This lesser energy expenditure leads to increased fat mass, decreased lean tissue mass, increased body mass index, declines in cardiac structure and function, reduced insulin sensitivity, and lower cardiorespiratory fitness. Collectively these physiological changes increase the risk of morbidity and mortality from cardiovascular diseases. Exercise as a therapy after an SCI may mitigate these negative health effects and improve quality and longevity of life. However, current exercise interventions for individuals with SCI may not be sufficient to prevent the elevations in risk factors for cardiovascular disease. Therefore, interventions to enhance the effectiveness of exercise therapy may be needed in this population in order to experience the same benefits seen by the uninjured population. Further, adjunctive therapies that mimic exercise may induce health benefits to combat cardiovascular disease. This chapter highlights novel interventions that may enhance function, increase exercise capacity, and decrease disease risk in individuals following an SCI. An effort was made to concentrate this chapter on human investigations of SCI but, where appropriate, investigations using animal models of SCI are referenced and specifically stated. Although this chapter highlights novel interventions to enhance the positive health benefits of exercise, combinations of these interventions may be necessary to improve the health of these individuals and warrants future investigation.

Keywords Spinal cord injury · Rehabilitation · Aerobic exercise · Cardiovascular disease · Regenerative medicine

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12.1 Introduction

Spinal cord injuries (SCI) occur in approximately 18,000 individuals in the United States each year, in 250,000–500,000 individuals globally, and are among the most catastrophic injuries that a person can experience (Jain et al. 2015; McDonald and Sadowsky 2002; Roberts et al. 2017; WHO 2013). An SCI results in lifelong disability in those who are typically young adults, predominantly men aged 16–44 years, and are primarily caused by vehicular accidents (DeVivo et al. 1999; Jain et al. 2015). An SCI disrupts neural connections below the level of injury that affect almost every major organ system, resulting in muscle paralysis, loss of sensation, and autonomic dysfunction. An SCI can occur anywhere along the 24 vertebrae and vary in severity from complete (American Spinal Injury Association Impairment Scale; AIS A) to incomplete impairment (AIS B, C, D). Complete impairments occur when there is an absence of all motor and sensory functions, including the sacral roots, distal to the site of the injury. Incomplete impairments occur when some voluntary movement or sensation is preserved. Additionally, SCIs may occur where normal motor and sensory function is retained but there may be abnormalities in reflex control (AIS E) (Roberts et al. 2017). Beyond neural disruption, SCI results in damage to vertebral bones, intervertebral disks, spinal ligaments, and blood vessels (McDonald and Sadowsky 2002).

Regardless of the neurological level of injury, there is rapid physical deconditioning secondary to the loss of voluntary motor control and increased sedentary activity following the injury (Pelletier and Hicks 2013). The reduced physical activity leads to a myriad of health issues associated with increased fat mass, decreased lean tissue mass, lipid disorders, blood pressure irregularities, abnormal glycemic control, and chronic inflammation (Bigford et al. 2017; Cragg et al. 2012; LaVela et al. 2006; Myers et al. 2007; Pelletier and Hicks 2013; Warburton et al. 2007; Weaver et al. 2007; Whiteneck et al. 1992). In addition, lesser activity induces structural and functional cardiovascular maladaptations (Ely et al. 2021; Williams et al. 2019). Together, these broad systemic physiological and structural changes increase the risk for cardiovascular diseases (Mercier and Taylor 2016; Myers et al. 2007). In fact, there is an increased prevalence and earlier onset of cardiovascular diseases, including heart failure, atrial fibrillation, atherosclerosis, and ischemic heart disease which are the leading causes of morbidity and mortality in individuals with chronic SCI (Cragg et al. 2012; Myers et al. 2007; Roger et al. 2012; Whiteneck et al. 1992).

12.2 Exercise Rehabilitation

Regular physical exercise is preventative for a broad range of diseases in uninjured individuals. Similarly, aerobic exercise in individuals with SCI is important to slow the progression or reverse negative health risks and minimize the incidence of

cardiovascular disease (Mercier and Taylor 2016; Myers et al. 2007; Qiu and Taylor 2016). However, exercise must meet certain intensity and volume criteria to create cardiovascular and metabolic demands sufficient to induce significant benefits across multiple physiological systems (Kikkinos et al. 2014; Qiu and Taylor 2016). These demands include increased oxygen consumption to elevate cardiac output and respiration, skeletal muscle blood flow demands to redistribute blood flow and increase vascular shear stress, and metabolic heat production sufficient to increase core temperature, all of which are implicated in the cardiometabolic benefits of exercise and are reduced in individuals with SCI (Green 2009; Joyner and Green 2009; Laughlin 1999; Laughlin et al. 2008). Muscle paralysis, as a consequence of SCI, reduces the amount of skeletal muscle that can voluntarily contribute to exercise, and therefore lessens the exercise intensity and duration that can be attained, and therefore the associated health benefits. Additionally, with an increased duration of time since injury, there are parallel declines in whole-body cardiorespiratory fitness and non-paralyzed muscle strength such that these individuals rank near the bottom of the physical fitness spectrum (Dearwater et al. 1986; Qiu and Taylor 2016). To maintain or increase cardiorespiratory fitness, it is currently recommended that individuals with SCI complete at least 30 min of moderate aerobic exercise 3 or more days per week or 20 min of vigorous aerobic exercise more than 3 days per week (Martin Ginis et al. 2018; Tweedy et al. 2017). Although these exercise guidelines are based on improvements in cardiorespiratory fitness, an increase in fitness occurs in parallel with reductions of many factors related to risk for cardiovascular disease (Franklin and McCullough 2009). However, the ability simply to participate in exercise, much less meet exercise intensity and duration guidelines is a challenge. Therefore, interventions to enhance exercise capacity or supplemental therapy to mimic exercise may be beneficial for those with SCI to confer the protective benefits of exercise.

12.3 Restoration of Function

Many types and modes of therapy are available for SCI rehabilitation but most do not fully restore the motor function of paralyzed limbs (Harvey et al. 2016). The lack of recovery is due to limited plasticity and regenerative capacity of the nervous system (Ashammakhi et al. 2019). In the past 10 years, there have been substantial advances in cell-based therapies, biomaterials, and biomolecules that aid in neuroregeneration but these techniques have not advanced to a point to restore functional recovery in humans (Ashammakhi et al. 2019). In general, treatment for SCI is focused on stabilization of the injury site, prevention of complications, and physical rehabilitation. Physical therapies are pragmatic and intended to improve quality of life (McDonald and Sadowsky 2002). Therefore, therapies for SCI are not "regenerative" but focus on maintaining or enhancing remaining function. In this context, exercise has become an important and quantifiable means for functional recovery (Fu et al. 2016; Sandrow-Feinberg et al. 2009; Warburton et al. 2007). Exercise not

only strengthens non-paralyzed and potentially paralyzed muscle but may also increase functional recovery through promoting brain remodeling, improving spinal microenvironments, and maintaining distal motor neuron function (Fu et al. 2016).

12.3.1 Spinal Stimulation

Motor deficits are considered the most significant barrier to functional recovery. Currently, some rehabilitative strategies attempt to activate and enhance remaining functional neurons in individuals with partially preserved motor function. Spinal stimulation (epidural or transcutaneous) requires a neural computer interfaced with an electrode to apply electrical impulses onto dorsal root spinal neurons (Ozpinar et al. 2016; Wagner et al. 2018). The impulses are synchronized with voluntary repetitive muscle contractions or joint movements (i.e., exercise) (Ievins and Moritz 2017; McPherson et al. 2015). Following the cessation of stimulation, there can be improvements in muscle activation and limb movement/mobility. While used primarily in rodents, this technique has resulted in large improvements of joint movements that aid walking, reaching, and grasping (Mushahwar et al. 2002; Sunshine et al. 2013; Zimmermann et al. 2011). In humans, smaller improvements in joint movement have occurred with spinal stimulation. Importantly, spinal stimulation in combination with physical therapy has shown greater recovery of movement compared to physical training alone and has improved lower limb flexion/extension, leg strength, sit-to-stand tasks, ankle mobility during walking, as well as hand control and grip strength (Al'joboori et al. 2020; Donovan et al. 2021; Jilge et al. 2004; Lu et al. 2016; Meyer et al. 2020; Minassian et al. 2016; Sayenko et al. 2019; Wagner et al. 2018). Although the precise mechanisms leading to the improved function are unknown, it is believed that the stimulation drives neural plasticity by increasing neural output, increasing neural activation, recruiting peripheral undamaged neurons, or increasing the sensitivity of proprioceptive pathways (Ievins and Moritz 2017; Wagner et al. 2018). The improved mobility and muscle activation may enhance exercise options for those with SCI. Unfortunately, continuous stimulation appears to lose its effect after an extended period of time, and the improvements in motor control gained from stimulation are often lost or significantly reduced in the hours to days following the cessation of stimulation.

12.3.2 Functional Electrical Stimulation (FES)

Most aerobic exercise options for those with SCI are limited to the volitional movement of the upper body given the loss of motor function in the legs. Unfortunately, the small muscle mass of the upper body is insufficient to produce sustainable high levels of aerobic work (Jacobs et al. 2001; Qiu and Taylor 2016). For example, peak oxygen consumption during arms-only exercise can reach 25 ml/kg/min at

workloads (~34 Watts) that can only be maintained for a few minutes (Glaser et al. 1980; Sawka et al. 1980). Hence, arms-only exercise is limited as a therapy to fulfill exercise intensity and duration requirements for cardiovascular health. This is likely the reason for the modest cardiovascular and respiratory improvements with arms-only training (Taylor et al. 1986). To overcome the limitations of arm-only exercise, external stimulation of paralyzed muscle, specifically the lower body, has been promoted as a practical and effective intervention to increase active muscle mass and whole-body oxygen consumption (Mutton et al. 1997).

Contraction of paralyzed skeletal muscle is accomplished by using an electrical stimulus applied through muscle/nerve implantable probes or skin electrodes. The electrical stimuli initiate action potentials within motor neurons resulting in muscle contraction (Peckham and Knutson 2005). When the electrically elicited muscle contractions are coordinated in a manner that provides functional movement, the technique is termed functional electrical stimulation (FES) (Peckham and Knutson 2005). The purpose of FES is to generate muscular contractions and produce useful movements such as leg flexion/extension for cycling or rowing exercises, and in some cases walking.

For example, FES-evoked cycling uses bilateral stimulation of the quadriceps, hamstrings, and gluteal muscles to perform cyclical pedaling movements of the legs (Deley et al. 2014; Qiu and Taylor 2016). This commonly used FES modality activates a relatively small amount of muscle mass and causes modest increases in oxygen consumption, heart rate, and cardiac output (Fornusek and Davis 2008; Hunt et al. 2007). FES activation of lower limb muscles has been shown to be important to the exercise response as it engages the skeletal muscle pump during rhythmic contractions to aid in venous return to the heart. Repeat sessions of FES have been shown to increase quadriceps torque, glucose transport, citrate synthase activity, capillary number, fatigue resistance, and muscle fiber cross sectional area (Chilibeck et al. 1999a, 1999b; Rodgers et al. 1991; Sabatier et al. 2006). This technique has been promoted as an effective way to increased exercise tolerance and improves overall cardiovascular health by mimicking moderate-to-vigorous intensity exercise training (Warburton et al. 2007). However, FES should not be considered synonymous with voluntary exercise. Externally activating skeletal muscle bypasses feedforward input to the cardiorespiratory system from the central nervous system (i.e., central command) and the paralyzed muscle provides minimal or no feedback from the periphery (i.e., group III/IV muscle afferents) to the cardiovascular and pulmonary centers in the brain stem Ely and Taylor 2021. Additionally, due to the nature of electrical stimulation, muscle fibers are activated in reverse physiological order. This reverse recruitment induces a high rate of muscle fatigue and a potentially altered metabolism (Binder-Macleod and Snyder-Mackler 1993; Gregory and Bickel 2005; Peckham and Knutson 2005). FES also results in low levels of systemic vascular shear stress and small elevations of body core temperature. These factors are not trivial and have causative connections to improving cardiovascular health.

12.3.3 Hybrid Functional Electrical Stimulation

To induce greater exercise benefits and better mimic exercise in uninjured individuals, a combination of FES of paralyzed leg muscle with voluntary arm exercise has been implemented for cycling and rowing (Laskin et al. 1993). This hybrid mode of exercise increases the mass of active musculature and produces simultaneous training of the upper and lower extremities (Qiu and Taylor 2016). Hybrid FES-exercise results in greater cardiovascular responses and higher oxygen consumption than either upper or lower body exercise alone (Brurok et al. 2011; Mutton et al. 1997). Importantly, exercise training using hybrid methods produce between 10 and 60% larger increases in cardiorespiratory fitness and cardiac function compared to arms-only or FES lower body exercise training (Brurok et al. 2011; Gibbons et al. 2016; Hettinga and Andrews 2008; Taylor et al. 2011). Importantly, studies have shown that hybrid exercise is well-tolerated by individuals with SCI and can be maintained at sufficient submaximal exercise intensities for long durations to meet exercise guidelines for cardiovascular health (Hettinga and Andrews 2008; Qiu and Taylor 2016; Taylor et al. 2011). In fact, hybrid FES-exercise has been shown to decrease blood pressure, insulin resistance, blood glucose, systemic inflammation, and improve overall cardiovascular health (Bakkum et al. 2015; Griffin et al. 2009; Warburton et al. 2007).

12.4 Ventilatory Limitations to Exercise in SCI

To meet the higher oxidative needs of muscle as exercise workload increases, pulmonary ventilation is normally increased in parallel by increases in tidal volume and breathing frequency. In most uninjured individuals ventilatory capacity is more than adequate to meet metabolic demands for all exercise intensities, even following large increases in muscle oxygen demand after strenuous training programs (Casaburi et al. 1992; McParland et al. 1992). Individuals with SCI can have impaired respiratory muscle control proportional to the level of injury. For example, individuals with SCI above the third thoracic vertebra (<T3) have profound motor loss/spasticity to accessory muscles of respiration, atrophy of respiratory muscles, and reduced compliance of the lungs and chest wall. These factors not only reduce the total amount of air an individual can move in and out of their lungs with each breath but also contribute to an increased oxygen cost of breathing (Shields 2002). A larger recruited skeletal muscle mass during exercise via FES creates a mismatch between the oxygen demand of the muscle and the ventilatory capacity of the lungs, especially in those with high-level injuries (Taylor et al. 2014). Therefore, when large amounts of muscle mass are active (i.e., hybrid FES-exercise), exercise intensity can be limited by pulmonary capacity (Qiu et al. 2016).

12.4.1 Non-Invasive Ventilation (NIV)

A novel approach to potentially improve exercise capacity would be a support of ventilation during exercise. Non-invasive ventilation (NIV) does not require intubation and provides external ventilatory support via positive air pressure through a facemask during inhalation. Current NIV machines use bi-level positive pressure to assist with lung expansion during inhalation and a reduced positive pressure upon exhalation to limit airflow back to the machine. This technique has been demonstrated to reduce the work of breathing, enhance exercise tolerance, and improve exercise capacity in individuals with obstructive and resistive pulmonary diseases (Borel et al. 2008; Dreher et al. 2010; van't Hul et al. 2006; Vila et al. 2007). Additionally, in individuals with chronic obstructive pulmonary disease (COPD), NIV during a single bout of exercise reduced dyspnea, improved breathing patterns, and enhanced oxygen and carbon dioxide exchange (Dreher et al. 2007; Maltais et al. 1995; van't Hul et al. 2004). One study examining maximal exercise capacity in individuals with SCI noted that NIV increased oxygen consumption only in individuals with high-level injuries and shorter time since injury. The improvement in this population likely reflects the greater amount of respiratory motor control loss due to the high injury and remaining muscle strength due to lesser atrophy from the shorter time since injury (Vivodtzev et al. 2020). Therefore, targeted use of NIV to support exercise could be an effective approach to overcome ventilatory limits.

12.4.2 Buspirone (Serotonergic Receptor Agonist)

Although paralyzed pulmonary musculature is partly responsible for the reduced function, spinal and supraspinal neural control of respiration are reduced after SCI and may also contribute to the reduced ventilation (De Troyer et al. 1986; De Troyer and Heilporn 1980; Schilero et al. 2014; Zimmer and Goshgarian 2007). In addition to damaged descending neurons, impaired ascending neuronal feedback contributes to dysregulation during inspiratory and expiratory phases of breathing (Bezdudnaya et al. 2017). One important neurotransmitter in both descending and ascending pathways is serotonin. As a result, the serotonin 5HT1A receptor agonist buspirone may increase the excitability of pulmonary neurons that survived the injury (Choi et al. 2005; Kheck et al. 1995). Although buspirone is commonly prescribed as an anxiolytic, it has been shown to increase respiratory responses to carbon dioxide in an animal model of SCI (Choi et al. 2005; Teng et al. 2003), and in human case studies, it has been found to improve chemosensitivity and respiratory rhythms in individuals with apneustic syndromes/injuries (El-Khatib et al. 2003; Saito et al. 1999). In patients with COPD, 14 days of buspirone treatment reduced symptoms of dyspnea and increased exercise tolerance (Argyropoulou et al. 1993). Interestingly, a retrospective analysis of individuals with SCI taking buspirone displayed greater increases in peak oxygen consumption and ventilation following 6 months of

FES-rowing compared to a matched group of individuals in the same training program not taking buspirone (Vivodtzev et al. 2021). Hence, this anxiolytic may have the potential to improve exercise respiration, exercise capacity, and health outcomes in those with SCI.

12.4.3 Drug Therapy that May Improve Locomotor Function

There are a number of medications that have displayed the potential to be neurorestorative or improve motor function following a SCI. Some of these medications include metformin (Afshari et al. 2018; Zhang et al. 2017), riluzole (Srinivas et al. 2019), dalfampridine (Hansebout et al. 1993), and antiNOGO (Zörner and Schwab 2010). These medications have various targets on motor neurons including modulating glutamine, potassium channels, and the myelin sheath. Individually, these medications have varying levels of efficacy at improving function in animal models of SCI. A medication that is showing some promise is spinalon. Spinalon, currently in Phase I/II trials, is an investigational drug that is a combination of monoamine receptor agonists, noradrenaline/dopamine precursors, and decarboxylase inhibitors (buspirone, levodopa, and carbodopa). This drug combination has enhanced walking coordination in mice, turtles, and humans with SCI. These drugs appear to stimulate the spinal walking reflex, allowing for up to 60 minutes of walking motions to occur after administration (Guertin and Guertin 2012; Guertin et al. 2010; Ung et al. 2012). Interestingly, this drug combination has initiated walking motions in individuals with motor incomplete (AIS B) and complete (AIS A) injuries. This combinational therapy may greatly improve exercise options, including bipedal exercise therapy, and improve the health of individuals with SCI. Unfortunately, early outcomes from transected mice models show that the long duration sessions of walking may not reach an exercise intensity to improve health outcomes in all body systems. In these mice, the walking attenuated loss of muscle mass but did not slow the rate of reduction in bone density (Guertin et al. 2011). These investigations suggest that there is promise in improving motor function through medications, and that combinational medications may be most efficacious. Additionally, combinational drug therapies may be an important avenue of enhancing exercise capabilities in those with SCI.

12.4.4 Intermittent Hypoxia

Intermittent hypoxia is a non-pharmacological intervention that may also increase respiratory responses to exercise. This technique exposes individuals to short (60 s to 5 min) bouts of air with reduced oxygen content (~5% O_2) which results in increased ventilation. This practice appears to strengthen synaptic pathways to respiratory motor neurons by a mechanism known as phrenic long-term facilitation (Ling et al.

2001). Long-term facilitation is a serotonin-dependent change in spinal plasticity that is characterized as a progressive increase in phrenic motor output during hypoxia which remains elevated upon return to normal arterial oxygen levels (Fuller et al. 2001, 2003). Only a small number of hypoxic events are required for a lasting increase in respiratory motor output. In rats, the increased motor output lasts approximately 90 min after three 90 sec hypoxic exposures, and it is reported that 10 exposures over 7 days could produce an effect that lasts 24 hours. In humans, there is elevated ventilation immediately after hypoxic exposure and the effect is larger in those with higher level injuries (Sankari et al. 2015). A case report in an individual with a chronic C4 injury showed that 10 days of intermittent hypoxia improved inspiratory capacity (Jaiswal et al. 2016). Therefore, longer duration hypoxic exposure may enhance the magnitude of ventilatory long-term facilitation in those with SCI (Jaiswal et al. 2016; Tester et al. 2014).

Intermittent hypoxia may also have positive effects on motor output, as hypoxia increased the size of the motor action potentials of finger muscles by 20% (Christiansen et al. 2021). In individuals with incomplete SCI, 15 90 s sessions of intermittent hypoxia in combination with overground walking improved speed of walking during 10-meter walk tests after 1 day and walking distance in a 6 min walk test after 2 weeks of exposure (Hayes et al. 2014). Hence, intermittent hypoxia may have therapeutic potential to enhance respiratory and motor function and may improve exercise tolerance and capacity in individuals with SCI (Fuller et al. 2003). However, it should be noted that, potentially counterproductive to decreasing risk factors for cardiovascular disease, intermittent hypoxia has been shown to increase serum levels of cholesterol, phospholipids, and triglycerides in lean mice (Li et al. 2005) and increase pro-inflammatory pathways in individuals with sleep apnea (Ryan et al. 2005).

12.5 Heat Stress

Individuals with SCI are unlikely to experience large increases in body core temperature during regular exercise therapies. Lesser whole-body metabolism from relatively low exercise intensities, short duration, and smaller total skeletal mass recruited to perform the exercise result in small elevations in core temperature. Some of the cardiovascular benefits of exercise training are related to repeated intermittent increases in body core temperature (Locke et al. 1990; Rhind et al. 2004) and resultant alterations in vascular shear stress (Laughlin et al. 2008). The reduced influence of this potentially important signaling pathway could limit cardiovascular and metabolic adaptations. Therefore, heat therapy, or repeated exposure to passive heat stress, has been proposed as a means to improve cardiovascular and metabolic health in individuals with SCI (Ely et al. 2018; Hooper and Hooper 2009; Neff et al. 2016). Exercise and heat stress elicit many common physiological responses, in addition to increasing core temperature, there are increases in cardiac chronotropy and inotropy, redistribution of blood flow, and increased endothelial shear stress, all

of which impact cardiovascular health (Johnson and Proppe 2011). Passive heat therapy, using either sauna or hot water immersion, has been shown to improve cardiovascular health in healthy, uninjured humans and in patients with elevated cardiovascular disease risk. Passive heating increases cardiac function (Tei et al. 1995), decreases systemic vascular resistance (Tei et al. 1995), improves autonomic profile (Ely et al., 2019b), augments brachial artery flow-mediated vasodilation (Brunt et al. 2016b; Ely et al. 2019b; Imamura et al. 2001; Kihara et al. 2002), elicits protection from ischemia-reperfusion injury (Brunt et al. 2016c; Ely et al. 2019b; Engelland et al. 2020), and improves microvascular function (Brunt et al. 2016a; Romero et al. 2017). Improvements have also been observed in cardiometabolic variables including fasting blood glucose (Ely et al. 2019a; Hooper 1992), blood lipid profile (Ely et al. 2019b), and markers of inflammation (Ely et al. 2019a). Additionally, repeated heat exposure leads to the induction of cytoprotective pathways which are associated with protection from cardiovascular and metabolic disease (Horowitz and Assadi 2010; Krause et al. 2015; Kurucz et al. 2002; Maloyan et al. 2005). Heat therapy research in individuals with SCI is currently limited to single sessions studies, but importantly, these studies indicate heat therapy is safe and well-tolerated. The single session studies indicate that passive heating interventions such as lower limb or whole-body hot water immersion lead to altered inflammatory profiles (Leicht et al. 2015) and endothelial cell activation (Coombs et al. 2019), similar to what is observed following acute exercise. These initial first studies indicate that heat therapy may be a novel and important approach to restore cardiometabolic function in individuals with SCI.

12.6 Exoskeleton/Body Weight Supported Treadmill Exercise

Robotic exoskeletons, limb orthoses, or bionic suits can allow individuals with varying levels of SCI to safely and functionally walk for mobility or exercise (Kandilakis and Sasso-Lance 2019). These orthoses increase walking/exercise time by increasing the number of steps individuals can take (Gorgey et al. 2017). A limitation often associated with exoskeletons is that they slow the movements of the individual and often require greater oxygen consumption than normal walking (Asselin et al. 2015; Evans et al. 2015; Massucci et al. 1998; Waters and Mulroy 1999). The greater oxygen consumption or metabolic load of movement may actually be a benefit, as this indicates a greater exercise intensity (Kandilakis and Sasso-Lance 2019). Previous individual sessions of exercise using exoskeletons in conjunction with bodyweight supported treadmill training have shown a prolonged exercise time, decreased ratings of fatigue, and improved muscle strength and endurance (Wu et al. 2012). Using exoskeletons for up to 6 months of exercise training has resulted in global changes in body composition such as an increased bone density and decreased intramuscular and subcutaneous adipose tissue (Gorgey

et al. 2017; Karelis et al. 2017). Six months of exoskeleton training also resulted in improved blood glucose regulation (Phillips et al. 2004). Cardiac improvements with exoskeleton exercise training include increased ejection fraction, increased heart mass, decreased end-systolic and increased end-diastolic volumes, and reduced isovolumetric relaxation times (Turiel et al. 2011). The positive changes in body composition, cardiac structure and function, and glucose regulation ultimately reduce the cardiovascular disease risk in those with SCI.

12.7 Combined Therapies

Exercise training in combination with other treatments that enhance or mimic exercise may be important to realize the benefits of exercise. Combination therapies may better mimic the stress of exercise upon the body than singular therapies and may be more effective at improving the cardiovascular health of individuals with SCI. For example, the combination of intermittent hypoxia with transcranial magnetic stimulation of the motor cortex produced larger motor evoked potentials of finger muscles than repeated stimulation alone (Christiansen et al. 2021). Similarly, the pairing of serotonin agonists drugs with electrical stimulation produced enhanced motor function and greater muscle movements in mice than stimulation alone (Gerasimenko et al. 2007, 2015; Van Den Brand et al. 2012). Recently, one study on individuals with incomplete SCI paired peripheral nerve stimulation and magnetic transcortical stimulation with exercise. The combination of exercise and stimulation contributed to a lasting retention of muscle strength and a decreased time in a 10-minute walk test (Jo and Perez 2020). Incredibly, this combination produced improvements in motor function that remained 6 months after the therapy. These combinational therapies are showing great promise at increasing mobility and exercise capacity. Therefore, combinational therapies with exercise may further decrease cardiovascular health risk in those with SCI. Moreover, SCI can be heterogenous; individuals with the same injury level and AIS scale may have a very different loss of respiratory or autonomic function (Draghici and Taylor 2018). Hence, some patients may respond better to some adjunctive therapies than others, and so it may be wise to apply combination therapies to ensure the greatest response across the spectrum of SCI.

12.8 Limitations

Many of the therapies to increase exercise tolerance may not be practical options for all individuals. For example, to complete FES-exercise, electrical stimulation units must be integrated with modified exercise equipment (e.g., bicycle or rowing ergometer). In general, a basic electrical stimulation unit is not cost prohibitive (<$200) but units that coordinate antagonistic muscle firing may be a few thousand

dollars and are not commonly covered by insurance. Additionally, exoskeletons for exercise rehabilitation are cost prohibitive for personal use (>$80,000) and require additional trained personnel to set up and operate. Therefore, these therapies are generally limited to clinical outpatient settings at hospitals or rehabilitation clinics where equipment and trained staff are available for guidance. Similarly, heat therapy using lower leg hot water immersion is a feasible home-based option using a bathtub or heated leg bath (<$200), but supervision may be recommended for individuals with higher level injuries (T6 and above) due to challenges with thermoregulation and blood pressure regulation during heat stress, in addition to potential burning of insensate skin (Schmidt and Chan 1992). Additionally, there are home-based units that are able to produce hypoxic environments (e.g., HYPO2XICO) which can be used in conjunction with exercise equipment, but these are often cost prohibitive at a few thousand dollars per unit. Finally, animal models do not approximate the effects of SCI in humans across all systems (Akhtar et al. 2008; Seok et al. 2013). Therefore, many animal studies should be interpreted with caution as they were conducted in murine species. Murine species are often used as surrogates for understanding human physiology, but genomic differences often result in divergent findings between the species (Seok et al. 2013).

12.9 Concluding Remarks and Future Directions

Individuals with SCIs are 2–6 times more likely to experience cardiovascular disease than uninjured individuals (Cragg et al. 2012, 2013). The increased incidence of CVD is due to amplified risk including increased physical inactivity, dyslipidemia, uncontrolled blood pressure, and uncontrolled blood glucose (Cragg et al. 2013). Currently, the best therapy to improve these cardiovascular disease risk factors is exercise. However, benefits to health and wellness may not be available to those with SCI since they may not be able to attain necessary exercise intensity or duration thresholds. Therefore, a combination of approaches including drug and adjunctive therapy in addition to exercise may be needed for this population to obtain reductions in cardiovascular disease risk. Future research focusing on combining exercise with other treatments to maximize benefits will further elucidate the potential for these adjunctive treatments to improve health and reduce morbidity and mortality from metabolic and cardiovascular diseases in individuals with SCI.

References

Afshari K, Dehdashtian A, Haddadi NS, Haj-Mirzaian A, Iranmehr A, Ebrahimi MA, Tavangar SM, Faghir-Ghanesefat H, Mohammadi F, Rahimi N, Javidan AN, Dehpour AR (2018) Anti-inflammatory effects of metformin improve the neuropathic pain and locomotor activity in spinal cord injured rats: introduction of an alternative therapy. Spinal Cord 56:1032–1041

Akhtar AZ, Pippin JJ, Sandusky CB (2008) Animal models in spinal cord injury: a review. Rev Neurosci 19:47–60

Al'joboori Y, Massey SJ, Knight SL, Donaldson N d N, Duffell LD (2020) The effects of adding transcutaneous spinal cord stimulation (tSCS) to sit-to-stand training in people with spinal cord injury: a pilot study. J Clin Med 9:2765

Argyropoulou P, Patakas D, Koukou A, Vasiliadis P, Georgopoulos D (1993) Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease. Respiration 60:216–220

Ashammakhi N, Kim H-J, Ehsanipour A, Bierman RD, Kaarela O, Xue C, Khademhosseini A, Seidlits SK (2019) Regenerative therapies for spinal cord injury. Tissue Eng Rev 25:471–491

Asselin P, Knezevic S, Kornfeld S, Cirnigliaro C, Agranova-Breyter I, Bauman WA, Spungen AM (2015) Heart rate and oxygen demand of powered exoskeleton-assisted walking in persons with paraplegia. J Rehabil Res Dev 52:147–158

Bakkum A, Paulson T, Bishop N, Goosey-Tolfrey V, Stolwijk-Swüste J, Kuppevelt D, Groot S, Janssen T (2015) Effects of hybrid cycle and handcycle exercise on cardiovascular disease risk factors in people with spinal cord injury: a randomized controlled trial. J Rehabil Med 47:523–530

Bezdudnaya T, Marchenko V, Zholudeva LV, Spruance VM, Lane MA (2017) Supraspinal respiratory plasticity following acute cervical spinal cord injury. Exp Neurol 293:181–189

Bigford GE, Mendez AJ, Betancourt L, Burns-Drecq P, Backus D, Nash MS (2017) A lifestyle intervention program for successfully addressing major cardiometabolic risks in persons with SCI: a three-subject case series. Spinal Cord Ser Cases 3:1–8

Binder-Macleod SA, Snyder-Mackler L (1993) Muscle fatigue: clinical implications for fatigue assessment and neuromuscular electrical stimulation. Phys Ther 73:902–910

Borel JC, Wuyam B, Chouri-Pontarollo N, Deschaux C, Levy P, Pépin JL (2008) During exercise non-invasive ventilation in chronic restrictive respiratory failure. Respir Med 102:711–719

Brunt VE, Eymann TM, Francisco MA, Howard MJ, Minson CT (2016a) Passive heat therapy improves cutaneous microvascular function in sedentary humans via improved nitric oxide-dependent dilation. J Appl Physiol 121:716–723

Brunt VE, Howard MJ, Francisco MA, Ely BR, Minson CT (2016b) Passive heat therapy improves endothelial function, arterial stiffness and blood pressure in sedentary humans. J Physiol 594: 5329–5342

Brunt VE, Jeckell AT, Ely BR, Howard MJ, Thijssen DHJ, Minson CT (2016c) Acute hot water immersion is protective against impaired vascular function following forearm ischemia-reperfusion in young healthy humans. Am J Physiol - Regul Integr Comp Physiol 311: R1060–R1067

Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J (2011) Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. Am J Phys Med Rehabil 90:407–414

Casaburi R, Barstow TJ, Robinson T, Wasserman K (1992) Dynamic and steady-state ventilatory and gas exchange responses to arm exercise. Med Sci Sports Exerc 24:1365–1374

Chilibeck PD, Bell G, Jeon J, Weiss CB, Murdoch G, MacLean I, Ryan E, Burnham R (1999a) Functional electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle. Metabolism 48:1409–1413

Chilibeck PD, Jeon J, Weiss C, Bell G, Burnham R (1999b) Histochemical changes in muscle of individuals with spinal cord injury following functional electrical stimulated exercise training. Spinal Cord 37:264–268

Choi H, Liao WL, Newton KM, Onario RC, King AM, Desilets FC, Woodard EJ, Eichler ME, Frontera WR, Sabharwal S, Teng YD (2005) Respiratory abnormalities resulting from midcervical spinal cord injury and their reversal by serotonin 1A agonists in conscious rats. J Neurosci 25:4550–4559

Christiansen L, Chen B, Lei Y, Urbin MA, Richardson MSA, Oudega M, Sandhu M, Rymer WZ, Trumbower RD, Mitchell GS, Perez MA (2021) Acute intermittent hypoxia boosts spinal plasticity in humans with tetraplegia. Exp Neurol 335:113483

Coombs GB, Barak OF, Phillips AA, Mijacika T, Sarafis ZK, Lee AHX, Squair JW, Bammert TD, DeSouza NM, Gagnon D, Krassioukov AV, Dujic Z, DeSouza CA, Ainslie PN (2019) Acute heat stress reduces biomarkers of endothelial activation but not macro- or microvascular dysfunction in cervical spinal cord injury. Am J Physiol Circ Physiol 316:H722–H733

Cragg JJ, Stone JA, Krassioukov AV (2012) Management of Cardiovascular Disease Risk Factors in individuals with chronic spinal cord injury: an evidence-based review. J Neurotrauma 29: 1999–2012

Cragg JJ, Noonan VK, Krassioukov A, Borisoff J (2013) Cardiovascular disease and spinal cord injury results from a national population health survey. Neurology 81:723–728

De Troyer A, Heilporn A (1980) Respiratory mechanics in quadriplegia. The respiratory function of the intercostal muscles. Am Rev Respir Dis 122:591–600

De Troyer A, Estenne M, Heilporn A (1986) Mechanism of active expiration in tetraplegic subjects. N Engl J Med 314:740–744

Dearwater SR, Laporte RE, Robertson RJ, Brenes G, Adams LL, Becker D (1986) Activity in the spinal cord-injured patient: an epidemiologic analysis of metabolic parameters. Med Sci Sports Exerc 18:541–544

Deley G, Denuziller J, Babault N (2014) Functional electrical stimulation: cardiorespiratory adaptations and applications for training in paraplegia. Sport Med 45:71–82

DeVivo MJ, Krause JS, Lammertse DP (1999) Recent trends in mortality and causes of death among persons with spinal cord injury. Arch Phys Med Rehabil 80:1411–1419

Donovan J, Forrest G, Linsenmeyer T, Kirshblum S (2021) Spinal cord stimulation after spinal cord injury: promising multisystem effects. Curr Phys Med Rehabil Reports 9:23–31

Draghici AE, Taylor JA (2018) Baroreflex autonomic control in human spinal cord injury: physiology, measurement, and potential alterations. Auton Neurosci Basic Clin 209:37–42

Dreher M, Storre JH, Windisch W (2007) Noninvasive ventilation during walking in patients with severe COPD: a randomised cross-over trial. Eur Respir J 29:930–936

Dreher M, Kabitz H-J, Burgardt V, Walterspacher S, Windisch W (2010) Proportional assist ventilation improves exercise capacity in patients with obesity. Respiration 80:106–111

El-Khatib MF, Kiwan RA, Jamaleddine GW (2003) Buspirone treatment for Apneustic breathing in brain stem infarct. Respir Care 48:956–958

Ely BR, Clayton ZS, McCurdy CE, Pfeiffer J, Minson CT (2018) Meta-inflammation and cardiometabolic disease in obesity: can heat therapy help? Temperature 5:9–21

Ely BR, Clayton ZS, McCurdy CE, Pfeiffer J, Needham KW, Comrada LN, Minson CT, Wiedenfeld-Needham K, Comrada LN, Minson CT, Needham KW, Comrada LN, Minson CT (2019a) Heat therapy improves glucose tolerance and adipose tissue insulin signaling in polycystic ovary syndrome 317:E172–E182

Ely BR, Francisco MA, Halliwill JR, Bryan SD, Comrada LN, Larson EA, Brunt VE, Minson CT (2019b) Heat therapy reduces sympathetic activity and improves cardiovascular risk profile in women who are obese with polycystic ovary syndrome. Am J Physiol Integr Comp Physiol 317: R630–R640

Ely MR, Taylor JA (2021) The practical utility of functional electrical stimulation exercise for cardiovascular health in individuals with spinal cord injury. Curr Phys Med Rehabil Rep 9 (3):154–162

Ely MR, Singh TK, Baggish AL, Taylor JA (2021) Reductions in cardiac structure and function 24 months after spinal cord injury: a cross-sectional study. Arch Phys Med Rehabil 102(8): 1490–1498

Engelland RE, Hemingway HW, Tomasco OG, Olivencia-Yurvati AH, Romero SA (2020) Acute lower leg hot water immersion protects macrovascular dilator function following ischaemia–reperfusion injury in humans. Exp Physiol 105:302–311

Evans N, Hartigan C, Kandilakis C, Pharo E, Clesson I (2015) Acute cardiorespiratory and metabolic responses during exoskeleton-assisted walking overground among persons with chronic spinal cord injury. Top Spinal Cord Inj Rehabil 21:122–132

Fornusek C, Davis GM (2008) Cardiovascular and metabolic responses during functional electric stimulation cycling at different cadences. Arch Phys Med Rehabil 89:719–725

Franklin BA, McCullough PA (2009) Cardiorespiratory fitness: an independent and additive marker of risk stratification and health outcomes. Mayo Clin Proc 84:776–779

Fu J, Wang H, Deng L, Li J (2016) Exercise training promotes functional recovery after spinal cord injury. Neural Plast 2016:1–7

Fuller DD, Zabka AG, Baker TL, Mitchell GS (2001) Physiological and genomic consequences of intermittent hypoxia selected contribution: phrenic long-term facilitation requires 5-HT receptor activation during but not following episodic hypoxia. J Appl Physiol 90:2001–2006

Fuller DD, Johnson SM, Olson EB, Mitchell GS (2003) Synaptic pathways to phrenic motoneurons are enhanced by chronic intermittent hypoxia after cervical spinal cord injury. J Neurosci 23: 2993–3000

Gerasimenko YP, Ichiyama RM, Lavrov IA, Courtine G, Cai L, Zhong H, Roy RR, Edgerton VR (2007) Epidural spinal cord stimulation plus quipazine administration enable stepping in complete spinal adult rats. J Neurophysiol 98:2525–2536

Gerasimenko YP, Lu DC, Modaber M, Zdunowski S, Gad P, Sayenko DG, Morikawa E, Haakana P, Ferguson AR, Roy RR, Edgerton VR (2015) Noninvasive reactivation of motor descending control after paralysis. J Neurotrauma 32:1968–1980

Gibbons RS, Stock CG, Andrews BJ, Gall A, Shave RE (2016) The effect of FES-rowing training on cardiac structure and function: pilot studies in people with spinal cord injury. Spinal Cord 54: 822–829

Glaser RM, Sawka MN, Brune MF, Wilde SW (1980) Physiological responses to maximal effort wheelchair and arm crank ergometry. J Appl Physiol Respir Environ Exerc Physiol 48:1060–1064

Gorgey AS, Wade R, Sumrell R, Villadelgado L, Khalil RE, Lavis T (2017) Exoskeleton training may improve level of physical activity after spinal cord injury: a case series. Top. Spinal Cord Inj. Rehabil. 23:245–255

Green DJ (2009) Exercise training as vascular medicine: direct impacts on the vasculature in humans. Exerc Sport Sci Rev 37:196–202

Gregory CM, Bickel CS (2005) Recruitment patterns in human skeletal muscle during electrical stimulation. Phys Ther 85:358–364

Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z, Ivy JL (2009) Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. J Electromyogr Kinesiol 19:614–622

Guertin P, Guertin PA (2012) Two promising novel classes of drug treatment in clinical development for acute and chronic spinal cord injury. J Neurol Neurophysiol 3:107

Guertin PA, Ung R-V, Rouleau P (2010) Oral administration of a tri-therapy for central pattern generator activation in paraplegic mice: proof-of-concept of efficacy. Biotechnol J 5:421–426

Guertin PA, Ung RV, Rouleau P, Steuer I (2011) Effects on locomotion, muscle, bone, and blood induced by a combination therapy eliciting weight-bearing stepping in nonassisted spinal cord-transected mice. Neurorehabil Neural Repair 25:234–242

Hansebout RR, Blight AR, Fawcett S, Reddy K (1993) 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. J Neurotrauma 10:1–18

Harvey LA, Glinsky JV, Bowden JL (2016) The effectiveness of 22 commonly administered physiotherapy interventions for people with spinal cord injury: a systematic review. Spinal Cord 54:914–923

Hayes HB, Jayaraman A, Herrmann M, Mitchell GS, Rymer WZ, Trumbower RD (2014) Daily intermittent hypoxia enhances walking after chronic spinal cord injury a randomized trial. Neurology 82:104–113

Hettinga DM, Andrews BJ (2008) Oxygen consumption during functional electrical stimulation-assisted exercise in persons with spinal cord injury: implications for fitness and health. Sport. Med. 38:825–838

Hooper PL (1992) Hot-tub therapy for type 2 diabetes mellitus. N Engl J Med 327:742–747

Hooper PL, Hooper PL (2009) Inflammation, heat shock proteins, and type 2 diabetes. Cell Stress Chaperones 14:113–115

Horowitz M, Assadi H (2010) Heat acclimation-mediated cross-tolerance in cardioprotection: do HSP70 and HIF1α play a role? Ann N Y Acad Sci 1188:199–206

Hunt KJ, Saunders BA, Perret C, Berry H, Allan DB, Donaldson N, Kakebeeke TH (2007) Energetics of paraplegic cycling: a new theoretical framework and efficiency characterisation for untrained subjects. Eur J Appl Physiol 101:277–285

Ievins A, Moritz CT (2017) Therapeutic stimulation for restoration of function after spinal cord injury. Physiology 32:391–398

Imamura M, Biro S, Kihara T, Yoshifuku S (2001) Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors. J Am Coll Cardiol 38:1083–1088

Jacobs P, Nash M, Rusinowski JW (2001) Circuit training provides cardiorespiratory and strength benefits in persons with paraplegia. Med Sci Sports Exerc 33:711–717

Jain NB, Ayers GD, Peterson EN, Harris MB, Morse L, O'Connor KC, Garshick E (2015) Traumatic spinal cord injury in the United States, 1993-2012. JAMA - J Am Med Assoc 313: 2236–2243

Jaiswal PB, Tester NJ, Davenport PW (2016) Effect of acute intermittent hypoxia treatment on ventilatory load compensation and magnitude estimation of inspiratory resistive loads in an individual with chronic incomplete cervical spinal cord injury. J Spinal Cord Med 39:103–110

Jilge B, Minassian K, Rattay F, Pinter MM, Gerstenbrand F, Binder H, Dimitrijevic MR (2004) Initiating extension of the lower limbs in subjects with complete spinal cord injury by epidural lumbar cord stimulation. Exp Brain Res 154:308–326

Jo HJ, Perez MA (2020) Corticospinal-motor neuronal plasticity promotes exercise-mediated recovery in humans with spinal cord injury. Brain 143:1368–1382

Johnson JM, Proppe DW (2011) Cardiovascular adjustments to heat stress. In: Handbook of physiology. Environmental Physiology, Bethesda, MD

Joyner MJ, Green DJ (2009) Exercise protects the cardiovascular system: effects beyond traditional risk factors. J Physiol 587:5551–5558

Kandilakis C, Sasso-Lance E (2019) Exoskeletons for personal use after spinal cord injury. Arch Phys Med Rehabil 102:331–337

Karelis AD, Carvalho LP, Castillo MJE, Gagnon DH, Aubertin-Leheudre M (2017) Effect on body composition and bone mineral density of walking with a robotic exoskeleton in adults with chronic spinal cord injury. J Rehabil Med 49:84–87

Kheck NM, Gannon PJ, Azmitia EC (1995) 5-HT1A receptor localization on the axon hillock of cervical spinal motoneurons in primates. J Comp Neurol 355:211–220

Kihara T, Biro S, Imamura M, Yoshifuku S (2002) Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. J Am Coll Cardiol 39: 754–759

Kikkinos P, Faselis C, Meyers J, Sui X, Zhang J, Blair SN (2014) Age-specific exercise capacity threshold for mortality risk assessment in male veterans. Circulation 130:653–658

Krause M, Ludwig MS, Heck TG, Takahashi HK (2015) Heat shock proteins and heat therapy for type 2 diabetes. Curr Opin Clin Nutr Metab Care 18:374–380

Kurucz I, Morva A, Vaag A, Eriksson K, Huang X, Groop L, Koranyi L (2002) Decreased expression of heat shock protein 72 in skeletal muscle of patients with type 2 diabetes correlates with insulin resistance. Diabetes 51:1102–1109

Laskin JJ, Ashley EA, Olenik LM, Burnham R, Cumming DC, Steadward RD, Wheeler GD (1993) Electrical stimulation-assisted rowing exercise in spinal cord injured people. A pilot study. Paraplegia 31:534–541

Laughlin MH (1999) Cardiovascular response to exercise. Adv. Physiol. Educ 22(1):S244–S259
Laughlin MHH, Newcomer SCSC, Bender SBSB (2008) Importance of hemodynamic forces as signals for exercise-induced changes in endothelial cell phenotype. J Appl Physiol 104:588–600
LaVela SL, Weaver FM, Goldstein B, Chen K, Miskevics S, Rajan S, Gater DR (2006) Diabetes mellitus in individuals with spinal cord injury or disorder. J Spinal Cord Med 29:387–395
Leicht CA, Kouda K, Umemoto Y, Banno M, Kinoshita T, Moriki T, Nakamura T, Bishop NC, Goosey-Tolfrey VL, Tajima F (2015) Hot water immersion induces an acute cytokine response in cervical spinal cord injury. Eur J Appl Physiol 115:2243–2252
Li J, Thorne LN, Punjabi NM, Sun CK, Schwartz AR, Smith PL, Marino RL, Rodriguez A, Hubbard WC, O'Donnell CP, Polotsky VY (2005) Intermittent hypoxia induces hyperlipidemia in lean mice. Circ Res 97:698–706
Ling L, Fuller DD, Bach KB, Kinkead R, Olson EB, Mitchell GS (2001) Chronic intermittent hypoxia elicits serotonin-dependent plasticity in the central neural control of breathing. J Neurosci 21:5381–5388
Locke M, Noble EG, Atkinson BG (1990) Exercising mammals synthesize stress proteins. Am J Physiol - Cell Physiol 258:C723–C1246
Lu DC, Edgerton VR, Modaber M, Auyong N, Morikawa E, Zdunowski S, Sarino ME, Sarrafzadeh M, Nuwer MR, Roy RR, Gerasimenko Y (2016) Engaging cervical spinal cord networks to Reenable volitional control of hand function in tetraplegic patients. Neurorehabil Neural Repair 30:951–962
Maloyan A, Eli-Berchoer L, Semenza GL, Gerstenblith G, Stern MD, Horowitz M (2005) HIF-1alpha-targeted pathways are activated by heat acclimation and contribute to acclimation-ischemic cross-tolerance in the heart. Physiol Genomics 23:79–88
Maltais F, Reissmann H, Gottfried SB (1995) Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. Am J Respir Crit Care Med 151: 1027–1033
Martin Ginis KA, Van Der Scheer JW, Latimer-Cheung AE, Barrow A, Bourne C, Carruthers P, Bernardi M, Ditor DS, Gaudet S, De Groot S, Hayes KC, Hicks AL, Leicht CA, Lexell J, MacAluso S, Manns PJ, McBride CB, Noonan VK, Pomerleau P, Rimmer JH, Shaw RB, Smith B, Smith KM, Steeves JD, Tussler D, West CR, Wolfe DL, Goosey-Tolfrey VL (2018) Evidence-based scientific exercise guidelines for adults with spinal cord injury: an update and a new guideline. Spinal Cord 56:308–321
Massucci M, Brunetti G, Piperno R, Betti L, Franceschini M (1998) Walking with the advanced reciprocating gait orthosis (ARGO) in thoracic paraplegic patients: energy expenditure and cardiorespiratory performance. Spinal Cord 36:223–227
McDonald JW, Sadowsky C (2002) Spinal-cord injury. Elsevier Limited, Lancet, pp 417–425
McParland C, Krishnan B, Lobo J, Gallagher CG (1992) Effect of physical training on breathing pattern during progressive exercise. Respir Physiol 90:311–323
McPherson JG, Miller RR, Perlmutter SI, Poo MM (2015) Targeted, activity-dependent spinal stimulation produces long-lasting motor recovery in chronic cervical spinal cord injury. Proc Natl Acad Sci U S A 112:12193–12198
Mercier HW, Taylor JA (2016) The physiology of exercise in Spinal Cord Injury (SCI): an overview of the limitations and adaptations. In: The physiology of exercise in spinal cord injury. Springer US, Berlin, pp 1–11
Meyer C, Hofstoetter US, Hubli M, Hassani RH, Rinaldo C, Curt A, Bolliger M (2020) Immediate effects of transcutaneous spinal cord stimulation on motor function in chronic, sensorimotor incomplete spinal cord injury. J Clin Med 9:3541
Minassian K, Hofstoetter US, Danner SM, Mayr W, Bruce JA, McKay WB, Tansey KE (2016) Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. Neurorehabil Neural Repair 30:233–243
Mushahwar VK, Gillard DM, Gauthier MJA, Prochazka A (2002) Intraspinal microstimulation generates locomotor-like and feedback-controlled movements. IEEE Trans Neural Syst Rehabil Eng 10:68–81

Mutton DL, Scremin AME, Barstow TJ, Scott MD, Kunkel CF, Cagle TG (1997) Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. Arch Phys Med Rehabil 78:712–718

Myers J, Lee M, Kiratli J (2007) Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am. J. Phys. Med. Rehabil 86:142–152

Neff D, Kuhlenhoelter AM, Lin C, Wong BJ, Motaganahalli RL, Roseguini BT (2016) Thermotherapy reduces blood pressure and circulating endothelin-1 concentration and enhances leg blood flow in patients with symptomatic peripheral artery disease. Am. J. Physiol. Integr. Comp. Physiol. 311:R392–R400

Ozpinar A, Tempel ZJ, Monaco EA (2016) Targeted, activity-dependent spinal stimulation produces long-lasting motor recovery in chronic cervical spinal cord injury. Neurosurgery 78:N18–N19

Peckham PH, Knutson JS (2005) Functional electrical stimulation for neuromuscular applications. Annu Rev Biomed Eng 7:327–360

Pelletier CA, Hicks AL (2013) Importance of exercise in the rehabilitation process after spinal cord injury. Crit Rev Phys Rehabil Med 25:143–158

Phillips SM, Stewart BG, Mahoney DJ, Hicks AL, McCartney N, Tang JE, Wilkinson SB, Armstrong D, Tarnopolsky MA (2004) Body-weight-support treadmill training improves blood glucose regulation in persons with incomplete spinal cord injury. J Appl Physiol 97: 716–724

Qiu S, Taylor JA (2016) Hybrid functional electrical stimulation exercise for improved cardiorespiratory fitness in SCI. In: The physiology of exercise in spinal cord injury. Springer US, New York, pp 269–286

Qiu S, Alzhab S, Picard G, Taylor JA (2016) Ventilation limits aerobic capacity after functional electrical stimulation row training in high spinal cord injury. Med Sci Sports Exerc 48:1111–1118

Rhind SG, Gannon GA, Shephard RJ, Buguet A, Shek PN, Radomski MW (2004) Cytokine induction during exertional hyperthermia is abolished by core temperature clamping: neuroendocrine regulatory mechanisms. Int J Hyperth 20:503–516

Roberts TT, Leonard GR, Cepela DJ (2017) Classifications in brief: American spinal injury association (ASIA) impairment scale. Clin Orthop Relat Res 475:1499–1504

Rodgers MM, Figoni S, Hooker S, Glaser RM, Figoni SI, Rkt P, Hooker SP, Ezenwa BN, Collins SR, Nlathews T, Gupta SC (1991) Musculoskeletal responses of spinal cord injured individuals to functional neuromuscular stimulation-induced knee extension exercise training REGARDS-physical activity view project impacts of encouraging dog walking on returns of new adopted dogs to a shelter view project Department of Veterans Affairs Musculoskeletal responses of spinal cord injured individuals to functional neuromuscular stimulation-induced knee extension exercise. Artic J Rehabil Res Dev 28:19–26

Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB (2012) Heart disease and stroke statistics-2012 update: a report from the American heart association. Circulation 125:e2

Romero SA, Gagnon D, Adams AN, Cramer MN, Kouda K, Crandall CG (2017) Acute limb heating improves macro- and microvascular dilator function in the leg of aged humans. Am. J. Physiol. Circ. Physiol. 312:H89–H97

Ryan S, Taylor CT, McNicholas WT (2005) Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112:2660–2667

Sabatier MJ, Stoner L, Mahoney ET, Black C, Elder C, Dudley GA, McCully K (2006) Electrically stimulated resistance training in SCI individuals increases muscle fatigue resistance but not femoral artery size or blood flow. Spinal Cord 44:227–233

Saito Y, Hashimoto T, Iwata H, Takahashi K, Fukumizu M, Sasaki M, Hanaoka S, Sugai K (1999) Apneustic breathing in children with brainstem damage due to hypoxic-ischemic encephalopathy. Dev Med Child Neurol 41:560–567

Sandrow-Feinberg HR, Izzi J, Shumsky JS, Zhukareva V, Houle JD (2009) Forced exercise as a rehabilitation strategy after unilateral cervical spinal cord contusion injury. J Neurotrauma 26: 721–731

Sankari A, Bascom AT, Riehani A, Badr MS (2015) Tetraplegia is associated with enhanced peripheral chemoreflex sensitivity and ventilatory long-term facilitation. J Appl Physiol 119: 1183–1193

Sawka MN, Glaser RM, Wilde SW, Von Luhrte TC (1980) Metabolic and circulatory responses to wheelchair and arm crank exercise. J Appl Physiol Respir Environ Exerc Physiol 49:784–788

Sayenko DG, Rath M, Ferguson AR, Burdick JW, Havton LA, Edgerton VR, Gerasimenko YP (2019) Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. J Neurotrauma 36:1435–1450

Schilero GJ, Radulovic M, Wecht JM, Spungen AM, Bauman WA, Lesser M (2014) A center's experience: pulmonary function in spinal cord injury. Lung 192:339–346

Schmidt KD, Chan CW (1992) Thermoregulation and fever in Normal persons and in those with spinal cord injuries. Mayo Clin Proc 67:469–475

Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, Mcdonald-Smith GP, Gao H, Hennessy L, Finnerty CC, López CM, Honari S, Moore EE, Minei JP, Cuschieri J, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Jeschke MG, Klein MB, Gamelli RL, Gibran NS, Brownstein BH, Miller-Graziano C, Calvano SE, Mason PH, Cobb JP, Rahme LG, Lowry SF, Maier RV, Moldawer LL, Herndon DN, Davis RW, Xiao W, Tompkins RG (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 110:3507–3512

Shields RK (2002) Muscular, skeletal, and neural adaptations following spinal cord injury. J Orthop Sports Phys Ther 32:65–74

Srinivas S, Wali AR, Pham MH (2019) Efficacy of riluzole in the treatment of spinal cord injury: a systematic review of the literature. Neurosurg Focus 46:1–18

Sunshine MD, Cho FS, Lockwood DR, Fechko AS, Kasten MR, Moritz CT (2013) Cervical intraspinal microstimulation evokes robust forelimb movements before and after injury. J Neural Eng 10:036001

Taylor AW, McDonell E, Brassard L (1986) The effects of an arm ergometer training programme on wheelchair subjects. Paraplegia 24:105–114

Taylor JA, Picard G, Widrick JJ (2011) Aerobic capacity with hybrid FES rowing in spinal cord injury: comparison with arms-only exercise and preliminary findings with regular training. PM R 3:817–824

Taylor JA, Picard G, Porter A, Morse LR, Pronovost MF, Deley G (2014) Hybrid functional electrical stimulation exercise training alters the relationship between spinal cord injury level and aerobic capacity. Arch Phys Med Rehabil 95:2172–2179

Tei C, Horikiri Y, Park JC, Jeong JW, Chang KS, Toyama Y, Tanaka N (1995) Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. Circulation 91:2582–2590

Teng YD, Bingaman M, Taveira-DaSilva AM, Pace PP, Gillis RA, Wrathall JR (2003) Serotonin 1A receptor agonists reverse respiratory abnormalities in spinal cord-injured rats. J Neurosci 23: 4182–4189

Tester NJ, Fuller DD, Fromm JS, Spiess MR, Behrman AL, Mateika JH (2014) Long-term facilitation of ventilation in humans with chronic spinal cord injury. Am J Respir Crit Care Med 189:57–65

Turiel M, Sitia S, Cicala S, Magagnin V, Bo I, Porta A, Caiani E, Ricci C, Licari V, De Gennaro Colonna V, Tomasoni L (2011) Robotic treadmill training improves cardiovascular function in spinal cord injury patients. Int J Cardiol 149:323–329

Tweedy SM, Beckman EM, Geraghty TJ, Theisen D, Perret C, Harvey LA, Vanlandewijck YC (2017) Exercise and sports science Australia (ESSA) position statement on exercise and spinal cord injury. J Sci Med Sport 20:108–115

Ung RV, Rouleau P, Guertin PA (2012) Functional and physiological effects of treadmill training induced by buspirone, carbidopa, and L-DOPA in clenbuterol-treated paraplegic mice. Neurorehabil Neural Repair 26:385–394

Van Den Brand R, Heutschi J, Barraud Q, DiGiovanna J, Bartholdi K, Huerlimann M, Friedli L, Vollenweider I, Moraud EM, Duis S, Dominici N, Micera S, Musienko P, Courtine G (2012) Restoring voluntary control of locomotion after paralyzing spinal cord injury. Science (80-) 336: 1182–1185

van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G (2004) Acute effects of inspiratory pressure support during exercise in patients with COPD. Eur Respir J 23:34–40

van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G (2006) Training with inspiratory pressure support in patients with severe COPD. Eur Respir J 27:65–72

Vila B, Servera E, Marín J, Díaz J, Giménez M, Komaroff E, Bach J (2007) Noninvasive Ventilatory assistance during exercise for patients with kyphoscoliosis. Am J Phys Med Rehabil 86:672–677

Vivodtzev I, Picard G, Cepeda FX, Taylor JA (2020) Acute Ventilatory support during whole-body hybrid rowing in patients with high-level spinal cord injury: a randomized controlled crossover trial. In: Chest. Elsevier Inc, Amsterdam, pp 1230–1240

Vivodtzev I, Picard G, O'Connor K, Taylor JA (2021) Serotonin 1A agonist and cardiopulmonary improvements with whole-body exercise in acute, high-level spinal cord injury: a retrospective analysis. Eur J Appl Physiol 121:453–463

Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, Rowald A, Seáñez I, Caban M, Pirondini E, Vat M, McCracken LA, Heimgartner R, Fodor I, Watrin A, Seguin P, Paoles E, Van Den Keybus K, Eberle G, Schurch B, Pralong E, Becce F, Prior J, Buse N, Buschman R, Neufeld E, Kuster N, Carda S, von Zitzewitz J, Delattre V, Denison T, Lambert H, Minassian K, Bloch J, Courtine G (2018) Targeted neurotechnology restores walking in humans with spinal cord injury. Nature 563:65–93

Warburton DER, Eng JJ, Krassioukov A, Sproule S (2007) Cardiovascular health and exercise rehabilitation in spinal cord injury. Top Spinal Cord Inj Rehabil 13:98–122

Waters RL, Mulroy S (1999) The energy expenditure of normal and pathologic gait. Gait Posture 9(3):207–231

Weaver FM, Collins EG, Kurichi J, Miskevics S, Smith B, Rajan S, Gater D (2007) Prevalence of obesity and high blood pressure in veterans with spinal cord injuries and disorders. Am J Phys Med Rehabil 86:22–29

Whiteneck GG, Charlifue SW, Frankel HL, Fraser MH, Gardner BP, Gerhart KA, Krishnan KR, Menter RR, Nuseibeh I, Short DJ, Silver JR (1992) Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. Paraplegia 30:617–630

WHO (2013) World Health Organization and international spinal cord society. International perspectives on spinal cord injury. [WWW Document]

Williams AM, Gee CM, Voss C, West CR (2019) Cardiac consequences of spinal cord injury: systematic review and meta-analysis. Heart 105:217–225

Wu M, Landry JM, Schmit BD, Hornby TG, Yen SC (2012) Robotic resistance treadmill training improves locomotor function in human spinal cord injury: a pilot study. Arch Phys Med Rehabil 93:782–789

Zhang D, Xuan J, Zheng BB, Zhou YL, Lin Y, Wu YS, Zhou YF, Huang YX, Wang Q, Shen LY, Mao C, Wu Y, Wang XY, Tian NF, Xu HZ, Zhang XL (2017) Metformin improves functional recovery after spinal cord injury via autophagy flux stimulation. Mol Neurobiol 54:3327–3341

Zimmer MB, Goshgarian HG (2007) Spinal cord injury in neonates alters respiratory motor output via supraspinal mechanisms. Exp Neurol 206:137–145

Zimmermann JB, Seki K, Jackson A (2011) Reanimating the arm and hand with intraspinal microstimulation. J Neural Eng 8:054001

Zörner B, Schwab ME (2010) Anti-Nogo on the go: from animal models to a clinical trial. Ann N Y Acad Sci 1198:E22–E34