THE EFFECTS OF NOVEL HYBRID EXERCISE REHABILITATION ON CARDIOVASCULAR FUNCTION AND ORTHOSTATIC TOLERANCE IN INDIVIDUALS WITH SPINAL CORD INJURY

by

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ABSTRACT

Persons with spinal cord injury (SCI) often suffer from orthostatic hypotension (marked reduction in blood pressure upon assuming an upright posture) and exercise may assist with its treatment by improving cardiovascular health and autonomic regulation. Hybrid exercise (concurrent movement of the arms and legs) promotes enhancements in venous return, ventricular filling, and cardiorespiratory function. However, limited research has evaluated the effects of hybrid exercise on orthostatic tolerance. Accordingly, this study evaluated the effects of arm and hybrid exercise on orthostatic response and on cardiorespiratory function during peak exercise. Additionally, the effects of spinal cord lesion level were examined. Asymptomatic persons with SCI (C4-T6) and age- and gender-matched able-bodied controls participated in four testing days. The first two testing days examined participants' orthostatic tolerance following rest followed by a peak arm cycle or hybrid exercise test (in random order). The final two testing days assessed the acute effects of steady state arm and hybrid exercise on orthostatic response (in random order). There was no significant decrease ($p=0.07$) in middle cerebral artery blood velocity upon assuming the upright position following a bout of hybrid steady state exercise in participants with SCI (67.2 ± 18.8 to 61.8 ± 14.8 cm $\cdot s^{-1}$, respectively). Hybrid exercise resulted in significantly ($p<0.05$) greater cardiorespiratory requirements throughout incremental exercise in comparison to arm ergometry in all groups. The average peak oxygen uptake (across all groups) was 21 ± 9 vs. 19 ± 7 $mL \cdot kg \cdot min^{-1}$, for hybrid exercise vs. arm ergometry, respectively. The average peak oxygen uptake (across all modes of exercise) was 24.9 ± 7.9 vs. 15.7 ± 4.2 $mL \cdot kg \cdot min^{-1}$, for able-bodied participants vs. participants with SCI, respectively. Furthermore, persons with paraplegia had significantly ($p<0.05$) higher oxygen uptake than persons with tetraplegia and the average peak oxygen uptake (across all modes of exercise) was 18.5 ± 3.7 vs. 12.9 ± 2.4 $mL \cdot kg \cdot min^{-1}$ for these groups, respectively. Hybrid exercise improved cardiovascular response to an orthostatic challenge and promoted greater cardiorespiratory response in comparison to arm exercise in persons with SCI. Furthermore, lesion level of SCI affects responses to an orthostatic challenge and peak exercise.

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DEDICATION

I would like to dedicate this thesis to my Mum, Ann Wong, and my Dad, Peter Wong, who have always allowed me to select my own path, and never expressed that I cannot pursue or accomplish everything I want. With their unconditional love, support, and encouragement, I am inspired everyday to be more than I am today for tomorrow.

1 INTRODUCTION

One of the many physiological changes that Individuals with spinal cord injury (SCI) experience includes dramatic changes to the functioning of their autonomic nervous system. Subsequently, impaired sympathetic activity and complete muscle paralysis below the level of the spinal cord lesion produces an absence of sympathetic-mediated vasoconstriction and voluntary muscle pump action[1], which contributes to orthostatic intolerance in this population. Orthostatic hypotension is a common clinical problem for individuals with cervical or high thoracic level injuries[2]. It is a condition that is generally characterized by a reduction in blood pressure of 20 mmHg or more, or an attenuation in diastolic blood pressure of 10 mmHg or more, upon a change in body position from a supine position to an upright posture, in the presence or absence of symptoms[3-5]. The potential for participation in exercise to help manage orthostatic hypotension in the persons with SCI is important since orthostatic intolerance has been found to limit active and effective participation in rehabilitation programs[3, 6] and delay the achievement of associated goals[7]. These have the potential to hasten the deteriorating effects of immobilization and the development of undesirable secondary medical complications[7, 8]. Low blood pressure is also associated with other conditions which may negatively impact health, such as autonomic dysreflexia[9]. Additionally, learning more about methods to ameliorate orthostatic hypotension has the potential to help improve participation in rehabilitation as orthostatic hypotension is a common obstacle delaying adaptation to sitting during the initial phase of rehabilitation following SCI[10]. Increasing understanding about orthostatic response following a bout of exercise in this population may also be beneficial in determining the cardiovascular response to assuming an upright posture in a wheelchair following participation in exercise. Accordingly, exercise rehabilitation has been shown to have the ability to help treat orthostatic hypotension as it improves cardiovascular health and autonomic regulation[11], and stabilizes central blood volume[12].

Cardiovascular disease is the leading cause of death not only in able-bodied individuals[13], but in persons with SCI as well[14, 15]. Morbidity from cardiovascular causes in the population with SCI is relatively higher than that seen in the able-bodied population, and the onset of cardiovascular disease tends to occur earlier in persons with SCI[16-18]. Cardiovascular disorders in both the acute and chronic stages of SCI are among the most common causes of death in this population[17, 19, 20]. Evidence demonstrates that physical inactivity is a major independent risk factor for cardiovascular disease and premature mortality[21-26]. Previous studies have demonstrated that participation in physical activity in persons with SCI helps to improve fitness levels and exercise capacity[27-30]. Furthermore, exercise training involving the legs has been found to promote improvements in lower-limb circulation and vasodilatory capacity[31, 32], body composition[33, 34] and insulin resistance[35], all of which are important as paralysis and inactivity predispose individuals with SCI to decreased lower limb circulation[36-39], and increased body fat composition and insulin resistance[37-39]. Accordingly, it may be postulated that exercise that combines concurrent activity of the arms and legs may help to promote greater benefits to health than either arm or leg exercise alone. With the expected increase in longevity in the SCI population, current research is focusing on the management of health issues associated with long-term survival[40].

While results from several studies suggest that exercise can help to improve cardiovascular health, and, thus, potentially orthostatic intolerance, and that passively exercising the lower limbs can help promote greater cardiorespiratory response in persons with SCI[41-44], it remains unclear what the effects of an acute bout of steady state exercise are on orthostatic hypotension, and whether passive inclusion of the legs with concurrent arm exercise promotes greater cardiorespiratory response to exercise in comparison to arm exercise alone. Thus, these warrant further investigation.

1.1 Orthostatic Hypotension

1.1.1 Background

Orthostatic hypotension, as previously defined, is characterized by a reduction in blood pressure upon a change in posture. It may be asymptomatic or symptomatic and symptoms include dizziness, visual impairment, feeling faint or presyncope, nausea, fatigue, ringing in the ears, cognitive impairment, palpitations, headache, neck ache, and blacking out[5, 45]. In able-bodied individuals, heart rate and blood pressure control are coordinated by the two components of the autonomic nervous system: the sympathetic and parasympathetic nervous systems[9]. The parasympathetic nervous system is dominant during rest and reflexly decreases heart rate when activated. In contrast, the sympathetic nervous system has a counteracting and, thus, more excitatory role. Peripheral resistance is also increased, and the combination of these responses to sympathetic activation ultimately produces an increase in blood pressure. However, SCI results in alterations to autonomic nervous system activity, affecting spinal pathways that modulate cardiovascular control[9]. Spinal cord injury is characterized by a disruption of the normal autonomic cardiovascular control mechanisms[1, 46], leading to various physiological changes in cardiovascular health and functioning. In relation to blood pressure control, sympathetic hypoactivity and unopposed vagal parasympathetic control often result following injury[47], ultimately leading to low resting blood pressure[48, 49]. Following injury, autonomic nervous system impairments result in a variety of cardiovascular abnormalities, including alterations in blood pressure control[9], as previously mentioned. Specifically, low levels of efferent sympathetic nervous activity and the loss of reflex vasoconstriction following SCI have been associated with orthostatic hypotension[3].

1.1.2 Underlying Mechanisms of Orthostatic Hypotension

There are several mechanisms that are postulated to lead to orthostatic hypotension. Impaired sympathetic control and cerebral autoregulation were the main focuses of this investigation.

Impaired sympathetic control is common following injury when SCI occurs above the major sympathetic splanchnic outflow (T6). This causes sympathetic impulses to the splanchnic vascular beds and lower limbs o be restricted[50]. This limits vasoconstriction and subsequently affects blood pressure regulation, leading to an inability to counteract a drop in arterial blood pressure[51]. Injury above T6 alters the efferent discharges from the brain stem to the sympathetic nerves that cause vasoconstriction in the splanchnic circulation and lower limbs. This has a large negative impact on the body's ability to properly regulate short-term pressure control[52]. Furthermore, impaired sympathetic activity, or a low level of efferent sympathetic nervous activity, and complete muscle paralysis below the lesion level limits sympathetic-mediated vasoconstriction and voluntary muscle pumping action[53], respectively, and these are associated with orthostatic hypotension[3]. Subsequently, following injury, persons with SCI experience sympathetic hypoactivity as a result of disruption of the descending spinal cardiovascular pathways[9]. Individuals with SCI generally have average basal systolic and diastolic blood pressures about 15mmHg lower than their able-bodied counterparts[1].

Another mechanism that has been postulated relates to cerebral autoregulation. In the able-bodied population, cerebral blood flow is governed by autoregulation and changes in pressure are counteracted by changes in cerebrovascular resistance in order to maintain relatively constant flow[54]. When in the supine position, blood is evenly distributed throughout the body and mean arterial pressure measured at the level of the heart matches the mean cerebral perfusion pressure (85 mmHg)[54]. When in an upright posture, cerebral arterial pressure decreases (15 to 30 mmHg) in comparison to pressure at the level of the heart (aortic arch) as a result of the vertical height, or hydrostatic, difference between the head and the heart[54]. Furthermore, it has been found that there may be a disruption of cerebral blood flow when standing upright, and if there is a subsequent decrease in cerebral perfusion, this may lead to symptoms of orthostatic hypotension[55].

Cerebral hypoperfusion is commonly elicited by an orthostatic challenge, revealing symptoms of orthostatic hypotension such as dizziness or fainting (syncope)[9]. Individuals who are able to maintain consciousness when experiencing low arterial pressures likely have a shift in cerebral autoregulation which allows them to maintain cerebral blood flow despite low perfusion pressures[56-58], since the underlying cause symptoms of hypotension are due to cerebral hypoperfusion[9]. Approximately 60% of individuals who experience orthostatic hypotension have altered cerebral haemodynamics and exhibit symptoms[7].

There is evidence to suggest that cerebral autoregulation is altered in the persons with SCI. In individuals with tetraplegia, those with a greater decline in cerebral blood flow experience symptoms of orthostatic hypotension[59]. Subsequently, it has been suggested that adaptation to orthostatic hypotension predominantly involves cerebral blood flow, rather than systemic blood pressure in persons with SCI[9]. Furthermore, the importance of cerebral blood flow in helping to control orthostatic hypotension ultimately involves cerebral oxygenation[55]. This is important to consider when in the upright posture because if systemic blood pressure decreases to low levels, cerebral perfusion pressure declines even further due to the vertical height difference[54]. Individuals with SCI have been found to experience similar declines in cerebral oxygenation as their able-bodied counterparts, despite greater falls in systemic blood pressure[60]. Thus, whether or not there is an experience of orthostatic hypotension may be dependent on the amount of decline in cerebral blood flow, which in turn may affect cerebral oxygenation, but this is still unclear[9]. It has been postulated that the extent to which cerebral blood flow is altered following injury, and thus, affects orthostatic tolerance, may be related to lesion level or completeness of the injury[9].

1.1.3 Orthostatic Hypotension and Exercise

The ability to contract the muscles of the lower limbs has been found to have the potential to ameliorate orthostatic hypotension. Orthostatic challenges produce translocations in blood volume away from the thoracic region into the lower extremities[61], leading to blood pooling. As a result, ventricular filling pressures are attenuated and stroke volume is reduced[61]. In able-bodied individuals, the redistribution of blood volume from the lower limbs and splanchnic region is mediated by the combined action of various neurohumoral and motor reflexes, helping to meet the demand of the exercising upper extremity muscles[62]. Conversely, vasomotor dysfunction below the level of the spinal cord lesion limits the ability to redistribute blood from the lower extremities and splanchnic region[63]. However, there is a paucity of information examining the effects of exercise, without any electrical stimulation, on orthostatic hypotension in persons with SCI, and the majority of the existing literature considers persons with paraplegia.

1.2 Cariodrespiratory Response to Exercise

Aerobic fitness is a strong predictor of the capacity for activities of daily living, and exercise training commonly leads to enhancements in aerobic fitness in the general population[64, 65]. Furthermore, aerobic fitness, as well as other components of health-related fitness are positively associated with functional improvements in individuals with SCI[66, 67]. Accordingly, exercise is a means by which this population can enhance aerobic fitness and promote the associated benefits.

1.2.1 Upper Extremity Exercise

Participation in exercise has been shown to help improve functional capacity in persons with SCI. Due to the lower limb paralysis following SCI, individuals generally perform upper body exercise in the form of arm cycling[68]. During upper body exercise, it is generally observed in the able-bodied population that their ability to activate the skeletal muscle pump enhances aerobic capacity and overall exercise performance[69]. The skeletal muscle pump helps maintain venous return, which produces sufficient cardiac output, and thus, oxygen uptake. However, even for able-bodied individuals, upper extremity activity is very physically demanding and elicits unique cardiovascular responses in comparison with leg exercise at equivalent power outputs[70], such as decreases in ventricular filling and stroke volume[71], and increases in total peripheral resistance[70], heart rate, and blood pressure[72, 73]. Persons with SCI also experience problems that arise from circulatory hypokinesis, a cardiac output that is lower than expected for a given oxygen uptake, which is subsequent to insufficient venous return as a result of inactivity of the skeletal muscle pump[1, 74-76], leading to blood pooling in the paralyzed lower limbs[70]. Whole-body exercise has been shown to enhance cardiorespiratory response to a greater extent then arm exercise alone in individuals with SCI[77-79].

Furthermore, voluntary arm exercise elicits only small increases in maximal oxygen uptake and is thought to be insufficient to promote maintenance of a high level of fitness in persons with SCI[80]. Upper extremity exercise capacity is limited since venous return and, subsequently, cardiac output, are compromised, leading to insufficient blood flow to the active muscles during exercise[70].

1.2.2 Lower Extremity Exercise

Exercise involving the lower extremities incorporates the ability to utilize the skeletal muscle pump which helps to ensure adequate venous return of blood during activity. However, in individuals with SCI, the ability to contract the muscles of the legs independently is often lost as a result of lower limb paralysis following injury, and this, in turn, limits the cardiorespiratory response to exercise. Fortunately, in persons with SCI, active contraction of the lower limbs via the application of electrical stimulation has the potential to activate the skeletal muscle pump. Muscle contractions are induced through microprocessor-controlled electrical stimulation that is delivered via skin surface electrodes placed over motor points of the quadriceps, hamstring, and gluteal muscle groups[81, 82]. The skeletal muscle pump has an important function during exercise. In able-bodied individuals, an increase in venous return is elicited by contractions of the leg muscles, which provide pressure against the veins and help the venous valves return blood to the heart and central circulation[83, 84]. As demonstrated in the literature, leg muscle contractions significantly augment cardiovascular dynamics in able-bodied participants in comparison to participants with SCI[69, 85].

1.2.3 Hybrid Exercise

Since the ability to utilize the leg muscle pump during exercise has been shown to help improve performance[86], it is logical that recent research examines cardiorespiratory measures during activity involving simultaneous activity of the upper and lower limbs. As previously discussed, hybrid exercise involves concurrent exercise of the arms and legs and facilitates activation of a larger muscle mass in comparison to upper or lower body exercise alone. A few studies comparing hybrid exercise to arm cycle exercise illustrate that there is greater cardiorespiratory response to hybrid exercise in individuals with SCI[77-79]. Furthermore, increases in maximal oxygen uptake have been found when arm exercise has been added to lower extremity activity elicited by electrical stimulation[87]. Hybrid exercise elicits increases in oxygen uptake[88], and stroke volume[78, 78]. The enhancement in stroke volume may imply that exercise involving the legs promotes reductions in venous pooling, and subsequently, augmentations in venous return[78, 79, 89]. While there are several studies examining cardiorespiratory response to hybrid exercise in individuals with SCI, there is a paucity of information about the effects of passively incorporating the legs during hybrid exercise in this population, warranting further investigation.

1.3 Lesion Level of Spinal Cord Injury

The common ways in which SCI are classified are by level, and completeness, or severity of injury. There are two levels of injury, tetraplegia and paraplegia. The neurological level of injury refers to the most caudal level whereby both sensory and motor levels remain intact[90]. The American Spinal Injury Association (ASIA) has international standards for the neurological classification of SCI consisting of: 1) a five category ASIA impairment scale (A-E), 2) motor score, and 3) sensory score[91]. Tetraplegia is characterized by impairment or loss of motor and/or sensory function in the cervical segments (C1-C8) of the spinal cord[92] or the highest thoracic segment (T1)[93]. Tetraplegia is also characterized by impairment or loss of motor and/or sensory function in the upper and lower extremities, trunk and pelvic organs[93]. Paraplegia is the subsequent result of damage to thoracic (T1-T12), lumbar, or sacral segments of the cauda equina (L1-L5, S1-S4) of the spinal cord[93]. Injury to the thoracic segments impairs the trunk, legs, and/or pelvic organs, while damage to the lumbar or sacral segments leads to impairments of the legs and/or pelvic organs[93]. Accordingly, paraplegia leaves motor and sensory function intact and normal in the upper extremities.

Completeness of injury is based on the ASIA standards[92, 94, 95]. In terms of completeness or severity of SCI, an incomplete injury is characterized by the partial preservation of some sensory and/or motor function below the level of the lesion, and this includes sensory and/or motor function in the lowest sacral segments of the spinal cord (S4 and S5)[90]. In contrast, subsequent to complete injuries, there is a loss of motor and sensory functions that are conducted via afferent and efferent spinal pathways as well as disruption of the pathways from the brain to the peripheral sympathetic nervous system[96], and an absence of sensory and motor function in the lowest sacral segments of the spinal cord[90]. This ultimately leads to cardiovascular and metabolic changes at rest and during exercise[97-101]. The ASIA impairment scale[91] further specifies the severity of an injury beyond its classification as complete or incomplete. Thus, SCI can be classified as follows: complete tetraplegia, incomplete tetraplegia, complete paraplegia, and incomplete paraplegia, as well as corresponding ASIA level.

1.3.2 Lesion Level and Orthostatic Hypotension

Orthostatic hypotension is more commonly experienced in individuals with tetraplegia[7, 48, 102]. Upon a change in posture, tetrplegics experience greater decreases in blood pressure than paraplegics[7]. The synergistic relationship between parasympathetic and sympathetic control is lost following injury, and this is more pronounced in individuals with cervical and high thoracic injuries[9]. Higher levels of injury lead to greater impairments of the efferent sympathetic nerves[48] and it is highly probable that this affects vascular responses to orthostasis[47-49]. Furthermore, lesions above T6 disrupt supraspinal control to the splachnic bed and thus, to major capacitance vessels, promoting orthostatic instability[9]. Normally, while in an upright posture, there is a baroreceptor-mediated vasoconstriction that occurs in response to an increase in tonic sympathetic outflow, and this works to maintain blood pressure and cerebral perfusion[9]. These vascular resistance responses are largely involved in cardiovascular control during orthostatic stress[103-105]. Subsequently, any disruption to these responses following injury promotes orthostatic intolerance[103].

1.3.2 Lesion Level and Exercise

Lesion level also affects exercise performance in persons with SCI. Depending on the level of injury, venous dilation, venous insufficiency, and venous blood pooling can result in paralyzed lower limbs, affecting exercise capacity[96]. Research has shown that maximal power output, maximal oxygen uptake, and total work is higher in athletes with lower lesion levels[106]. Furthermore, during exercise, it has been found that higher lesion levels produce blunted cardiorespiratory responses to exercise in comparison to persons with lower level injuries. Whether at rest or during submaximal or maximal levels of exercise, individuals with tetraplegia have been found to have lower values for oxygen uptake, heart rate, work rate, and ventilation in comparison to paraplegics[96, 107, 108]. On a continuum of injury levels from tetraplegic to paraplegic, moderate level paraplegia results in higher resting and maximal heart rate and maximal oxygen uptake in comparison to individuals with higher lesion levels.

2 OBJECTIVES

The primary objective of this investigation was to examine the effects of acute steady state exercise on orthostatic hypotension. Upon review of the literature, previous studies have evaluated the effects of functional electrical stimulation, or functional neuromuscular stimulation, on orthostatic hypotension following injury. Overall, the methodology commonly used in these studies involved evaluating cardiovascular responses with and without stimulation during graded-tilt tests[53, 109]. Generally, it has been found that in participants with SCI, both systolic and diastolic blood pressure responses are higher during tilt tests when stimulation is applied in comparison to when it is nt. Accordingly, it has been proposed that stimulation may be an important treatment component of rehabilitation programs, allowing these individuals to more easily withstand postural changes involved in standardized mobilization (e.g., sitting or standing). In a novel approach, this study was designed assess the effects of hybrid exercise incorporating passive lower extremity exercise on orthostatic hypotension instead of employing electrical stimulation during orthostatic stress.

The secondary objective of this study was to examine and compare the similarities and differences in cardiorespiratory response during peak arm cycle exercise and peak hybrid exercise in individuals with SCI and their able-bodied counterparts. Upon review of the literature, many existing studies that have investigated the use of hybrid exercise utilize functional electrical stimulation to elicit muscle contraction in the lower limbs. This warranted investigation into the effectiveness of passive leg cycling in conjunction with arm cycling to determine if active muscle contraction is required to promote enhancements in cardiorespiratory response during whole-body exercise in persons with SCI. Accordingly, this study was designed to evaluate hybrid exercise that incorporates passive cycling of the lower limbs in individuals with SCI.

The final objective of this study was to examine the effects of lesion level on orthostatic response and cardiorespiratory response to exercise in individuals with SCI. It was anticipated that these findings would be useful for future studies involving the population with SCI that investigate the development of optimal exercise prescriptions with the appropriate mode of physical activity, or for the improvement of exercise rehabilitation programs. In this way, appropriate exercise prescriptions and rehabilitation programs may be developed for persons with SCI based on their physiological differences according to injury level. Additionally, the effects of acute steady state exercise on orthostatic hypotension can be taken into consideration when working to improve exercise rehabilitation practices for individuals with SCI. This approach was merited as a review of the literature revealed that lesion level has a significant impact on exercise capacity and response to orthostatic challenge.

3 HYPOTHESES

3.1. Orthostatic Hypotension

It was anticipated that physiological responses associated with orthostatic hypotension would be improved following a bout of steady state exercise in individuals with SCI and able-bodied individuals. It was also postulated that persons with SCI would experience blunted blood pressure responses in comparison to their able-bodied counterparts. Hybrid exercise was also expected to improve orthostatic tolerance to a greater extent than arm cycling exercise.

3.2 Cardiorespiratory Response to Incremental Exercise

We hypothesized that individuals with SCI would exhibit lower cardiorespiratory response (i.e., heart rate, stroke volume, cardiac output, oxygen uptake, etc.) to exercise in comparison to able-bodied individuals. We also hypothesized that, for both groups of participants, hybrid exercise would elicit greater cardiorespiratory response than arm cycling exercise, illustrating the greater potential to improve aerobic fitness with whole-body exercise

3.3 Lesion Level

We hypothesized that lesion level would have an impact on various cardiovascular responses to the orthostatic challenge and on cardiorespiratory responses to peak exercise. It was anticipated that individuals with tetraplegia would have blunted cardiorespiratory response to exercise and demonstrate a decreased ability to regulate blood pressure in comparison to individuals with paraplegia and able-bodied individuals.

4 RESEARCH METHODS

4.1 Participants

Six persons with SCI (C4-T6 lesions) and six age- and gender-matched controls were recruited for this investigation (Table 1). Participants were 27 to 39 years of age, asymptomatic, non-smokers, and were not using medications that would affect their autonomic, cardiovascular, respiratory, or metabolic responsiveness to exercise or the orthostatic challenge employed during this study. In order to assess the effect of injury level on exercise response and orthostatic tolerance, participants with cervical SCI and thoracic SCI were recruited. Amongst these participants, individuals with ASIA incomplete and complete injuries were included. Individuals were not eligible for this study if they had a documented history of cardiovascular disease, uncontrolled high blood pressure, or injuries to muscles, bones, ligaments, tendons or joints, respiratory illness, increased pain with arm activities, a brain injury which would stop them from understanding the instructions that were given during the study, or could not communicate English. Individuals were also excluded from the study if they and acute medical conditions (i.e., acute urinary tract infection, pressure sores, etc.).

Table 1. Participant characteristics

Subject No	Age, yr	Height, cm	Weight, kg	Sex	Lesion Leve	ASIA Class	Time Since Injury
SCI							
1	39	183	61	M	C6/C7	A	14
2	32	185.4	84.5	M	T6	B	11
3	39	157.5	63.9	F	C6/C7	B	8
4	32	180	72.5	M	C4/C5	B	13
5	32	177.6	57.9	F	T4	A	17
6	33	182.9	88.2	M	T4	A	9
Mean	**34.5**	**177.7**	**71.3**				**12.0**
SD	**3.5**	**10.3**	**12.7**				**3.3**
AB							
1	33	168.8	68.2	M			
2	30	183	79.5	M			
3	39	161.9	66.1	F			
4	31	190.2	97.9	M			
5	27	165	60.6	M			
6	38	161.8	61.8	F			
Mean	**33**	**171.8**	**72.4**				
SD	**4.7**	**12.0**	**14.2**				

4.1.1 Recruitment

Participants with SCI were recruited primarily through the G.F. Strong rehabilitation centre via poster advertisements that were distributed and placed at this site. Able-bodied participants were recruited from the student population at the University of British Columbia, and from the general population. Able-bodied participants were recruited via advertisements that were distributed and placed at several communal buildings within the university community (e.g., student union building, eateries).

4.2 General Protocol

This was a prospective, controlled investigation. Each participant completed four testing days at the Cardiovascular Physiology and Rehabilitation Laboratory at the University of British Columbia. Information on participants' height, weight, age, date of birth, and (for participants with SCI) lesion level, time since injury, and severity of SCI and ASIA score were collected on the first testing day (Table 1). Participants with SCI were asked to empty their bladders to minimize the influence of reflex sympathetic activation on peripheral vascular tone. On Test Day One each participant signed an informed consent form outlining the experimental procedures and completed the Physical Activity Readiness Questionnaire (PAR-Q) to ensure that participation in physical activity could be permitted. Test Days One and Two examined the effects of rest on cardiovascular response to the orthostatic stress, and assessed peak oxygen uptake during hybrid exercise and arm cycling exercise. Test Days Four and Five examined the effects of bouts of steady state arm cycle and hybrid exercise on cardiovascular response to the orthostatic challenge.

4.3 Orthostatic Testing

Participants underwent an orthostatic tolerance test on all four testing days. On the first two testing days, participants underwent the orthostatic challenge prior to performing a peak exercise test. On the final two testing days, participants underwent the orthostatic challenge following a bout of either arm or hybrid steady state exercise. On each testing day, prior to undergoing the orthostatic challenge, participants completed a fatigue scale[110].

While there is a known link between SCI and orthostatic hypotension[9, 111], orthostatic stress testing is not commonly performed in individuals with SCI because of the technical difficulties associated with changes in posture. Orthostatic tolerance is usually evaluated using tilt table testing[6]. However, in persons with SCI, this requires extensive strapping to prevent buckling of the paralyzed lower extremities, which could potentially lead to autonomic dysreflexia. This would potentially mask orthostatic hypotension and invalidate any assessment of orthostatic tolerance in these individuals. A simple bedside "sit up test" that has been developed was used for the evaluation of orthostatic tolerance in this study[6]. This procedure requires minimal strapping and is sufficient to evaluate orthostatic cardiovascular control in persons with cervical and thoracic SCI[6]. Prior to testing days, participants were instructed to abstain from caffeine and alcohol, and exercise for at least 12 hours the night before, and to consume only a light breakfast on testing days.

While supine, participants were instrumented with an electrocardiogram (Powerlab 16/30, ADInstruments, Colorado Springs, CO) and a beat-to-beat blood pressure monitoring device (Finapres; Ohmeda); the beat-to-beat blood pressure readings were verified with automated blood pressure readings. Stroke volume was measured via impedance cardiography (HIC-3000, Bio Impedance Technology, Inc.) during the orthostatic challenge. Participants were also instrumented with an ultrasound probe to make transcranial Doppler (Companion III, Nicolet Vascular, SciMed Ltd., UK) measurements of blood flow velocity in the middle cerebral artery. Following 15 minutes of supine rest, participants underwent a 15-minute passive orthostatic challenge ("sit up test"[6]). Heart rate, stroke volume, cardiac output, and blood pressure were continuously monitored and recorded.

4.3.1 Sit Up Test

Participants were positioned on the chair used to elicit the orthostatic challenge in such a way as to prevent and minimize slipping during the passive manoeuvre. To ensure this, proper alignment of participants' hips and knees with the chair were made prior to the test. Following instrumentation, baseline recordings were made during a 15-minute supine rest period. Participants were informed about the importance of this test being passive and were instructed not to assist at all during the sit up procedure[6]. Following the 15-minute supine rest period, participants were passively moved into an upright seated position by raising the head of the chair and dropping the base of the chair from the knees. This sit up position is essentially the same as when individuals are seated in a wheelchair or chair, but the feet are not supported and the legs are freely dangling from the knees. This position was maintained for 15 minutes, during which time recordings were continued. This test was terminated early and participants were returned to the supine position if they experienced any symptoms of presyncope (i.e., dizziness, lightheadedness, fainting, etc.).

4.4 Testing Days One and Two (Randomized)

Participants underwent an orthostatic stress test followed by an assessment of oxygen uptake and cardiac function during either peak arm cycle or peak hybrid exercise, performing one of these tests on each of these first two testing days (randomized). The orthostatic challenge has been described previously. Arterial compliance was also assessed pre- and post-exercise on the first two testing days.

4.4.1 Peak Aerobic Fitness Testing Protocol (VO_2peak Test)

Prior to completing peak exercise testing, participants were instructed to refrain from alcohol, coffee, tobacco, exercise, and food for at least 12 hours. Participants performed two peak exercise tests on two separate days separated by a minimum of 24 hours. Both testing days consisted of the continuous measurement of heart rate via electrocardiogram, heart rate variability (to assess autonomic tone), oxyhaemoglobin saturation (pulse oximeter), and the assessment of arterial compliance (applanation tonometry). Expired gas and ventiliatory parameters were acquired throughout the peak arm cycle and peak hybrid exercise tests using a metabolic cart. This permit the determination of oxygen uptake and ventilation.

Participants were asked to sit for five minutes before commencing the exercise tests and during this time baseline measures of oxygen uptake, heart rate, blood pressure, and ventilation were collected. Additionally, at every second minute of the rest period before commencing the exercise test, and twice during each exercise stage (once during, and once at the end of each exercise stage), measures of cardiac output, stroke volume, total peripheral resistance, and arterio-venous oxygen difference were be assessed non-invasively utilizing inert gas rebreathing (acetylene rebreathe via mass spectrometry). Participants started with a five-minute warm-up at a self-selected cadence (between 50-80rpm) and power output to allow them to become accustomed to the experimental setup and the cycling. The peak exercise tests consisted of incremental exercise stages where power output (Watts) was increased until the participants reached volitional fatigue (i.e., participants with SCI and able-bodied participants were not able to maintain a cycling rate of approximately 50 rpm, despite maximal effort and verbal encouragement; this was verified in conjunction with their reported rating of perceived exertion. For all participants, the workload was increased from 5 to 35 W per stage for the arms for both modes of exercise. Exercise began at a power output from 10 to 30 W. The resistance at which participants started the exercise tests and the progressive increases in power output during the successive stages were determined during a brief familiarization prior to commencing testing. Exercise tests were terminated immediately if one or more of the following symptoms occurred: 1) tightness and/or pain in the chest, 2) dizziness, lightheadedness, and/or nausea, 3) extreme shortness of breath, 4) a significant decrease in systolic blood pressure (> 10 mmHg), and/or 5) other abnormal electrocardiogram responses, all of which may infer the potential risk for a cardiovascular complication. A certified exercise physiologist was present at all tests. Gas analyzers were calibrated with gases of a known concentration prior to each experiment.

4.4.2 Peak Aerobic (VO_2peak) Arm Cycle Exercise Testing

Partcipants with SCI sat in the chair provided with the hybrid exercise machine (SCIFIT PRO II, SCI FIT, Tulsa, Oklahoma) or in their own wheelchairs which were positioned appropriately relative to the exercise machine. Able-bodied participants sat in the chair provided with the hybrid exercise machine. Participants were seated in an upright position with the fulcrum of the handlebars adjusted so that they were at shoulder height. Follwing a five-minute warm-up, the workload was gradually made more difficult by increasing the intensity of each exercise stage. The test allowed for the assessment of cardiorespiratory response to peak arm exercise including the determination of peak oxygen uptake.

4.4.3 Peak Aerobic (VO_2peak) Hybrid Exericse Testing

Participants with SCI sat in the chair provided with the hybrid exercise machine (SCIFIT PRO II, SCI FIT, Tulsa, Oklahoma) or in their own wheelchairs which were positioned appropriately relative to the exercise machine. Able-bodied participants sat in the chair provided with the hybrid exercise machine. Participants were seated in an upright position with the fulcrum of the handlebars adjusted so that they were at shoulder height. An ideal seat height was set for each individual so that the knee was slightly flexed at full extension. All participants were able to incorporate their legs into hybrid exercise passively since cycling the arms automatically allowed for passive cyclying of the lower limbs with the exercise machine. Participants' feet were strapped to the leg pedals. Following a five-minute warm-up, the workload for the arms was gradually made more difficult by increasing the intensity of each exercise stage. There was no resistance and the workload was not increased for the lower limbs since they were passively incorporated into exercise (electrical activity of the muscles of the right leg were monitored via electromyogram to try to monitor and minimize muscle contraction of the lower limbs). This test allowed for the assessment of cardiorespiratory response to hybrid exercise and the determination of peak oxygen uptake.

4.5 Testing Days Three and Four (Randomized)

As described previously, participants underwent the orthostatic challenge on all four testing days. For Testing Days Three and Four, participants completed a bout of either arm or hybrid steady state exercise prior to undergoing the orthostatic challenge. Participants completed 30 minutes of continuous and moderate (65% of heart rate reserve) intensity arm cycle or hybrid exercise (randomized) followed immediately by a sit up test[6] to evaluate the effects of each mode of exercise (i.e., arm cycle and hybrid) on orthostatic response.

4.6 Cardiovascular Measures

On all testing days, the following measures were collected: heart rate (electrocardiogram), heart rate variability, ventilation, blood pressure (finger plethysmography), oxyhaemoglobin saturation, arterial compliance (applanation tonometry), cardiac output and stroke volume (acetylene rebreathing and impedance cardiography), arterio-venous oxygen difference, total peripheral resistance, and rating of perceived exertion. For each participant, electromyogram data was also collected to monitor muscle contraction of the lower limbs during hybrid exercise in an attempt to minimize it. On each testing day during the assessment of orthostatic tolerance, blood flow velocity of the middle cerebral artery was measured (transcranial Doppler).

4.6.1 Middle Cerebral Artery Blood Velocity

Blood flow velocity of the middle cerebral artery was measured using a Companion III transcranial Doppler system (Companion III, Nicolet Vascular, SciMed Ltd., UK). A probe was fixed to the zygomatic arch of the participant and the probe directed ultrasound waves at a frequency of 2MHz to a depth of 3.5 to 5.5cm. Blood flow velocity was determined approximately at the midpoint of the middle cerebral artery upstream from the bifurcation to optimize the ultrasound waveform. The ultrasound probe was held in place using a transcranial Doppler fixation head frame to ensure the validity of the measurements. Both peak blood flow velocity and mean blood flow velocity (calculated using an algorithm which averages blood flow velocity and mean blood flow velocity over three second intervals) were taken.

4.6.2 Arterial Compliance

The non-invasive assessment of large and small artery compliance was be performed prior to and immediately following peak exercise tests using an applanation tonometer (CR-3000, HDI) that measures radial artery pulse waves. Radial arterial waveform acquisition of the right arm was be obtained in conjunction with automated blood pressure on the left arm. This technology is a simple, convenient, and operator-independent means of evaluating vascular function and health, making it particularly appropriate for use with persons with SCI.

4.6.3 Blood Pressure

Beat-by-beat arterial blood pressure was recorded via finger photoplethysmography (Finapres; Ohmeda) during the orthostatic assessment. Automated blood pressure measurements were also obtained to verify and correct the readings obtained from the Finapres. Mean arterial pressure has been calculated as [(systolic blood pressure-diastolic blood pressure)/3] + diastolic blood pressure.

4.6.4 Electromyogram

Electromyogram was continuously measured on muscles of the right leg for all participants during the performance of hybrid exercise, and a data acquisition system (Powerlab 16/30, ADInstruments, Colorado Springs, CO) and personal computer were used to record this data. The electromyogram represents the combined electrical activity that is generated by multiple action potentials of actively contracting muscles[112].

4.6.5 Fatigue Scale

The Lee Fatigue Scale[110] was administered to obtain a fatigue severity score. The Lee Fatigue Scale has been used to measure severity of fatigue in healthy individuals as well as in clinical populations[113-115]. This scale was chosen to measure fatigue for this study because it is relatively short and easy to administer. The Lee Fatigue Scale has well-established validity and reliability[110, 116].

4.6.6 Heart Rate

Heart rate was continuously measured via electrocardiogram. A data acquisition system (Powerlab 16/30, ADInstruments, Colorado Springs, CO) and a personal computer were used to record heart rate and electrocardiogram.

4.6.7 Heart Rate Variability

Heart rate was monitored via electrocardiogram and sections of this data may be visually examined and analyzed. The R-R intervals may be used to calculate heart rate variability, and commercially available software used to analyze it (Chart V5.02; ADInstruments).

4.6.8 Metabolic Cart and Impedance Cardiography

Expired gas and ventilatory parameters were acquired throughout the peak arm cycle and peak hybrid exercise tests using a mass spectrometer (Amis 2000, Innovision, Odense, Denmark), and this permit the determination of oxygen uptake. At the end of each exercise stage, measures of cardiac output and stroke volume were assessed non-invasively using inert gas rebreathing (mass spectrometry) (Amis 2000, Innovision, Odense, Denmark). On testing days involving assessment of orthostatic tolerance, stroke volume and cardiac output were also measured on a beat-by-beat basis during the orthostatic challenge via impedance cardiography (HIC-3000, Bio-Impedance Technology, Inc.).

4.6.9 Oxyhaemoglobin Saturation

Oxyhaemoglobin saturartion was continuously measured non-invasively by a pulse oximeter (Ohmeda Biox 3740, Louisville, Colorado) placed on the ear.

4.6.10 Total Peripheral Resistance

Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output.

4.6.11 Rating of Perceived Exertion

Participants reported their rating of perceived exertion immediately following the end of each exercise stage during peak exercise testing. This was used as a means to evaluate that exercise was performed to exhaustion. Prior to the exercise tests, there was an explanation of the rating of perceived exertion scale being used and any questions concerning the procedure for rating the intensity of perceived exertion were answered at this time. Participants were asked to report their rating of perceived exertion using the modified Borg scale[117].

5 STATISTICAL ANALYSIS

Differences between measures of middle cerebral artery blood velocity, blood pressure, heart rate, stroke volume, cardiac output, arterio-venous oxygen difference, total peripheral resistance, arterial compliance, and rating of perceived exertion between groups of participants and mode of exercise were examined using mixed model analysis of variance with Tukey post hoc comparisons. The level of significance was set a priori at $p < 0.05$. Data are presented as mean $\pm$ SD.

Additionally, to examine cerebral autoregulation, regressions of mean arterial pressure and middle cerebral artery blood velocity were examined by plotting them against one another and fitting them with a with a regression line. A coefficient of determination (R^2) was considered physiologically significant when $R^2 \geq 0.75$[118]. The coefficient of determination provides an index of autoregulatory failure, and the slope provides an index of the severity of such a failure. The linear regressions were obtained from a range of blood pressure values from the duration of the orthostatic challenge. Furthermore, in addition to the evaluation of the slope of the flow-blood pressure curve, the middle cerebral artery blood velocity corresponding to the maximal fall in mean arterial pressure was also obtained to provide insights into the range of autoregulatory responses to the orthostatic challenge. The level of significance was set a priori at $p < 0.05$. Data are presented as mean $\pm$ SD.

To analyze the difference in peak power output between groups of participants and modes of exercise, independent t-tests were employed. The level of significance was set a priori at $p < 0.05$. Data are presented as mean $\pm$ SD.

6 RESULTS

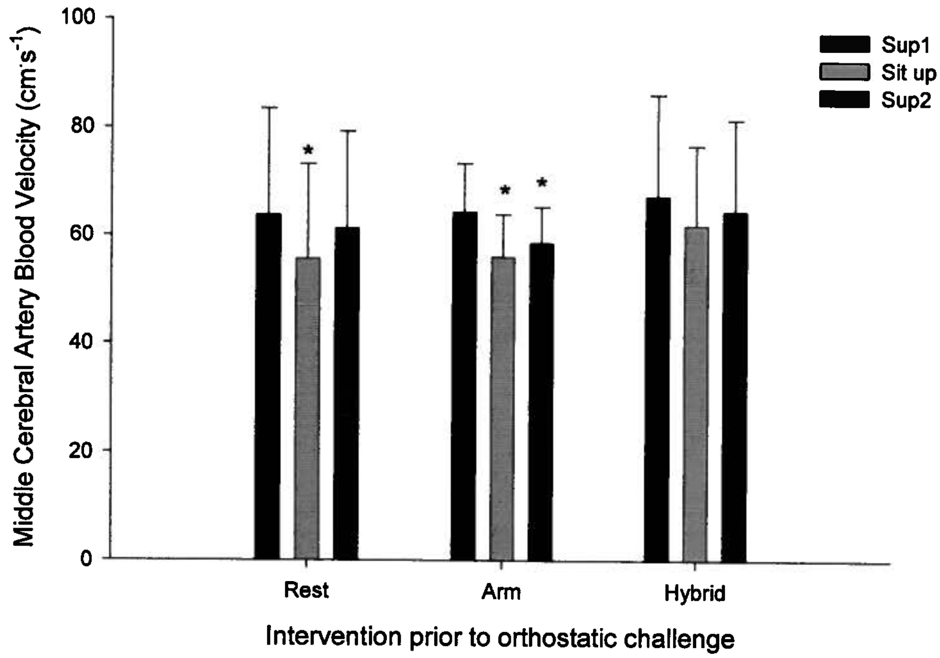
There were no significant differences at baseline between any groups (able-bodied, SCI, and paraplegics and tetraplegics) for middle cerebral artery blood velocity, blood pressure, heart rate, stroke volume, and cardiac output. Additionally, there was no significant difference in any of the aforementioned measures when comparing values at baseline and upon resuming the supine position for all participants.

6.1 Orthostatic Hypotension

6.1.2 Middle Cerebral Artery Blood Velocity

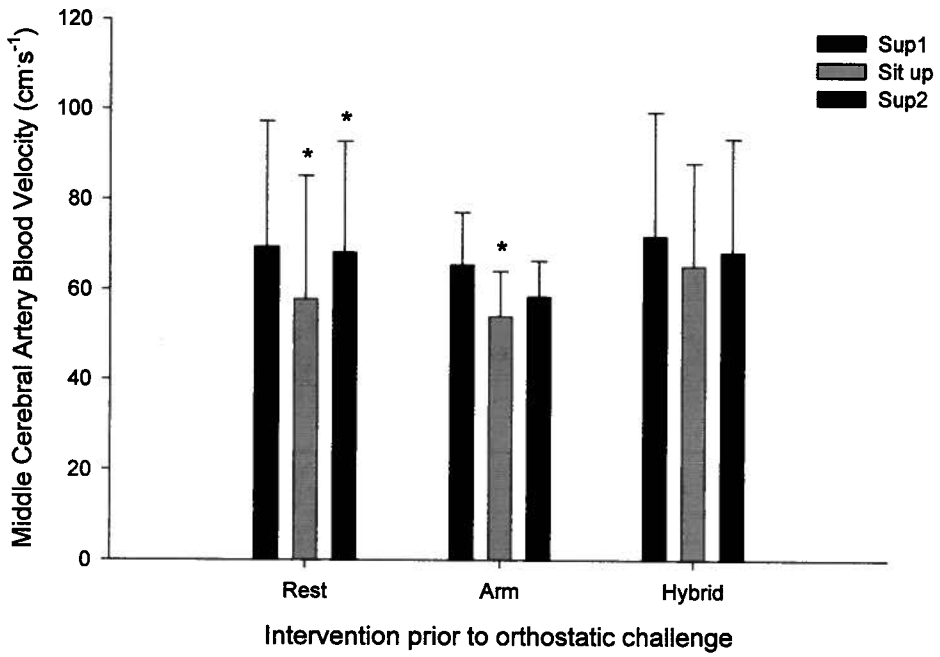
Participants with SCI (Figure 1), and participants with tetraplegia specifically, (Figure 2) did not experience significant decreases in middle cerebral artery blood velocity (MCABV) upon assuming an upright posture (64.3 $\pm$ 9.0 to 55.9 $\pm$ 7.9 $cm{\cdot}s^{-1}$, respectively) following a bout of hybrid steady state exercise. Paraplegics did not experience any significant decreases in MCABV on any of the testing days (Figure 3). Generally, across all testing days, MCABV increased when participants returned to the supine position (60.1 $\pm$ 1.5 to 66.6 $\pm$ 2.7 and 57.8 $\pm$ 3.5 to 61.4 $\pm$ 3.0 $cm{\cdot}s^{-1}$, for able-bodied participants and participants with SCI, respectively). However, MCABV remained significantly reduced in comparison to baseline values upon returning to the supine position following a bout of arm steady state exercise in participants with SCI (64.3 $\pm$ 9 vs. 58.5 $\pm$ 6.9 $cm{\cdot}s^{-1}$, respectively). Overall, examination of changes in MCABV revealed that orthostatic responses were affected by the intervention that preceded the orthostatic challenge, with hybrid exercise promoting improved orthostatic response in persons with SCI. Furthermore, able-bodied participants (Figure 4) showed less decrement to MCABV when assuming the upright posture and greater recovery in MCABV upon resuming the supine position in comparison to the group with SCI. A comparison of changes in MCABV between groups during the orthostatic challenge are illustrated in Figure 5.

Figure 1. Middle cerebral artery blood velocity during the orthostatic challenge in participants with SCI



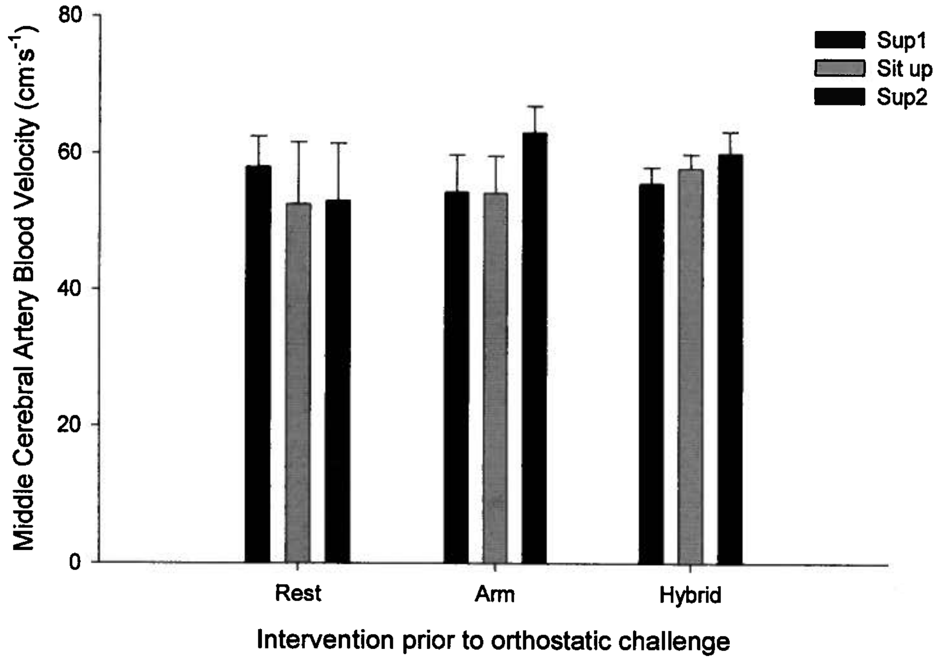
Changes in middle cerebral artery blood velocity in participants with SCI during the orthostatic challenge following rest, or either arm or hybrid steady state exercise. The orthostatic challenge includes three segments: 1) The baseline supine position (Sup1), 2) sit up (Sit up), and 3) the return to the supine position (Sup2). * $p<0.05$ vs. baseline. Values are mean ± SD.

Figure 2. Middle cerebral artery blood velocity during the orthostatic challenge in participants with tetraplegia



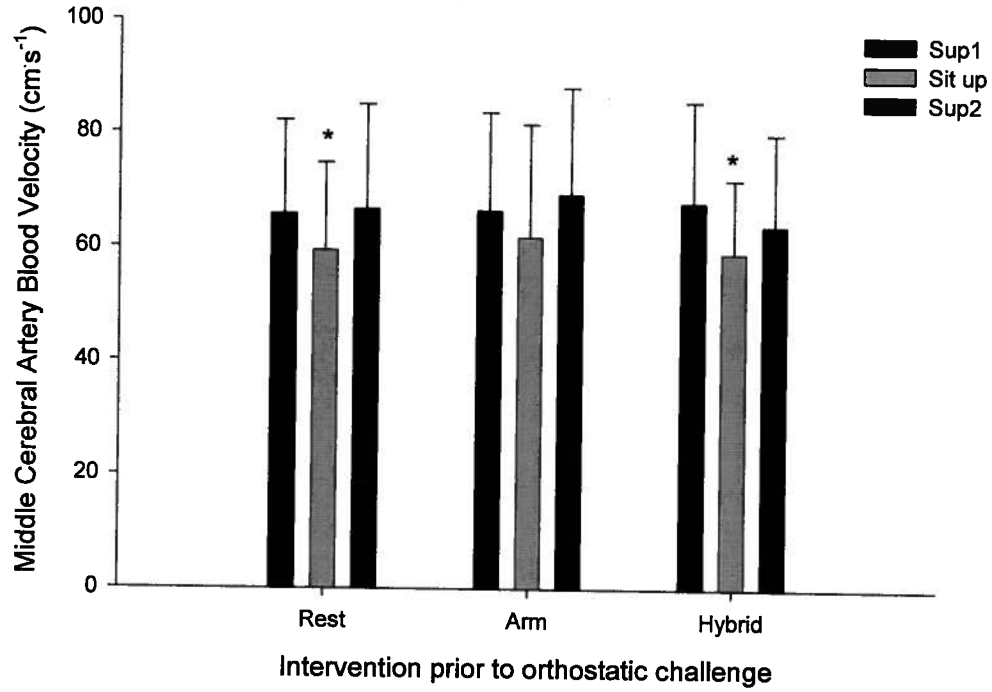
Changes in middle cerebral artery blood velocity in participants with tetraplegia during the orthostatic challenge following rest, or either arm or hybrid steady state exercise. The orthostatic challenge included three segments: 1) The baseline supine position (Sup1), 2) the sit up position (Sit up), and 3) the return to the supine position (Sup2). * $p<0.05$ vs. baseline. ** $p<0.05$ vs. sit up.

Figure 3. Middle cerebral artery blood velocity during the orthostatic challenge in participants with tetraplegia



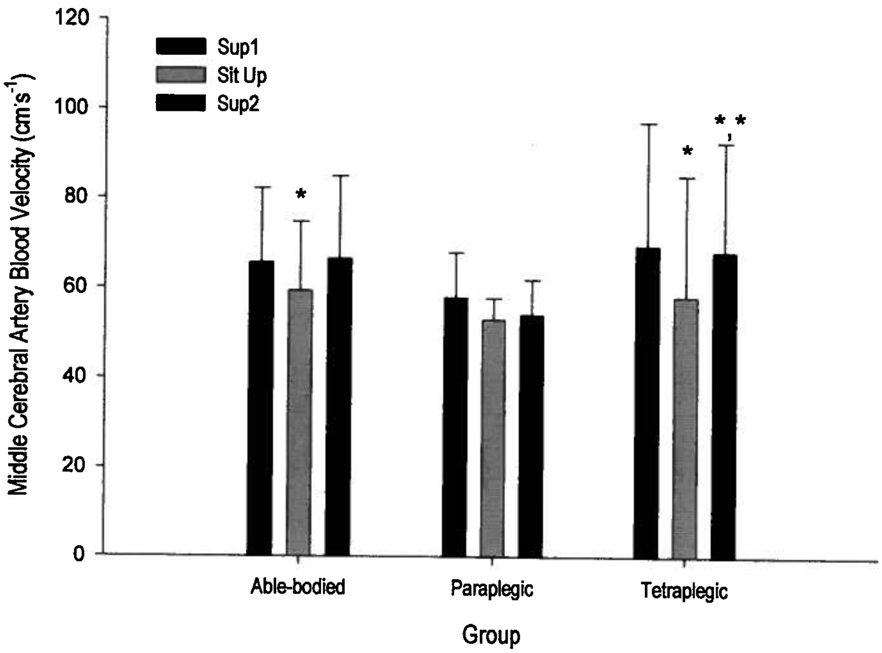
Changes in middle cerebral artery blood velocity in participants with paraplegia during the orthostatic challenge following rest, or either arm or hybrid steady state exercise. The orthostatic challenge included three segments: 1) The baseline supine position (Sup1), 2) the sit up position (Sit up), and 3) the return to the supine position (Sup2).

Figure 4. Middle cerebral artery blood velocity during the orthostatic challenge in able-bodied individuals



Changes in middle cerebral artery blood velocity during the orthostatic challenge in able-bodied participants following rest, or either arm or hybrid steady state exercise. The orthostatic challenge includes three segments: 1) The baseline supine position (Sup1), 2) the sit up position (Sit up), and 3) the return to the supine position (Sup2). * $p<0.05$ vs. baseline.

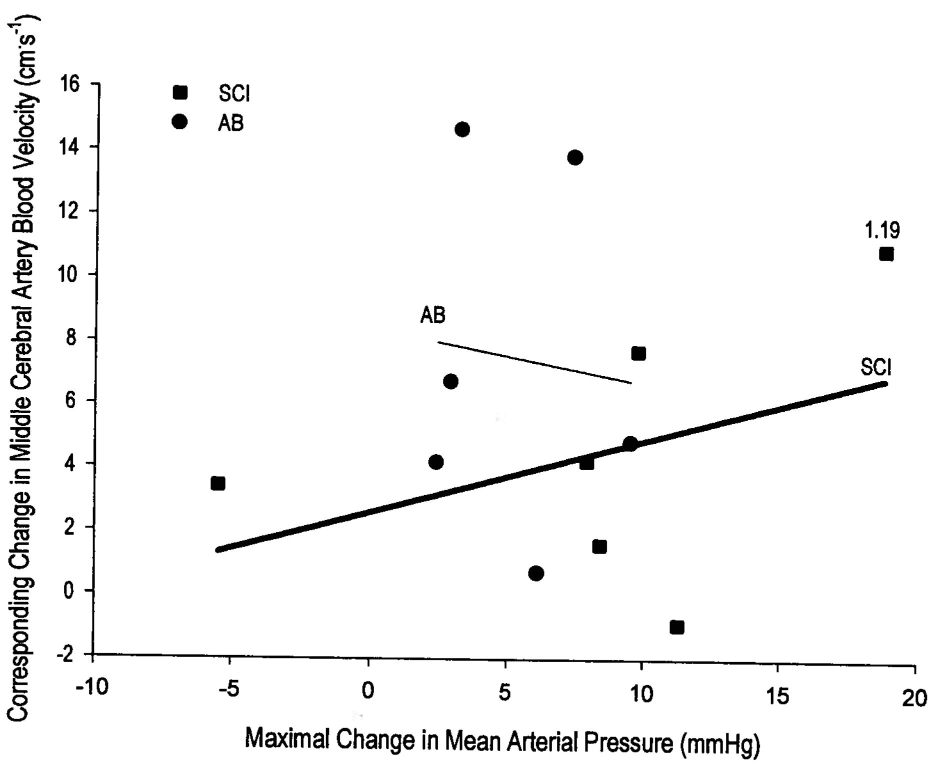
Figure 5. Middle cerebral artery blood velocity during the orthostatic challenge following rest in participants



Changes in middle cerebral artery blood velocity during the orthostatic challenge in able-bodied participants, and participants with paraplegia and tetraplegia following rest. The orthostatic challenge includes three segments: 1) The baseline supine position (Sup1), 2) the sit up position (Sit up), and 3) the return to the supine position (Sup2). * $p<0.05$ vs. baseline. ** $p<0.05$ vs. sit up.

Regression analysis was used to examine cerebral autoregulation in participants (Figure 5). Previous findings have illustrated that positive flow-pressure correlations and linear flow-pressure relationships can be predicative of autoregulation failure with the slope of the regression indicating the severity of the failure[118]. Able-bodied participants did not have any significant positive correlation of flow to pressure, indicating no failure of autoregulation. There was a similar finding in participants with SCI, except for one participant with tetraplegia who had a significantly positive correlation following a bout of hybrid steady state exercise. This suggests that, in this participant, cerebral autoregulation was impaired following a bout of hybrid steady state exercise. While no other participants with SCI had significant positive correlations, individuals with SCI generally had higher coefficients of determination in comparison to their able-bodied counterparts, suggesting that there is impairment of cerebral autoregulation in persons with SCI. A negative slope of the regression indicates that cerebral autoregulation is intact. This was illustrated by the corresponding changes in blood pressure and middle cerebral artery blood velocity in able-bodied participants. Upon assumption of the upright posture, these participants experienced increases in blood pressure despite concurrent decreases in cerebral blood flow. The inverse response of these two cardiovascular parameters is indicative of intact cerebral autoregulation. Participants with paraplegia also exhibited intact autoregulation since they had negative slopes of regression as well. The tetraplegic with high correlation, on the other hand, had a steep and positive slope of regression following a bout of hybrid steady state exercise, suggesting that cerebral autoregulation was impaired in this individual (Figure 6). That is, upon assumption of the upright posture, a decline in middle cerebral artery blood velocity was accompanied by a concurrent decrease in blood pressure.

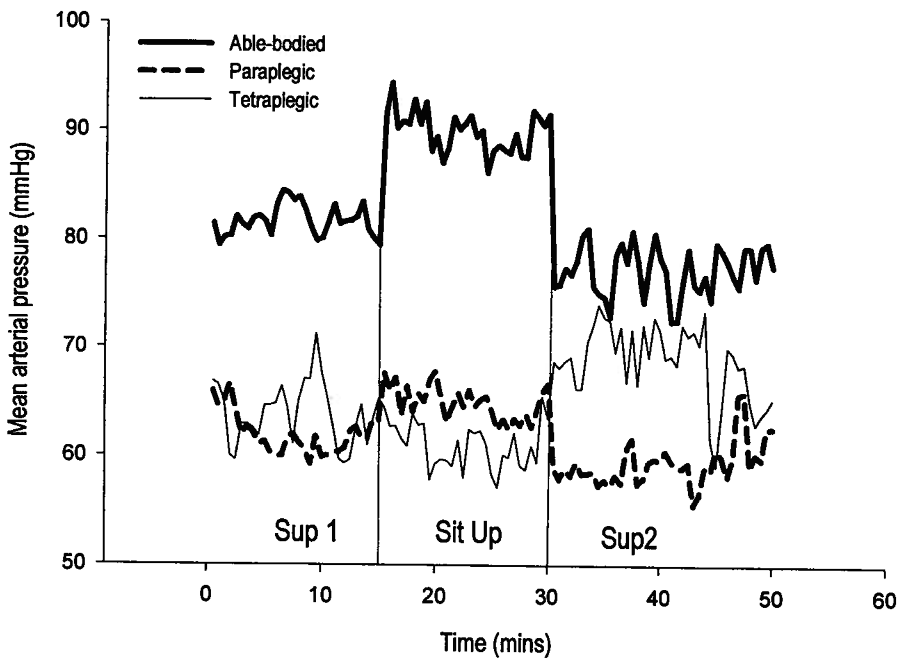
Figure 6. The flow-pressure relationship between the initial supine position and assumption of the upright posture during the orthostatic challenge



Calculated regression in participants with SCI and able-bodied participants for maximal change in mean arterial pressure plotted against the corresponding middle cerebral artery blood velocity during the orthostatic challenge during the transition from the initial supine position to the assumption of the upright posture. Data illustrated are following a bout of hybrid steady state exercise. There were n= 6 for each of the participants with SCI and able-bodied participants. Numbers indicate the slope of regression, if the correlation coefficient was >0.75.

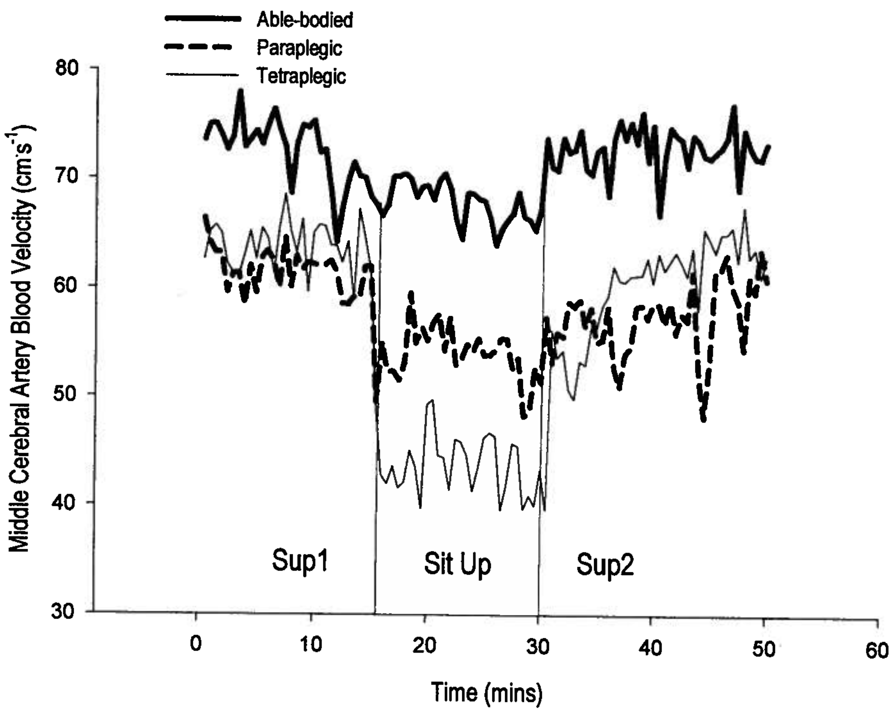
The changes in mean arterial blood pressure and MCABV following assumption of the upright posture (Figure 7 and Figure 8, respectively) were modest for persons with SCI and able-bodied individuals collectively, ranging from -2 to 18 mmHg, and 3 to 23 $cm{\cdot}s^{-1}$, respectively. The reduction in both of these measures was generally larger in participants with SCI in comparison to able-bodied participants while these differences were not statistically significant. Furthermore, at the time when participants reached their lowest mean arterial pressure during the orthostatic challenge, the corresponding decrease in MCABV was generally similar across all testing days, indicating that changes in MCABV were similar between testing days. However, following a bout of hybrid steady state exercise, individuals with SCI experienced a smaller decline in MCABV corresponding to their greatest fall in mean arterial pressure (-5.4 $\pm$ 4.3 $cm{\cdot}s^{-1}$ and -10.1 $\pm$ 7.9 mmHg following a bout of hybrid steady state exercise vs. -8.6 $\pm$ 6.1 $cm{\cdot}s^{-1}$ and -9.9 $\pm$ 5.9 mmHg and -8.5 $\pm$ 5.0 $cm{\cdot}s^{-1}$ and -8.8 $\pm$ 6.8 mmHg following rest and a bout of arm steady state exercise, respectively). When examining tetraplegics and paraplegics specifically, individuals with tetraplegia had significantly greater decreases in mean arterial pressure (-6.8 $\pm$ 6.3 vs. -12.9 $\pm$ 4.7, -3.2 $\pm$ 4.6 vs. -14.4 $\pm$ 4.8, and -3.6 $\pm$ 12.2 vs. -13.3 $\pm$ 4.8 mmHg for paraplegics vs. tetraplegics during the orthostatic challenge following rest, and bouts of arm and hybrid steady state exercise, respectively) and MCABV (-5.9 $\pm$ 3.2 vs. -11.4 $\pm$ 8.2, -5.0 $\pm$ 4.9 vs. -12.0 $\pm$ 2.9, and -3.1 $\pm$ 5.0 vs. -5.9 $\pm$ 6.1 $cm{\cdot}s^{-1}$ for paraplegics vs. tetraplegics and the orthostatic challenge following rest, and bouts of arm and hybrid steady state exercise, respectively) than paraplegics.

Figure 7. Temporal changes in mean arterial pressure during the orthostatic challenge



Able-bodied participants, and participants with paraplegia generally had similar changes in mean arterial pressure in response to the orthsostatic challenge, while participants with tetraplegia tended to respond in an opposite manner. The former two groups experienced increases in mean arterial pressure upon assuming the upright posture, and a subsequent decline upon resuming the supine position. Tetraplegics had a decline in mean arterial pressure upon moving to the upright position, and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response to the orthostatic challenge following rest.

Figure 8. Temporal changes in middle cerebral artery blood velocity during the orthostatic challenge

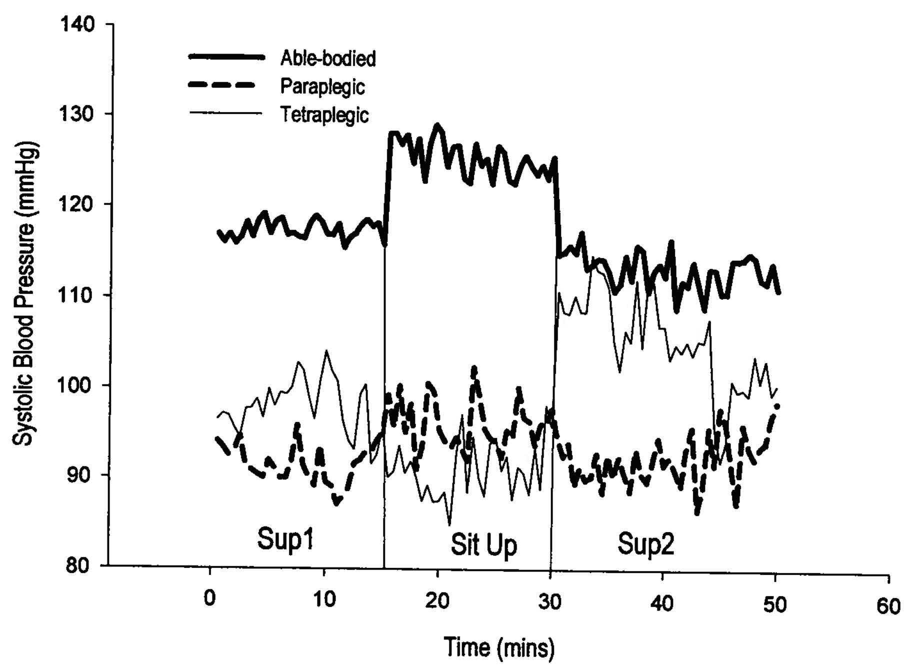


All participants experienced declines in middle cerebral artery blood velocity upon assumption of the upright posture and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response to the orthostatic challenge following rest.

6.1.2 Blood Pressure

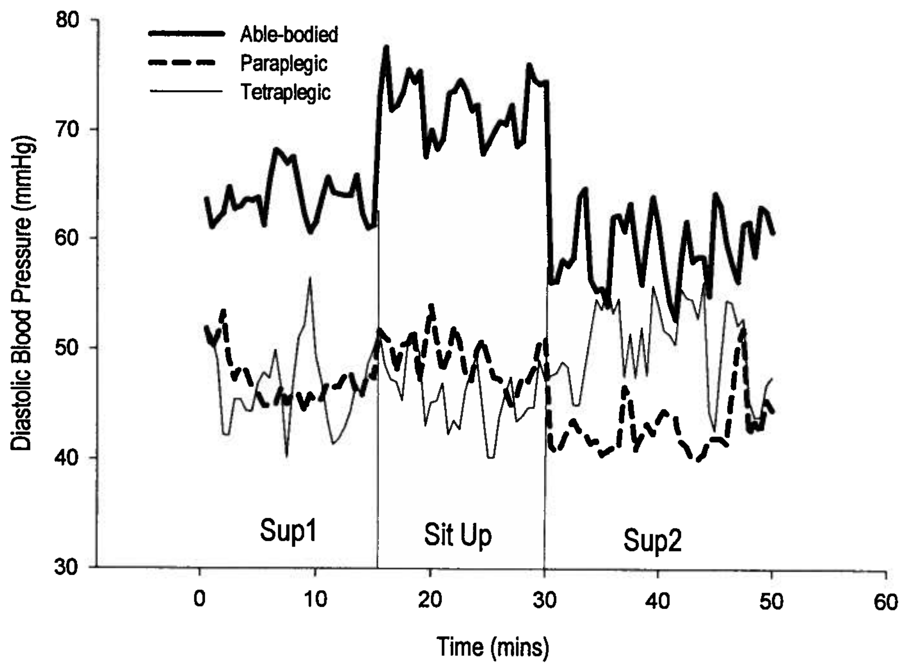
When examining blood pressure, participants were differentially affected by changes in posture during the orthostatic challenge. Specifically, for participants with SCI, blood pressure response was affected by lesion level. Able-bodied participants experienced increases in systolic blood pressure (SBP) upon assuming the upright posture on all testing days (109.2 $\pm$ 0.4 to 114.9 $\pm$ 1.6 mmHg, across testing days). When returning to the supine position, able-bodied participants decreased their SBP on all testing days (112.9 $\pm$ 1.6 to 110.0 $\pm$ 0.9 mmHg, across testing days). Paraplegics responded similarly to able-bodied participants, which was illustrated by an increase in SBP when moved to the upright position (110.2 $\pm$ 2.3 to 113.6 $\pm$ 4.1 mmHg, across testing days), and a decrease in SBP when the supine position was resumed (113.6 $\pm$ 4.1 to 108.9 $\pm$ 4.6 mmHg, across testing days). The SBP response of tetraplegics was opposite to that of able-bodied participants and paraplegics. They experienced a decrease in SBP (across testing days) when assuming the upright posture (112.8 ± 2.2 to 107.0 ± 4.1 mmHg), and an increase in SBP (across testing days) when returning to the supine position (107.0 ± 4.1 to 109.9 ± 3.6 mmHg). Changes in diastolic blood pressure (Figure 10) during the orthostatic challenge were similar to the changes found for systolic blood pressure (Figure 9) during the orthostatic challenge. Overall, neither form of exercise appeared to differentially affect blood pressure response to the orthostatic challenge.

Figure 9. Temporal changes in systolic blood pressure during the orthostatic challenge



Able-bodied participants and participants with paraplegia generally had similar changes in systolic blood pressure in response to the orthostatic challenge, while participants with tetraplegia tended to respond in an opposite manner. The former two groups experienced increases in systolic blood pressure upon assuming the upright posture, and a subsequent decline upon resuming the supine position. Tetraplegics had a decline in systolic blood pressure upon moving to the upright position, and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response to the orthostatic challenge following rest.

Figure 10. Temporal changes in diastolic blood pressure during the orthostatic challenge

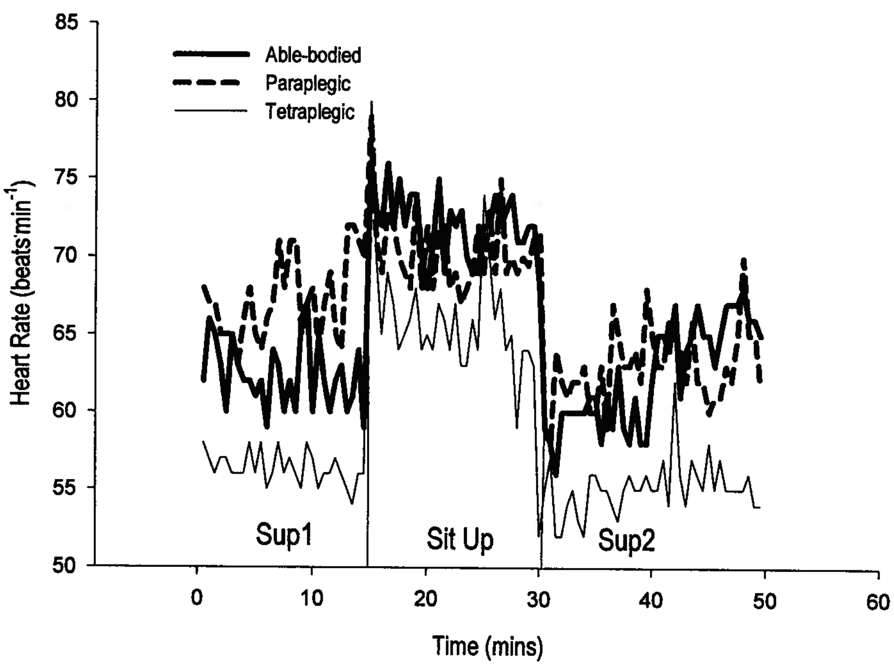


Able-bodied participants and participants with paraplegia generally had similar changes in diastolic blood pressure in response to the orthostatic challenge, while participants with tetraplegia tended to respond in an opposite manner. The former two groups experienced increases in diastolic blood pressure upon assuming the upright posture, and a subsequent decline upon resuming the supine position. Tetraplegics had a decline in diastolic blood pressure upon moving to the upright position, and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response to the orthostatic challenge following rest.

6.1.3 Heart Rate

Upon assuming the upright posture, able-bodied participants and participants with SCI (both paraplegics and tetraplegics) had significant increases in heart rate (HR) after performing bouts of arm and hybrid steady state exercise. The average values for HR (across groups) were 60.9 $\pm$ 6.8 to 67.6 $\pm$ 6.9 and 59.0 $\pm$ 4.7 to 66.4 $\pm$ 6.7 beats·min^{-1} for arm and hybrid steady state exercise, respectively. Upon returning to the supine position, both able-bodied participants and participants with paraplegia and tetraplegia had significant decreases in HR across all testing days (65.8 $\pm$ 0.9 to 58.7 $\pm$ 1.5, 68.9 $\pm$ 3.0 to 61.6 $\pm$ 1.7, and 66.7 $\pm$ 2.9 to 58.2 $\pm$ 1.0 beats·min^{-1}, respectively). Generally, all participants experienced increases in HR upon assuming the upright posture, and decreases in HR when returning to the supine position (Figure 11).

Figure 11. Temporal changes in heart rate during the orthostatic challenge



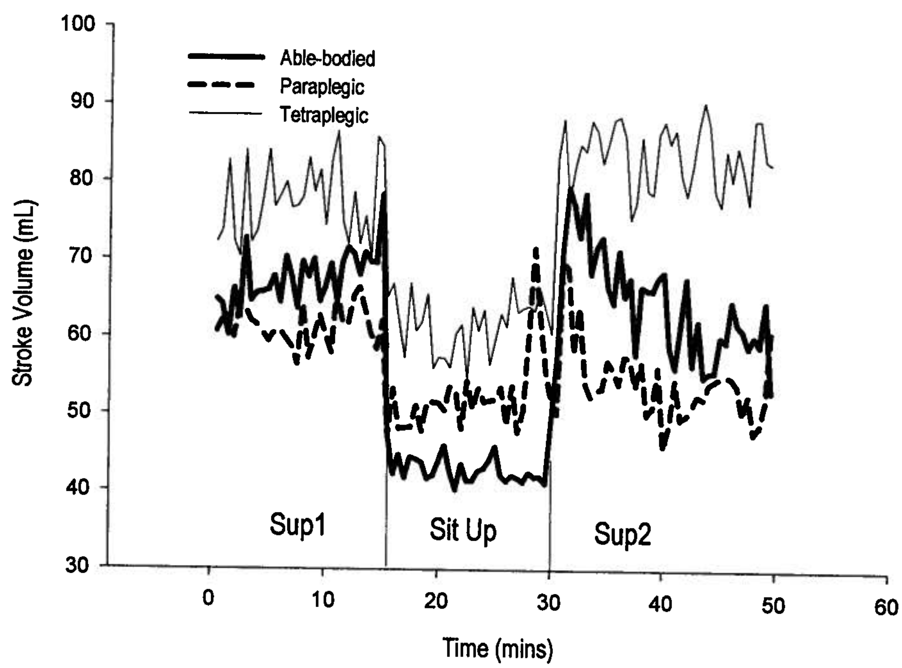
All participants experienced increases in heart rate upon assumption of the upright posture and a decrease when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response during the orthostatic challenge following rest.

6.1.4 Stroke volume

When assuming the upright posture, both able-bodied participants and participants with SCI experienced significant decreases in stroke volume (SV) on all testing days (57.3 $\pm$ 11.6 to 56.3 $\pm$ 8.6, 76.3 $\pm$ 11.4 to 56.5 $\pm$ 9.5, and 80.8 $\pm$ 1.9 to 56.8 $\pm$ 10.4 mL, following rest, and bouts of arm and hybrid steady state exercise, respectively, across groups). Similarly, upon resuming the supine position, all participants had increases in SV across all testing days (56.3 $\pm$ 8.6 to 75.9 $\pm$ 19.9, 56.5 $\pm$ 9.5 to 78.3 $\pm$ 19.9, and 56.8 $\pm$ 10.4 to 75.1 $\pm$ 16.7 mL, following rest, and bouts of arm and hybrid steady state exercise, respectively, across groups) (Figure 9). Similarly, paraplegics and tetraplegics decreased their stroke volume upon assuming the upright posture. When returned to the supine position, tetraplegics only increased their SV significantly following a bout of hybrid steady state exercise (52.0 $\pm$

11.7 to 67.1 ± 14.2 mL), and participants with paraplegia only after a bout of arm steady state exercise (52.3 ± 7.5 to 72.4 ± 3.1 mL). Generally, on all testing days, all participants experienced decreases in stroke volume upon moving to the upright position, and increases in SV toward baseline when the supine position was resumed. Additionally, exercise did not differentially affect the changes in stroke volume during the orthostatic challenge between any of the participants (Figure 12), though recovery of SV upon returning to the supine position was greater following a bouts steady state exercise in paraplegics and tetraplegics (54.2 ± 10.2 to 68.6 ± 11.8 mL, across paraplegics and tetraplegics, and across exercise mode), in comparison to following rest (55.8 ± 3.6 to 64.9 ± 5.7 mL, across paraplegics and tetraplegics).

Figure 12. Temporal changes in stroke volume during the orthostatic challenge

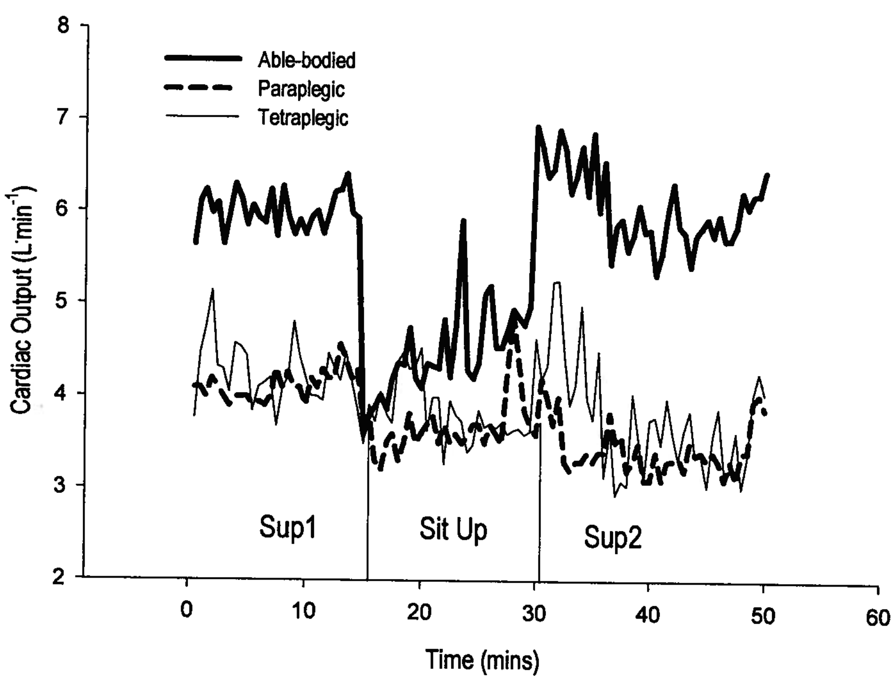


All participants experienced declines in stroke volume upon assumption of the upright posture and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response during the orthostatic challenge following rest.

6.1.5 Cardiac Output

After assuming the upright posture, both the able-bodied group and group with SCI decreased their cardiac output (Q) significantly on all testing days (4.6 ± 0.3 to 3.7 ± 0.1, 4.6 ± 0.3 to 3.7 ± 0.04, and 4.7 $\pm$ 0.8 to 3.8 $\pm$ 0.2, following rest, and bouts of arm and hybrid steady state exercise, respectively, across groups) (Figure 10). When returning to the supine position, able-bodied participants had significant increases in Q on all testing days. Participants with SCI also increased Q after returning to the supine position, but this increase was only significant following a bout of arm steady state exercise (3.8 $\pm$ 0.5 to 4.3 $\pm$ 0.5 L·min^{-1}). Participants (able-bodied, paraplegics, and tetraplegics) generally experienced decreases in Q when moved to the upright posture and increases when returned to the supine position (Figure 13). The intervention performed prior to the orthostatic challenge did not appear to differentially affect changes in Q significantly during the orthostatic test in participants with SCI.

Figure 13. Temporal changes in cardiac output during the orthostatic challenge

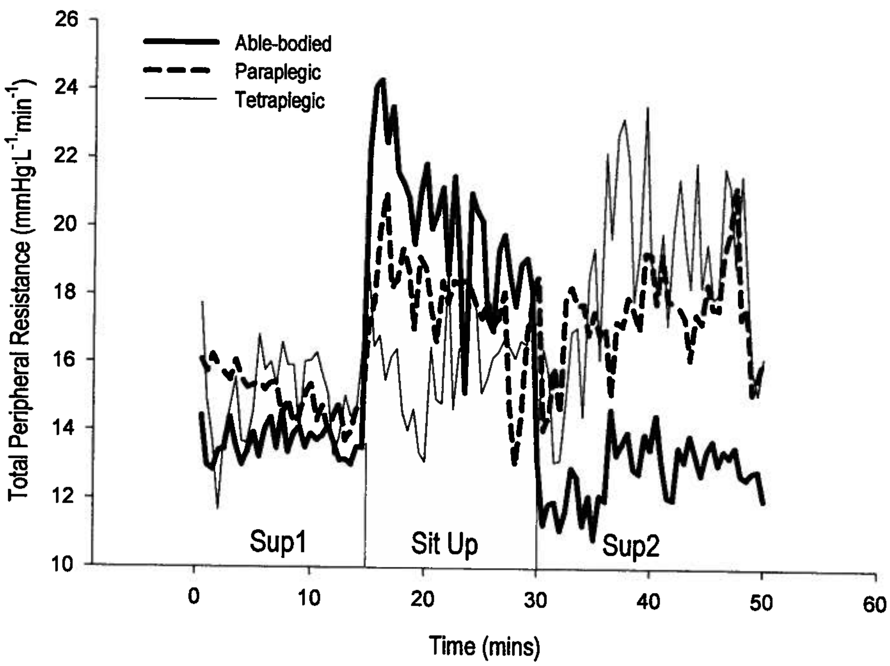


All participants experienced declines in cardiac output upon assumption of the upright posture and an increase when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response during the orthostatic challenge following rest.

6.1.6 Total Peripheral Resistance

During the orthostatic challenge on all testing days, participants with SCI and able-bodied participants experienced a significant increase in total peripheral resistance (TPR) upon assuming the upright posture, and a decrease in TPR when returned to the supine position (Figure 14). The average total peripheral resistance (across all testing days and groups of participants) when moving from the supine to the upright posture and then returning to the supine position was 17.8 $\pm$ 0.9 to 20.61 $\pm$ 1.3 to 16.9 $\pm$ 0.6 $mmHg \cdot L^{-1} \cdot min^{-1}$, respectively. Generally, able-bodied participants experienced greater increases in TPR when moved to the upright posture than individuals with SCI. The average percent increase (across all testing days) was 5.3 $\pm$ 13.8 % and 19.4 $\pm$ 10.1 % for participants with SCI and able-bodied participants, respectively.

Figure 14. Temporal changes in total peripheral resistance during the orthostatic challenge



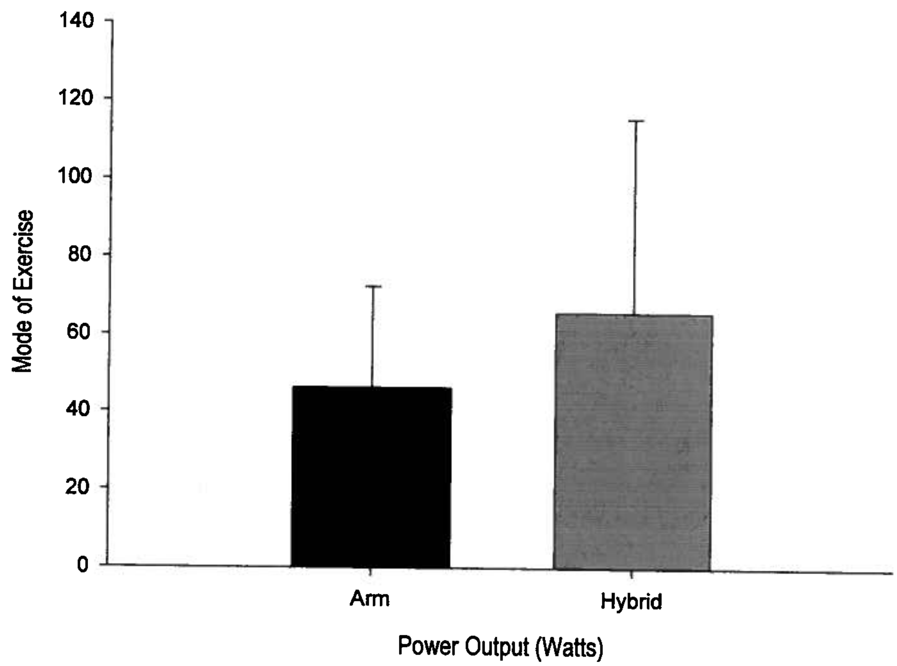
Across all groups, participants experienced increases in total peripheral resistance upon assumption of the upright posture and a decrease when returned to the supine position. Participants maintained the initial supine (Sup1), sit up (Sit Up), and final supine (Sup2) position for 15 minutes each. Data is from a representative participant for each group and represents cardiovascular response during the orthostatic challenge following rest.

6.2 Peak Exercise Testing

6.2.1 Power Output

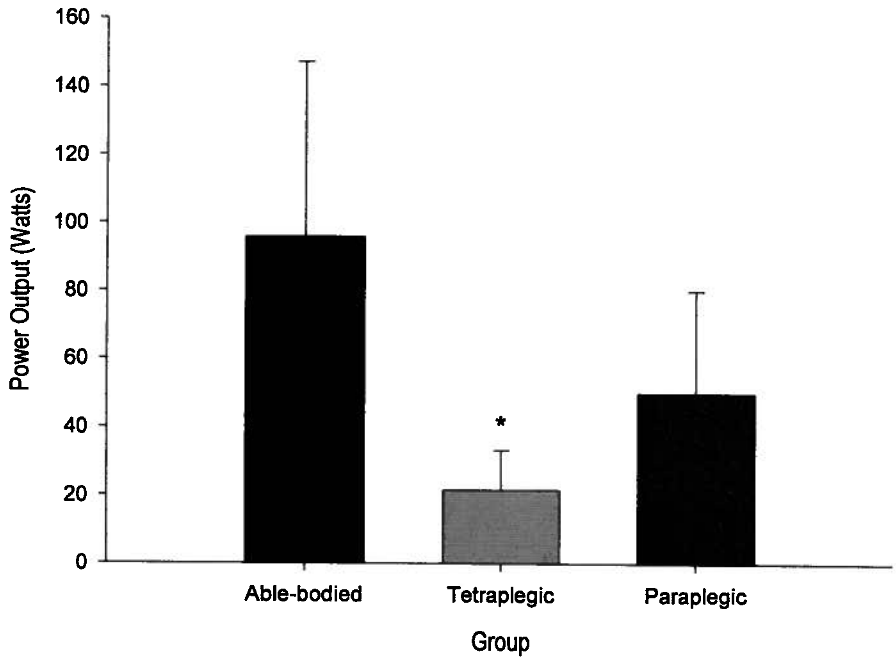
Both groups of participants were able to exercise to a greater peak power output during hybrid exercise in comparison to arm exercise (Figure 15). Able-bodied participants reached significantly greater peak power output in comparison to tetraplegics during peak hybrid exercise (95.8 $\pm$ 51.3 vs. 21.7 $\pm$ 11.5 W, respectively) (Figure 16).

Figure 15. Peak power output across groups during incremental arm and hybrid exercise



Peak power output was greater during hybrid exercise in comparison to arm exercise across all groups of participants.

Figure 16. Peak power output during incremental hybrid exercise



*p<0.05 vs. able-bodied.

6.2.2 Peak Oxygen Uptake (VO_2peak)

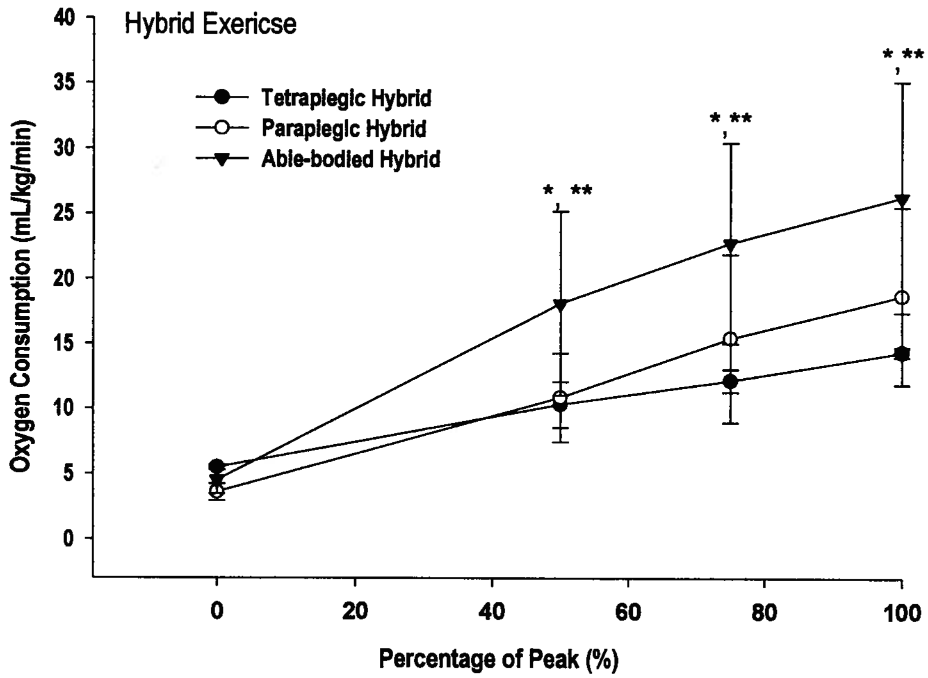
Hybrid exercise resulted in significantly greater cardiorespiratory requirements throughout incremental exercise in comparison to arm ergometry in both able-bodied individuals and persons with SCI (Table 2). The average VO_2peak (across all groups) was 21 ± 9 vs. 19 ± 7 $mL \cdot kg^{-1} \cdot min^{-1}$, for hybrid exercise vs. arm ergometry, respectively ($p < 0.05$). The cardiorespiratory responses to hybrid and arm exercise varied between groups. At higher exercise intensities, able-bodied individuals had a significantly higher oxygen uptake than persons with SCI for both modes of exercise (Figure 17). The average VO_2peak (across all modes of exercise) was 24.9 ± 7.9 vs. 15.7 ± 4.2 $mL \cdot kg^{-1} \cdot min^{-1}$, for able-bodied participants vs. participants with SCI, respectively. Furthermore, persons with paraplegia had significantly higher oxygen uptake than persons with tetraplegia with the average VO_2peak (across all modes of exercise) was 18.5 ± 3.7 vs. 12.9 ± 2.4 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively.

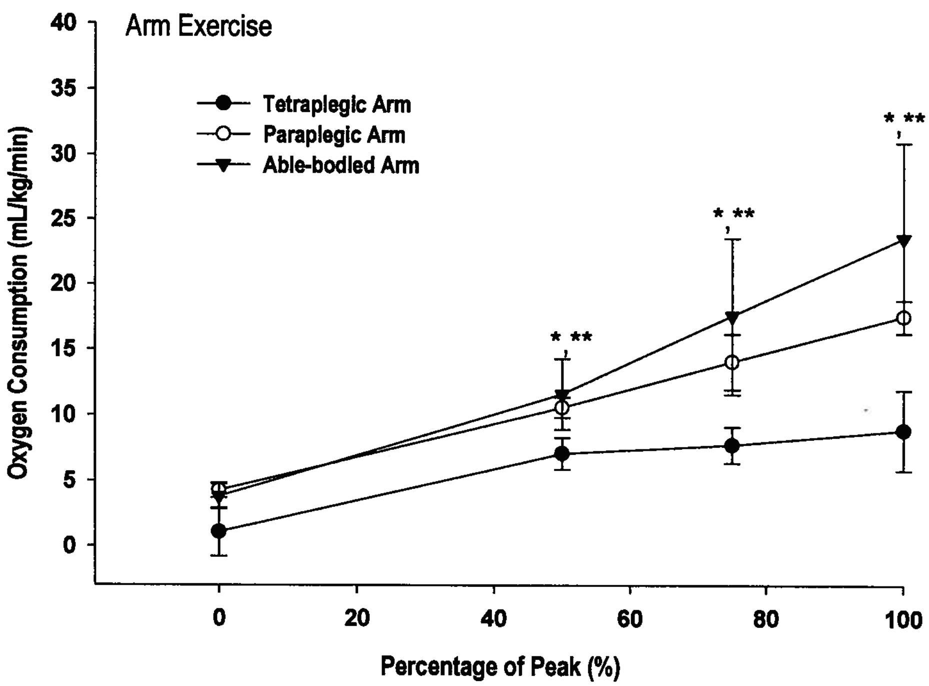
Table 2. Cardiorespiratory responses to peak exercise testing

	Mode of Exercise							
	Arm				Hybrid			
Variable	AB	SCI	P	T	AB	SCI	P	T
VO_2peak, $mL \cdot kg^{-1} \cdot min^{-1}$	23.6 ± 7.3*	14.9 ± 3.5	17.3 ± 1.5*	12.5 ± 3.4	26.3 ± 8.9*	16.5 ± 4.9	19.7 ± 5.3*	13.3 ± 1.5*
HRpeak, $beats \cdot min^{-1}$	146.8 ± 21.4*	134.2 ± 28.7	159.0 ± 13.0*	109.3 ± 6.8	153.7 ± 20.0*	136.8 ± 29.2	161 ± 18.2*	112.7 ± 7.1
SVpeak, mL	83.9 ± 12.7	73.0 ± 12.3	71.3 ± 10.0	75.4 ± 22.1	95.5 ± 13.1	84.2 ± 16.5	83.2 ± 22.5	85.1 ± 13.1
Qpeak, $L \cdot min^{-1}$	10.6 ± 2.7	9.5 ± 2.9	10.8 ± 2.8	7.6 ± 2.6	13.1 ± 3.9	10.1 ± 3.6	12.1 ± 4.0	8.2 ± 2.4
a-VO_2peak, mL $O_2 \cdot 100$mL blood	12.5 ± 3.1	15.2 ± 2.5†	15.5 ± 2.4	14.7 ± 3.6	12.2 ± 2.0	13.7 ± 6.1†	13.2 ± 5.5	14.2 ± 7.8

* $p<0.05$ vs. tetraplegics. † $p<0.05$ vs. able-bodied. Values are means ± SD.

Figure 17. Oxygen uptake for able-bodied participants, and participants with paraplegia and tetraplegia during incremental arm and hybrid exercise tests to exhaustion





Oxygen uptake increased in all participants during peak arm and hybrid exercise tests. Able-bodied participants and paraplegics had significantly greater oxygen uptake than tetraplegics during incremental arm and hybrid exercise. * $p<0.05$ able-bodied participants vs. tetraplegics. ** $p<0.05$ paraplegics vs. tetraplegics.

6.2.3 Peak Heart Rate, Stroke Volume, Cardiac Output, and Arterio-venous Oxygen Difference

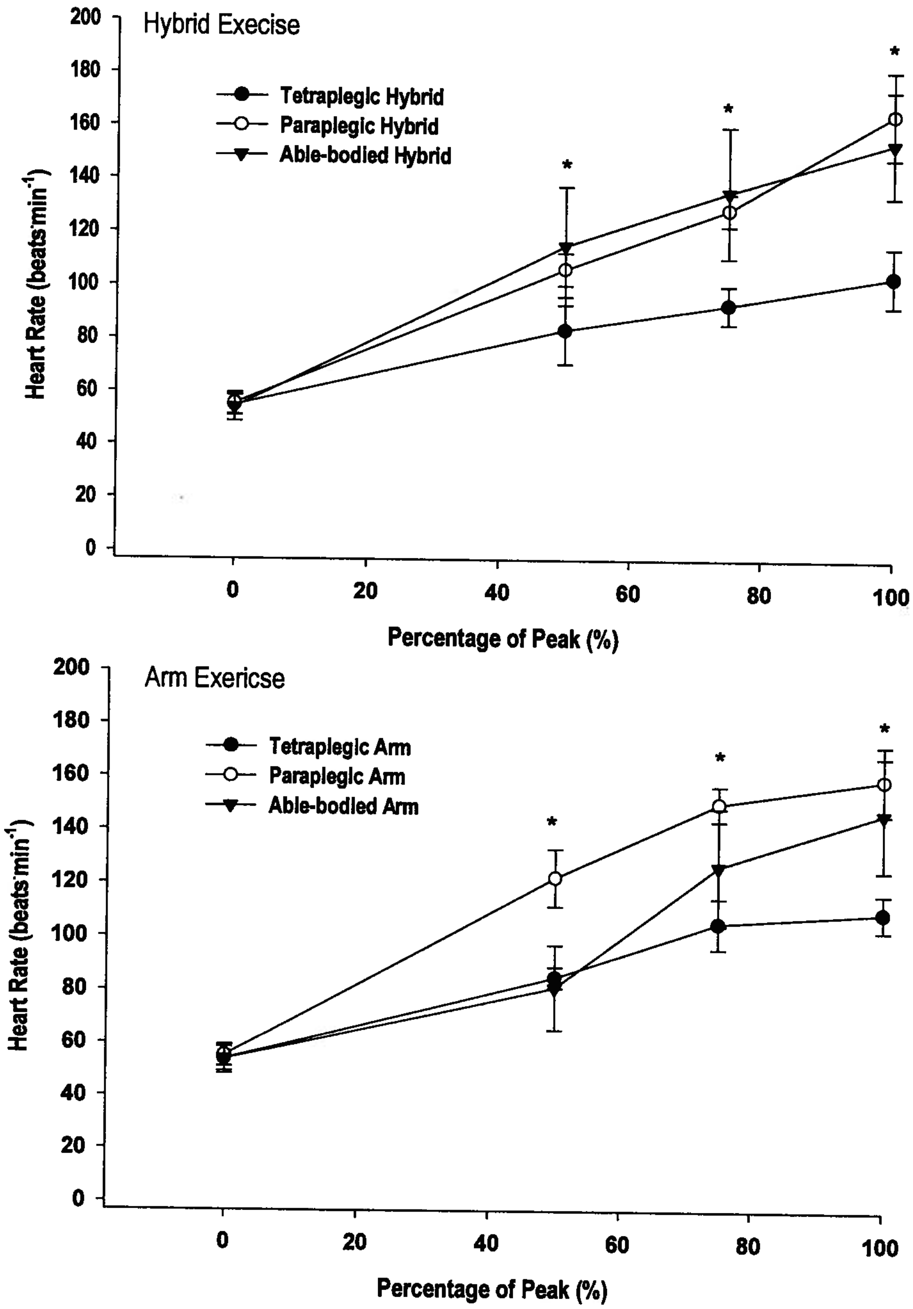
Heart rate response was not significantly different between participants with SCI and their able-bodied counterparts, nor between peak arm and hybrid exercise (Figure 18). The average value for peak heart rate across groups was 140.5 ± 25.1 and 144.8 ± 26.0 beats·min^{-1} for arm and hybrid exercise, respectively. The average value for peak heart rate across exercise modes was 135 ± 28.1 and 150.2 ± 20.1 beats·min^{-1} for participants with SCI and able-bodied participants, respectively. However, heart rate was significantly different between paraplegics and tetraplegics across time during both modes of incremental exercise. Paraplegics had higher peak heart rate during incremental exercise than tetraplegics (159.0 ± 13 beats·min^{-1} and 109.3 ± 6.8, respectively, across testing days).

The average value for resting and peak stroke volume (across testing days and groups) was 72.8 ± 13.4 and 84.6 ± 15.3 mL, respectively). Stroke volume significantly increased across time during incremental arm and hybrid exercise in able-bodied participants, and paraplegics and tetraplegics, though there were no significant differences between any of the groups (Figure 19).

The average value for resting and peak cardiac output (across exercise modes and groups) was 4.2 ± 0.7 and 10.5 ± 3.4 L·min^{-1}, respectively. Cardiac output increased significantly across time during both modes of peak exercise in able-bodied participants, and participants with paraplegia and tetraplegia(Figure 20). In the able-bodied group and the group with SCI, cardiac output was significantly higher during incremental hybrid exercise in comparison to incremental arm exercise (10.1 ± 2.7 vs. 12.7 ± 3.9, respectively, across groups at peak exercise) (Figure 21).

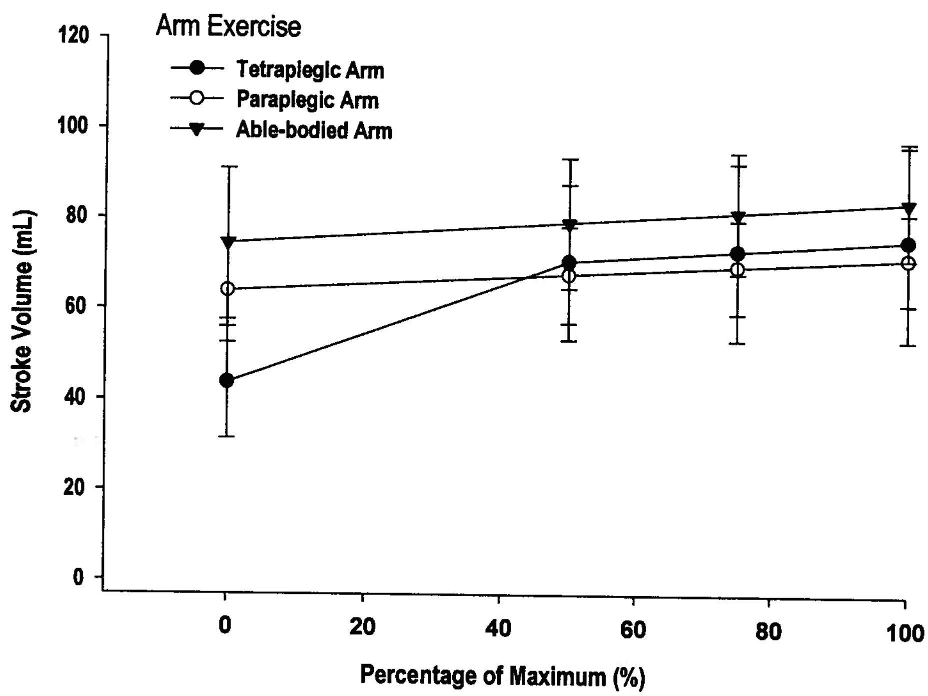
The average value for resting and peak arterio-venous oxygen difference (across exercise modes and groups) was 6.0 ± 4.1 and 13.1 ± 3.7 mL O_2·100mL blood^{-1}, respectively. Arterio-venous oxygen difference increased significantly across time during both peak arm and hybrid exercise (Figure 22). Furthermore, individuals with SCI (both paraplegics and tetraplegics) had significantly greater arterio-venous oxygen difference in comparison to able-bodied participants across time and both modes of exercise (14.4 ± 4.6 vs. 12.4 ± 2.5 for participants with SCI and able-bodied participants, respectively).

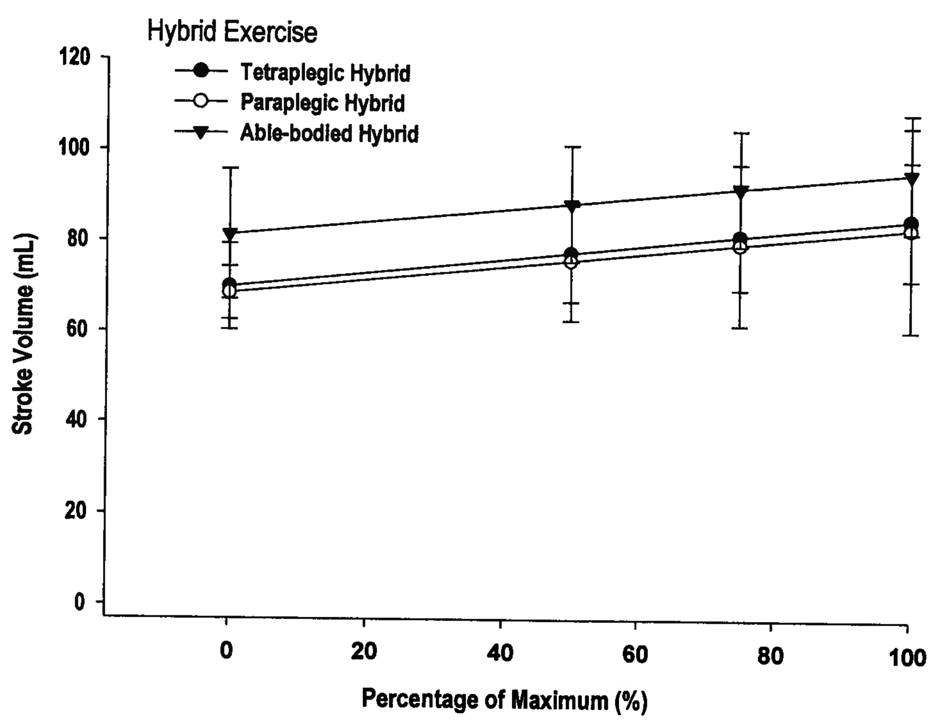
Figure 18. Heart rate in able-bodied participants, and participants with paraplegia and tetraplegia during incremental arm and hybrid exercise tests to exhaustion



Heart rate increased in all participants during incremental arm and hybrid exercise tests to exhaustion. Able-bodied participants and participants with paraplegia had greater peak heart rates for both modes of exercise than tetraplegics. * $p<0.05$ paraplegics vs. tetraplegics.

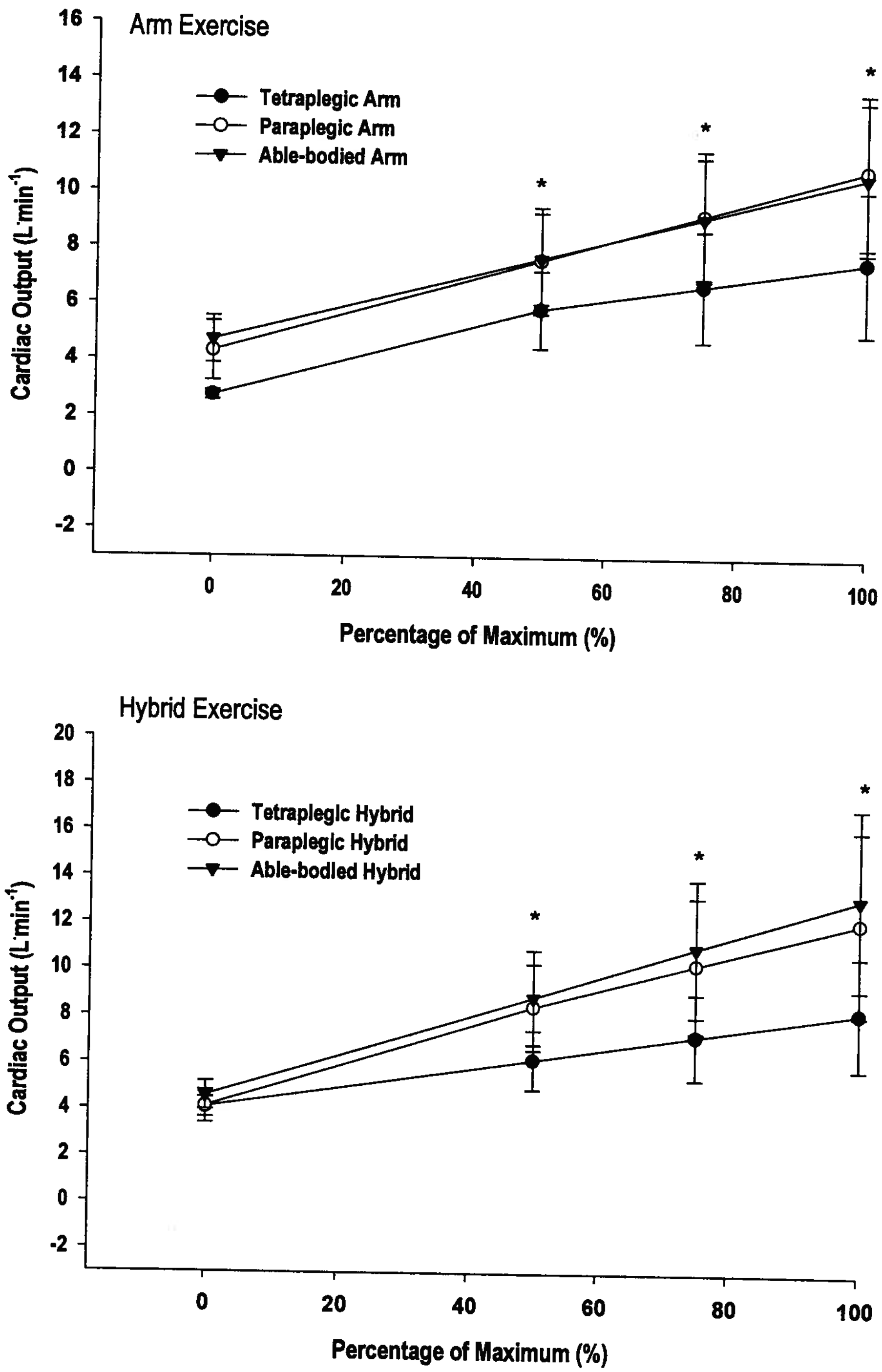
Figure 19. Stroke volume in able-bodied participants, and paraplegics and tetraplegics during incremental arm and hybrid exercise to exhaustion





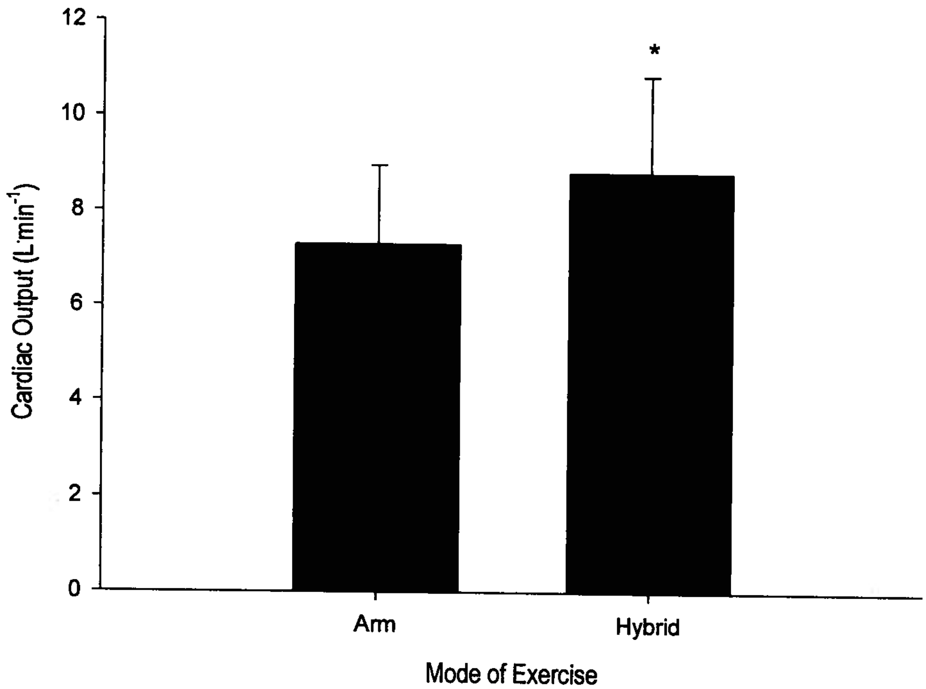
Stroke volume increased significantly ($p<0.05$) throughout incremental arm and hybrid exercise for all participants.

Figure 20. Cardiac output in able-bodied participants, and paraplegics and tetraplegics during incremental arm and hybrid exercise to exhaustion



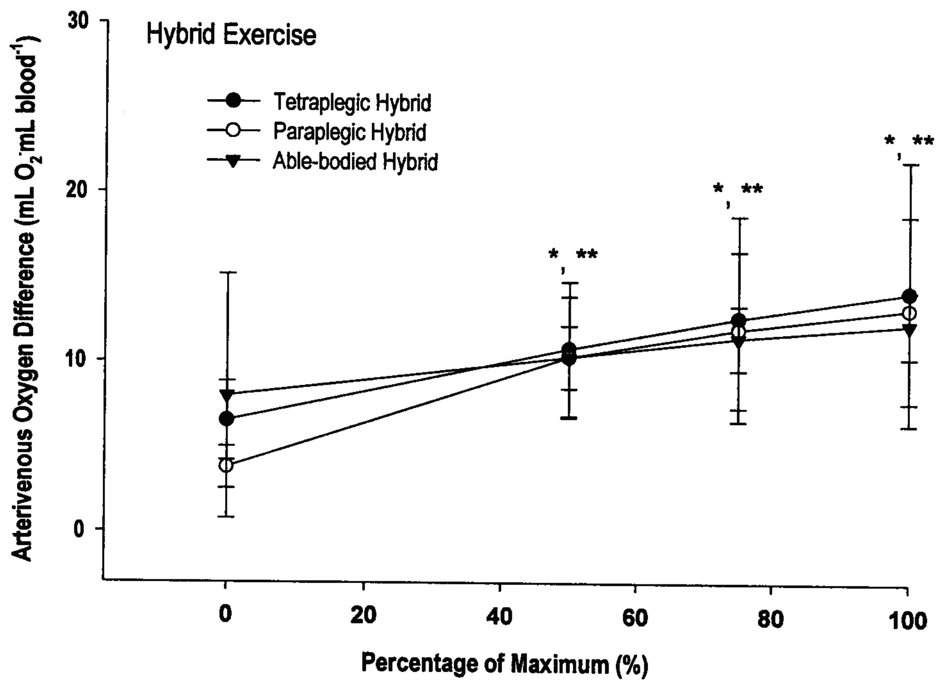
Cardiac output significantly ($p<0.05$) increased throughout incremental arm and hybrid exercise for all participants. Cardiac output was significantly higher during hybrid exercise in comparison to arm exercise. *$p<0.05$ vs. baseline.

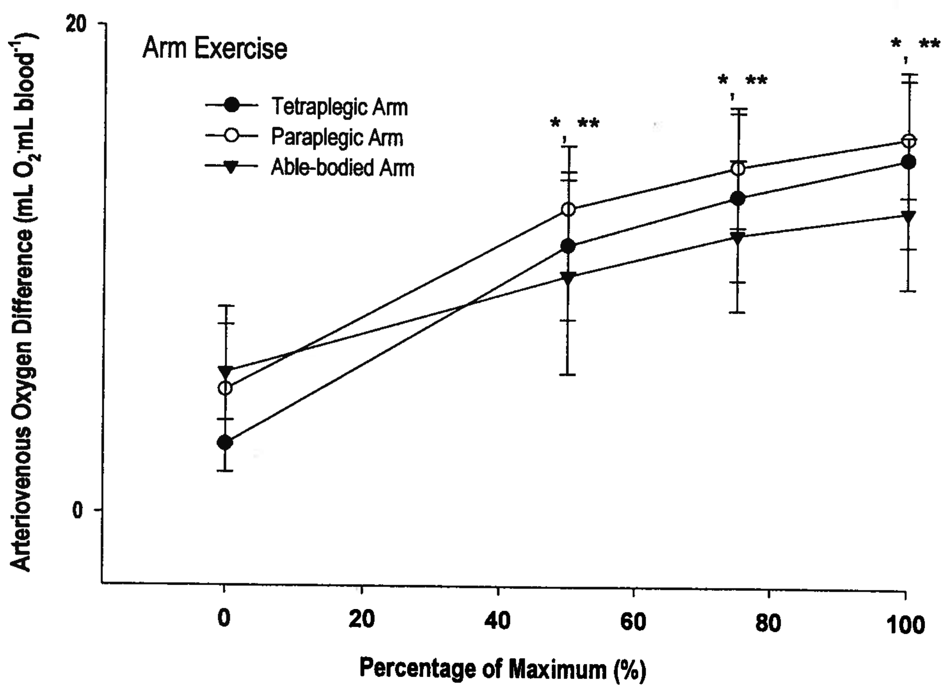
Figure 21. Peak cardiac output across groups



* p<0.05 vs. arm exercise.

Figure 22. Arterio-venous oxygen difference in able-bodied participants, and paraplegics and tetraplegics during incremental arm and hybrid exercise to exhaustion



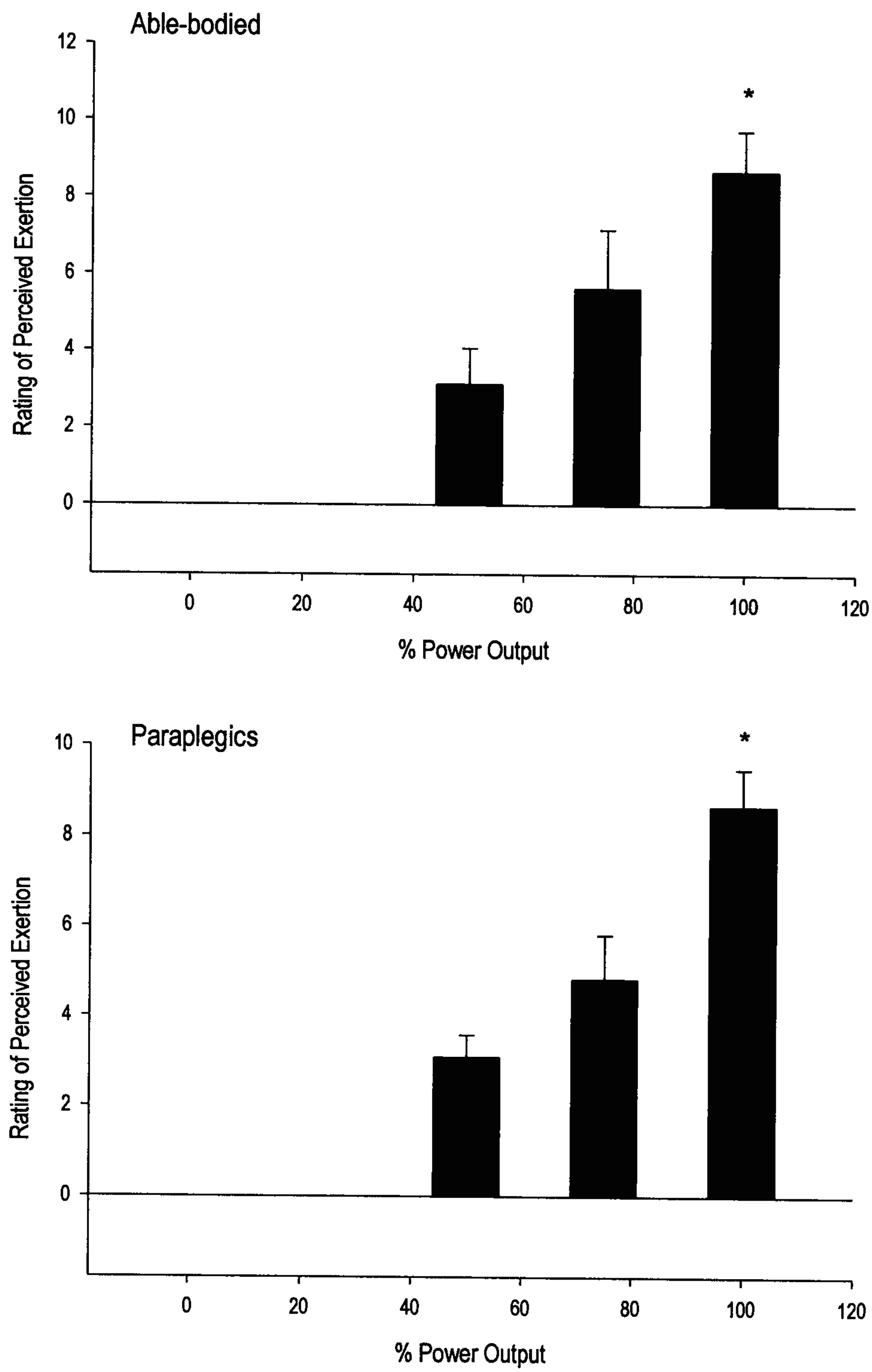


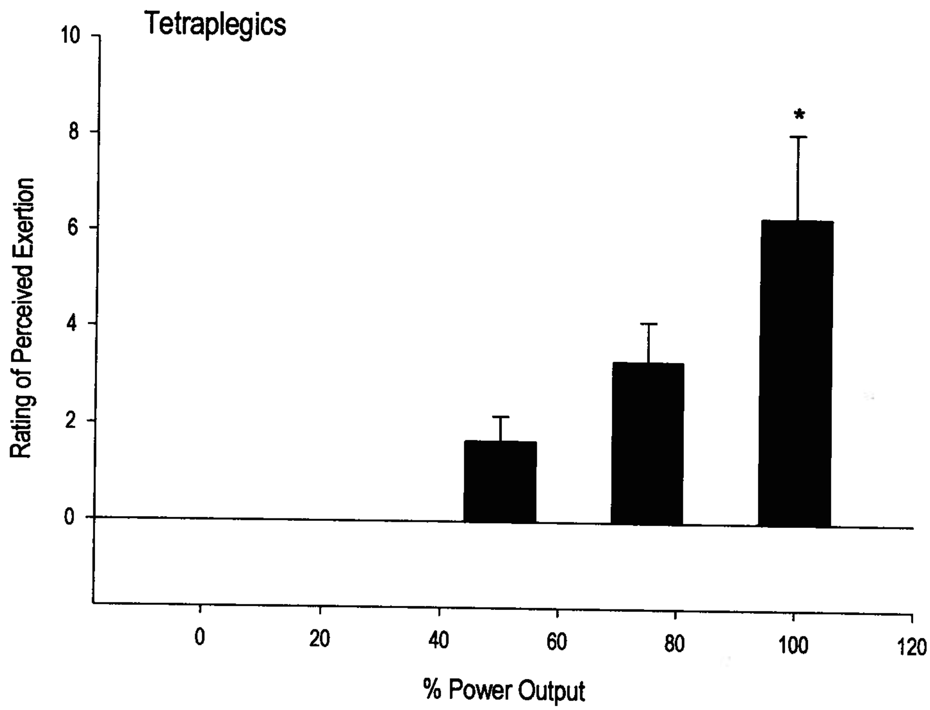
Arterio-venous oxygen difference is increased significantly during both modes of exercise for all participants. * $p<0.05$ paraplegics vs. able-bodied participants. ** $p<0.05$ tetraplegics vs. able-bodied participants.

6.2.4 Rating of Perceived Exertion

Both participants with SCI and able-bodied participants reported significantly increased ratings of perceived exertion (RPE) during both peak arm and hybrid exercise tests (Figure 23). The average reported values for RPE (across both groups) were 7.8 $\pm$ 1.5 and 8.3 $\pm$ 1.7 for peak arm and peak hybrid exercise, respectively. There were no significant differences in reported values of RPE between able-bodied participants and participants with SCI, though able-bodied individuals generally reported higher RPE values at the completion of peak exercise testing (across both modes of exercise) (8.7 $\pm$ 1.1 vs. 7.5 $\pm$ 1.8, for able-bodied participants and participants with SCI, respectively).

Figure 23. Rating of perceived exertion during incremental exercise to exhaustion for able-bodied participants, and paraplegics and tetraplegics



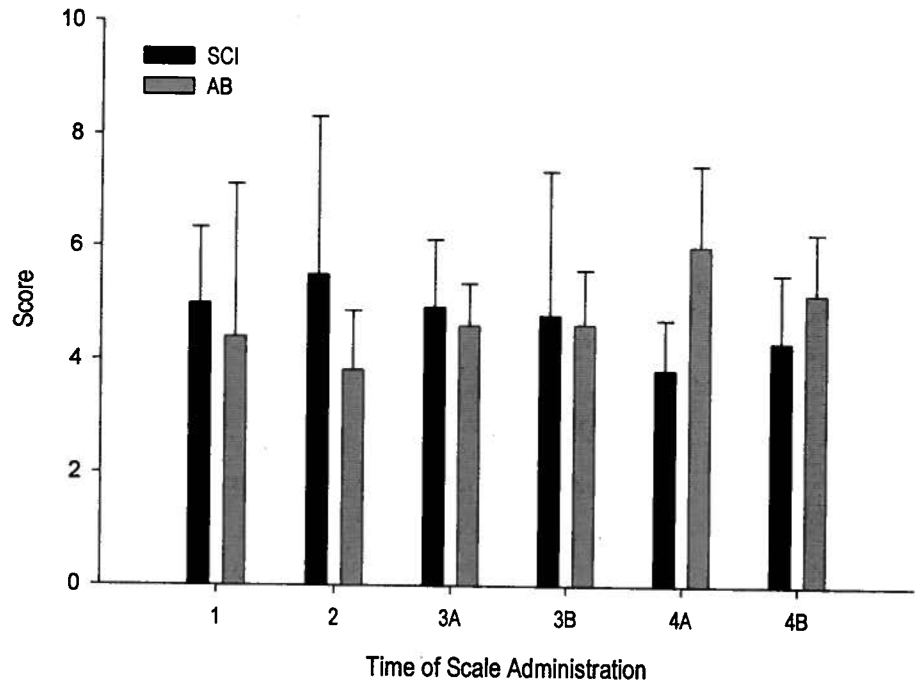


Rating of perceived exertion increased across both modes of exercise. * $p<0.05$ vs. baseline.

6.2.5 Fatigue Scale

No significant differences were found when examining the answers to the questions posed in the fatigue scale (Figure 24). There were no differences between testing days or groups of participants when comparing the same questions.

Figure 24. Response to questions in the fatigue scale (across groups)

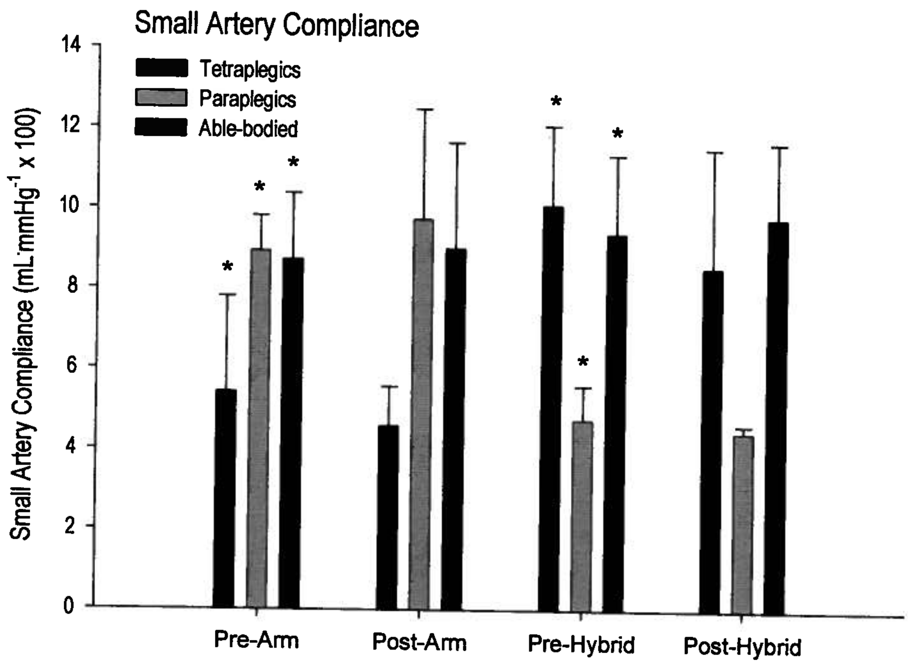


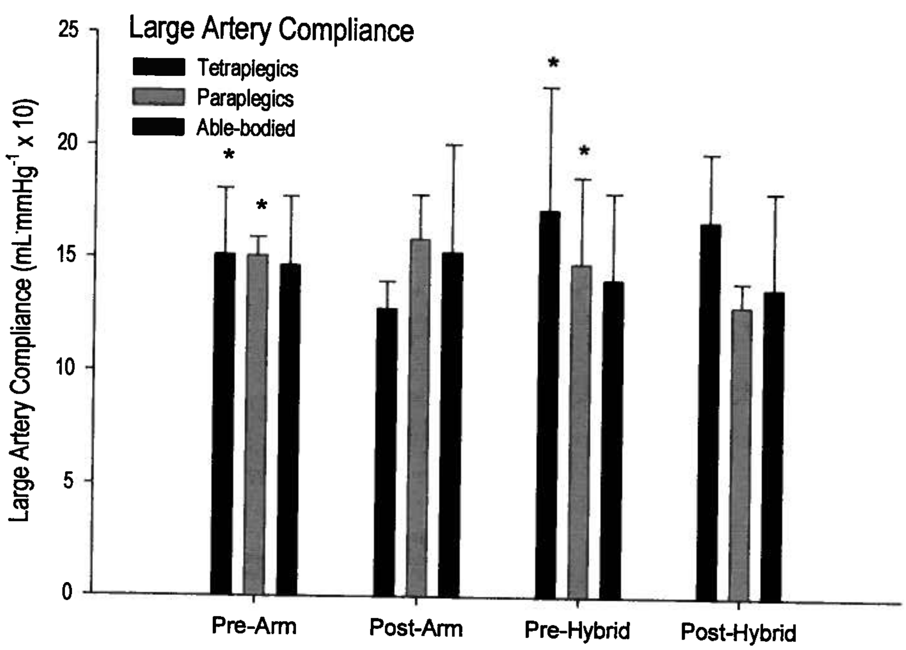
Response to questions on the fatigue scale were not significantly different across testing days or groups of participants. For time of fatigue scale administration (x-axis): 1 & 2 = rest; 3A = pre-arm steady state; 3B = post-arm steady state; 4A = pre-hybrid steady state; 4B = post-hybrid steady state.

6.2.6 Arterial Compliance

Both groups of participants had significant changes in small and large artery compliance from pre- to post-peak arm and hybrid exercise (Figure 22). The average values, pre-and post-exercise, across exercise modes were 7.3 $\pm$ 0.2 to 6.8 $\pm$ 0.5 mL·mmHg x 100 and 15.6 $\pm$ 0.6 to 14.6 $\pm$ 0.4 mL·mmHg^{-1} x 10 for small and large artery compliance, respectively) for participants with SCI. Conversely, the average values, pre- and post-exercise, across exercise modes, were 9.1 $\pm$ 0.5 to 9.4 $\pm$ 0.5 mL·mmHg^{-1} x 100 and 14.4 $\pm$ 0.4 to 14.5 $\pm$ 1.1 mL·mmHg^{-1} x 10, for small and large artery compliance, respectively) for able-bodied individuals. Able-bodied participants' changes in arterial compliance were different compared to participants with SCI. Able-bodied participants increased, while paraplegics and tetraplegics decreased, small artery compliance and large artery compliance from pre-to post- exercise across both modes of exercise.

Figure 25. Arterial compliance in participants with SCI and able-bodied participants





Arterial compliance pre- and post-arm and hybrid exercise. * $p<0.05$ vs. post, for corresponding mode of exercise.

7 DISCUSSION

The present study demonstrated that changes in middle cerebral artery blood velocity, heart rate, stroke volume, and cardiac output followed similar trends in both able-bodied individuals and persons with SCI, while blood pressure response to the orthostatic challenge was different when comparing able-bodied participants and paraplegics with tetraplegics. Additionally, both groups experienced significant changes to several cardiovascular measures when transitioning between stages of the orthostatic challenge, and while overall group differences may not be significant, examination of differences in some measures of cardiovascular response suggest that cardiovascular control not only differs between able-bodied individuals and individuals with SCI, but between paraplegics and tetraplegics as well. A small sample size likely limited the ability to find more statistically significant differences between the groups of participants in this study, though clinical significance and importance of these findings should not be overlooked.

This is the first investigation to examine cardiovascular responses to an orthostatic challenge following an acute bout of steady state exercise. Exercise appeared to help individuals with SCI improve their recovery following an orthostatic challenge. Exercise training has been found to have a positive effect on orthostatic tolerance by promoting increases in plasma volume[64, 119] and overall blood volume[120] which may be helpful since low blood volume is associated with orthostatic hypotension[121]. Furthermore, several studies have examined cardiovascular response to an orthostatic challenge following a single bout of maximal exercise and found that orthostatic hypotension and intolerance are ameliorated[122-126]. This is expected since the short-term impacts of maximal exercise include expansion or restoration of blood volume[127, 128], and increased sensitivity of the carotid-cardiac baroreflex[123, 124, 129-131]. Plasma volume may expand following a single bout of maximal exercise due to the secretion of hormones related to control of fluid-electrolyte homeostasis, increased thirst, increased plasma protein synthesis, and renal retention of sodium and water[132-137]. Maximal exercise has been found to help ameliorate orthostatic hypotension in individuals with SCI via increased vasoconstrictive reserve[138]. That is, the cardiovascular system remains vasodilated in response to an increase in blood volume and central venous pressure which result following exercise[139]. This increased vasodilation suggests that there is an increased capacity to vasoconstrict resulting from an increase in central venous pressure and plasma volume which are subsequent to a vasodliated cardiovascular system following maximal exercise[129].

Furthermore, exercise training improves sympathovagal tone in able-bodied individuals, which has been found to improve orthostatic tolerance in this population[120]. A shift in autonomic balance in persons with SCI would likely help to ameliorate symptoms associated with orthostatic hypotension since they experience impairment to their autonomic nervous system following injury. Exercise also has the potential to improve the myocardium by enhancing its contractility[140], and this, along with increased preload, and reduced afterload may help to improve functioning of the heart. Thus, it has been shown that exercise training has the ability to help reset the relationship between autonomic control and heart function (sympathovagal shift)[120], and based on findings of this investigation, it also appears as though an acute bout of steady state exercise promotes improved cardiovascular response to a subsequent orthostatic challenge.

Light to moderate levels of activity, such as that performed during a warm-up or recovery, have also been found to play an important role in promoting venous return, and subsequently to maintaining an elevated stroke volume. That is, when active recovery is performed instead of passive recovery, individuals have been found to have improved cardiovascular response which is illustrated by attenuated decreases in stroke volume and cardiac output, and restoration of elevated heart rate to pre-exercise resting levels[141]. While recovery following bouts of steady state exercise was not performed in this study, it may be postulated that for individuals with SCI, the moderate (65% of heart rate reserve) level of activity may have promoted elevations in stroke volume by promoting venous return. That is, the performance of a light to moderate level of activity, in and of itself, may be sufficient to promote improved circulation and cardiovascular function in individuals with SCI, thus helping to improve response to an orthostatic stress, which is in agreement with the findings of this study.

While acute bouts of steady state exercise may help promote improved cardiovascular response to an orthostatic challenge in individuals with SCI, other mechanisms for an improved response are related to adaptations individuals with SCI undergo subsequent to injury. Peripheral adaptations may also help individuals with SCI, specifically paraplegics, adapt to orthostatic intolerance and overcome the effect of vasomotor dysfunction. During exercise, paraplegics may have a smaller decrease in stroke volume than their able-bodied counterparts during an equivalent orthostatic challenge[63], and while not a significant finding in this investigation, a greater decrease in stroke volume was observed in able-bodied individuals in comparison to paraplegics following bouts of arm and steady state exercise. In individuals with paraplegia, venous distensibility and capacity are lower and venous flow resistance is higher in comparison to their able-bodied counterparts[97, 142], resulting in less blood pooling. It has been observed that at an equivalent level of orthostatic challenge the change in volume in the lower limbs of individuals with paraplegia is less than that in able-bodied persons[63]. A smaller reduction in stroke volume may or may not result, but its occurrence, should it occur, can be accounted for by a reduction in venous distensibility in the paralyzed lower limbs[63], suggesting that less blood pools in the lower limbs of persons with paraplegia.

An important consideration to make is that while previous studies have examined the effects of exercise training on orthostatic hypotension, similar benefits in cardiovascular response following acute bouts of exercise may exist as illustrated in this investigation by significant improvements in stroke volume following the orthostatic challenge. This may suggest that following an orthostatic challenge in a rehabilitative setting, persons with SCI may recover some cardiovascular parameters more effectively if exercise is performed prior to undergoing an orthostatic stress. While this may not increase tolerance to assuming an upright posture, it may have an impact on the level of discomfort experienced by individuals following completion of the challenge. This is important as it appears as though even an acute bout of exercise may help to improve recovery[143].

Individuals with SCI also had an improved cerebral blood flow response to an orthostatic challenge following a bout of hybrid exercise in comparison to following rest or a bout of arm steady state exercise. Furthermore, middle cerebral artery blood velocity remained significantly declined in comparison to the baseline value when the orthostatic challenge was performed following a bout of arm steady state exercise. This suggests that hybrid exercise performed immediately prior to an orthostatic challenge may be better able to attenuate the decrease in cerebral blood flow velocity normally experienced by individuals when assuming the upright posture. Possible explanations for this finding are explored by examining the role cerebral autoregulation and the impact of cardiovascular parameters.

Cerebral autoregulation normally ensures that cerebral blood flow remains relatively constant despite changes in blood pressure, provided mean arterial pressure does not exceed the autoregulation range, which is normally 50 to 170 mmHg[144, 145]. Retention of cerebral blood flow during changes in arterial pressure is accomplished by active constriction during higher pressures and dilation when there are declines in pressure[146]. Significant correlations between mean arterial pressure and middle cerebral artery blood velocity have been found[147-150], though this is not a universal correlation[151-158]. However, it has been found that, generally, mean arterial pressure may be used to represent cerebral perfusion pressure, and middle cerebral artery blood velocity is a reliable index of cerebral blood flow[159]. It is also important to note that changes in middle cerebral artery blood velocity that are measured by transcranial Doppler are known to be proportional to cerebral blood flow so long as the diameter of the middle cerebral artery remains constant[152, 160-162]. That is, interpretation of an increase or decrease in blood flow velocity as a reflection of an increase or decrease in flow, respectively, is also dependent upon the assumption of a constant diameter of the insonated vessel. It has been found that during a variety of stimuli that are known to affect cerebral blood flow, the diameter of the middle cerebral artery changes minimally (<3.0%)[162, 163]. Participants in this investigation remained within the autoregulated range, suggesting that based on the definition of autoregulation and the limits within which is works, participants in this study would be expected to have the ability to rely on cerebral autoregulation to prevent cerebral hypoprofusion when experiencing a reduction in blood pressure.

There was only one participant with tetraplegia who, following about of hybrid steady state exercise, had a positive correlation between flow and pressure. This was not found in any of the other participants, suggesting the presence of intact cerebral autoregulation in these individuals, as previously described. Tissues that autoregulate have no, or only a weak, correlation of change in flow to a corresponding change in pressure. In contrast, tissues that do not autoregulate have a linear or curvilinear relationship[164-166]. It has been described previously that a linear relationship exists between cerebral perfusion pressure and mean blood velocity below the autoregulated range while the pressure-flow relationship becomes progressively more linear with failure of autoregulation[167]. In the upright posture, if systemic blood pressure decreases to low levels, cerebral perfusion declines even further due to the vertical height difference[54]. However, individuals with SCI have been found to experience similar declines in cerebral oxygenation as their able-bodied counterparts, despite greater falls in systemic blood pressure[60]. Thus, whether or not these individuals experience of orthostatic hypotension may be dependent on the amount of decline in cerebral blood flow, which in turn may affect cerebral oxygenation, but this is still unclear[9]. While participants with SCI in this study generally experienced greater declines in mean arterial pressure in comparison to their able-bodied counterparts, their cerebral oxygenation may not have been reflected by parallel changes in mean arterial pressure. Despite large changes in autonomic control and function following SCI, function of cerebral autoregulation in participants with SCI in this study was similar to able-bodied participants. However, there are other factors that may affect orthostatic tolerance and response to an orthostatic challenge.

Similar to previous findings in persons suffering from orthostatic hypotension[168], individuals with SCI may experience an expansion of the autoregulated range at both the upper and lower limits, so that cerebral perfusion is able to remain relatively constant even during an orthostatic challenge. While this may help individuals with SCI to manage orthostatic hypotension, participants with in this study all remained within the autoregulated range, making an expansion of the autoregulated range in these individuals unnecessary.

Given that perfusion pressure plays a large role in cerebral blood flow, cardiac output is also examined for its role in cerebral autoregulation. A significant linear relationship between middle cerebral artery blood velocity and cardiac output at rest and during exercise has been previously demonstrated[169]. It is thought that cerebral blood flow is modulated by cardiac output and this has been demonstrated previously where attenuations in cardiac output, leading to decreased perfusion, have been postulated to attribute to a decrease in cerebral perfusion, which may lead to symptoms associated with orthostatic hypotension[55]. However, oxygen extraction has not been found to be a limiting factor to meeting oxygen demands of the brain, implying that the brain is well-protected[157]. This may help to explain why the single participant with tetraplegia had a significantly positive correlation between mean arterial pressure and middle cerebral artery mean blood velocity. Inspection of this participant's cardiac output during the orthostatic challenge following a bout of hybrid steady state exercise revealed that it decreased, when the upright posture was assumed during the test, to a level that appeared to compromise this participant's autoregulation. Thus, as there is a significant linear relationship between middle cerebral artery blood velocity and cardiac output at rest, it may be postulated that the improved response of middle cerebral artery blood velocity following a bout of hybrid steady state exercise, as illustrated by the finding that the decrease in cerebral blood flow was not significant during the orthostatic challenge only following a bout of hybrid steady state exercise, may be attributed to the corresponding significant increase in cardiac output that was found immediately following return to the supine position. This corresponds to the finding of no significant decreases in cerebral blood velocity following a bout of hybrid steady state exercise.

In contrast, the contribution of heart rate to cardiac output in the regulation of cerebral blood flow does not appear to have a significant effect on middle cerebral artery blood velocity[170].

Generally, all participants responded to the orthostatic stress as expected, with decreases in middle cerebral artery blood velocity, stroke volume, and cardiac output, and increases in heart rate, which are consistent with findings from previous studies[118, 171-173]. However, there were differences in blood pressure response between groups. Individuals with paraplegia responded in a similar manner to able-bodied persons, while tetraplegics responded in an opposite manner. Additionally, participants experienced an increase in total peripheral resistance upon assuming the upright posture. Changes in mean arterial pressure are often assumed to reflect changes in cardiac output[174], but this has only been illustrated during acute changes in cardiac output. This linear relationship was not apparent in participants during the orthostatic challenge and the relationship has not been found to be linear after a short period of time (15 seconds)[174]. Accordingly, to limit changes to mean arterial pressure despite declines in cardiac output, total peripheral resistance increased.

Differences in cardiovascular control and function of the autonomic system between able-bodied individuals paraplegics and tetraplegics affected cardiovascular, specifically blood pressure, response to the orthostatic challenge in this investigation. Upon moving to the upright and seated position, able-bodied individuals and paraplegics increased their blood pressure to counteract the movement and subsequent pooling of blood in the lower limbs. However, persons with tetraplegia experienced decreases in blood pressure upon assuming the upright posture, which is in agreement with findings from other studies[55, 173]. This is expected as previously mentioned, since individuals with tetraplegia are more likely to experience orthostatic hypotension because the balance between the parapsympathetic and sympathetic nervous system is altered to a greater extent in persons with cervical and high thoracic injuries[9].

Overall, while the examination of cardiovascular parameters reveals interesting and unique responses to an orthostatic challenge in participants in this study, it is also interesting to note that participants with SCI did not appear to experience any discomfort related to symptoms associated with orthostatic hypotension, which was reflected by responses to the questions posed in the fatigue scale and no reports of discomfort during the orthostatic challenge. This may be related to time since injury for persons with SCI. In individuals with chronic orthostatic hypotension, mean arterial pressure has been found to remain within the autoregulated range[118]. Accordingly, since only individuals with chronic injuries (> one year) were included in this investigation, it may be postulated that this affected cardiovascular response to the orthostatic challenge in comparison to the responses that would have been seen in individuals with acute injuries. The length of sustained injury may be a factor that differentiates several physiological responses in persons with SCI, including orthostatic tolerance. Individuals who have a recently sustained SCI are known to have lower blood pressure and higher heart rate than those with long-standing injuries[50]. Individuals with acute injuries are also more susceptible to orthostatic changes in blood pressure and experience more hypotension-related symptoms[50]. As the length of time since injury increases, accommodation to an upright posture is also enhanced[50]. Studies that include individuals with both acute and chronic injuries[50] have found differences in the ability to tolerate induced hypotension. Participants with chronic injuries are better able to tolerate tilting at various degrees. They elicit fewer symptoms of orthostatic hypotension, and have less pronounced blood pressure and heart rate response when tilted to the vertical position[50]. This may help to explain the tolerance observed in participants with SCI in this study since they all had longstanding injuries. Furthermore, responses to the fatigue scale did not reveal any significant differences between any of the groups of participants or between any of the testing days and times at which it was administered. This suggests that in individuals with chronic SCI, fatigue, as assessed by the scale, does not lend itself to associations with cardiovascular response to an orthostatic challenge, though this may not be the case for persons with acute SCI. Furthermore, it appears as though persons with chronic SCI do not report greater fatigue severity in comparison to their able-bodied counterparts, as illustrated in this study since participants with SCI did not report, like the able-bodied participants, any discomfort during or following the orthostatic challenge. The lack of statistical significance to indicate increased tolerance to orthostatic stress as revealed by cardiovascular parameters measured in this study is likely the consequence of a limited number of persons with SCI who participated in this investigation, as generally, cardiovascular responses to the orthostatic challenge were similar between individuals with SCI and their able-bodied counterparts, except for participants with tetraplegia, since their autonomic control and balance following injury is altered to a different extent in comparison to paraplegics.

As illustrated by the findings of this study, cardiorespiratory response to exercise was significantly different between able-bodied individuals and persons with SCI. Additionally, the responses to peak arm and peak hybrid exercise were different for both groups and exercise performance and capacity were different between these two groups. In agreement with previous studies comparing hybrid to arm cycle exercise[77-79], results of the current investigation illustrate that exercise incorporating the upper and lower limbs elicited greater cardiorespiratory response in comparison to arm exercise alone in both able-bodied individuals and persons with SCI. Furthermore, findings of this study demonstrate that the passive inclusion of the lower limbs into hybrid exercise was an effective means to promote enhancements in aerobic performance in comparison to arm exercise alone. This novel finding suggests that active muscle contraction was not necessary to enhance exercise capacity, which is beneficial for individuals with SCI, who commonly experience lower limb paralysis following injury. Previous investigations that have examined the effects of passive inclusion of the legs during exercise for persons with SCI have demonstrated an improvement in cardiorespiratory response[41-44]. It has been found that passive cycling movements are effective in promoting circulation in passively moved muscles in both able-bodied individuals[44] and individuals with SCI[41]. Thus, the passive incorporation of the legs along with active movement of the upper limbs has the potential to enhance cardiorespiratory response even further, as combined activity of the arms and legs utilizes a greater volume of muscle than either arm or leg exercise alone, and has been found to promote enhancements in aerobic capacity[82]. The improvements in cardiorespiratory response with the inclusion of passive leg exercise may be attributed to rhythmic lengthening and shortening of the leg muscles, specifically the paralyzed muscles in individuals with SCI, which helps to promote venous return during activity[41].

Venous return in able-bodied individuals is promoted by active contraction of the legs and the ability to activate the skeletal muscle pump. Contractions of the leg muscles provide pressure against the veins and help the venous valves return blood to the heart and central circulation[83, 84]. While individuals with SCI cannot actively contract the muscles of their lower limbs, the finding in this study that passive activity of the legs is able to help promote greater circulation helps to explain the enhanced cardiorespiratory response to hybrid exercise versus arm exercise. An increase in venous return leads to an increase in cardiac filling and preload, and ultimately, an increase in stroke volume[42, 78, 175], all of which enhance cardiorespiratory response and exercise performance.

Furthermore, the use of a greater volume of muscle during hybrid exercise in comparison to arm exercise alone may have helped individuals with SCI increase exercise. Exercise that uses more muscle enhances aerobic demand and capacity because of the greater stress that is placed on the central cardiovascular system to deliver a larger amount of oxygenated blood to active muscle[82]. The greater aerobic capacity found following a bout of peak hybrid exercise in comparison to peak arm exercise supports that idea that there is a linear relationship between the amount of active muscle mass and aerobic performance[176].

As expected, aerobic performance was significantly higher in able-bodied individuals in comparison to individuals with SCI, and higher in paraplegics than tetraplegics and this is the result of differences in autonomic function and control between these groups. Differences in performance are related to greater cardiovascular function and control as illustrated by greater heart rate, stroke volume, cardiac output, and oxygen uptake in able-bodied individuals. However, the fact that able-bodied individuals are able to actively contract their leg muscles cannot be disregarded. Even though muscle activity in the lower limbs was monitored during hybrid exercise, visual inspection of this recording revealed that able-bodied participants had a difficult time completely relaxing their legs and having them fully incorporated into exercise passively. This lends itself to the possibility that the exercise performance of able-bodied persons in this study was overestimated since some participants may have used their legs to increase exercise performance, enhancing their peak oxygen uptake beyond what they would be able to reach if the ability to use their legs was restricted. Incorporating the legs actively into exercise is able to enhance cardiorespiratory response by increasing venous return via activation of the skeletal muscle pump[83, 84]. However, this does not refute the finding in this study that whole-body exercise promotes greater cardiorespiratory response in comparison to arm exercise alone, and that aerobic fitness and capacity is greater in able-bodied individuals in comparison to persons with SCI.

An examination of peak heart rate response to both modes of exercise also reveals information about the impact of lesion level on exercise capacity and about the effects of different modes of exercise on cardiorespiratory response. Impairments of the autonomic nervous system following SCI leads to changes in cardiovascular control. There is a decrease in sympathetic tone below the lesion[48, 177, 178]. Previous studies have shown that maximal power output, maximal oxygen uptake, and total work is higher in athletes with lower lesion levels[106]. This is in accordance with the findings of this study as individuals with paraplegia had greater values for peak heart rate during both modes of exercise in comparison to tetraplegics. Furthermore, during exercise, it has been found that higher lesion levels produce blunted cardiorespiratory responses to exercise in comparison to persons with lower levels of SCI. Whether at rest or during submaximal or maximal levels of exercise, individuals with tetraplegia, in agreement with the findings of the present study, have been found to have lower values for oxygen uptake, heart rate, work rate, and ventilation in comparison to paraplegics[96, 107, 108]. Individuals with higher lesion levels may have more paralyzed muscle following injury as well as greater interruption to sympathetic pathways in comparison to individuals with lower lesion levels[107, 108]. This also corresponds with the finding in this investigation that individuals with paraplegia have similar cardiovascular responses to exercise as their able-bodied counterparts since individuals with lower level lesions are likely to have less impairment to their autonomic nervous system, subsequently decreasing cardiovascular limitations to exercise performance. In agreement with this, individuals with paraplegia had greater heart rate response to both modes of incremental exercise in comparison to tetraplegics. In addition to differences observed for peak heart rate, a corresponding finding for peak power output was found in this investigation. That is, able-bodied individuals were able to reach a significantly greater peak power output than participants with tetraplegia during hybrid exercise, and this difference was close to being statistically significant for arm exercise.

Furthermore, peak heart rate tended to be higher during hybrid exercise in comparison to arm exercise. This suggests that exercise capacity is greater during whole-body exercise and both persons with SCI and able-bodied individuals are able to enhance exercise performance by concurrently using their arms and legs, since heart rate is able to increase to a greater extent, and this has been shown previously in able-bodied individuals and persons with SCI[179].

While central factors appear to help augment exercise capacity when the legs are incorporated into exercise, peripheral factors are also important to consider. While cardiac output may increase in response to a greater need for oxygen at the level of the muscle during hybrid exercise in comparison to arm exercise, peripheral oxygen extraction may be elevated due to the activation of a greater volume of muscle mass[79, 180]. Interestingly, arterio-venous oxygen difference during exercise was significantly higher in individuals with SCI in this study. While there were no significant differences between arm and hybrid exercise, it may be postulated that performance of hybrid exercise helped to improve this parameter in the participants with SCI. While persons with SCI generally experience blunted cardiorespiratory response to exercise, the fact that oxygen extraction may be increased to an extent greater than that found in their able-bodied counterparts is worth examining. As illustrated in this study, cardiac output increases with exercise, in agreement with previous findings[41], leading to an enhanced capacity for oxygen delivery during activity. However, in individuals with SCI, alternations to the nervous system following injury affect the response of the central nervous system to exercise. This may limit effective redistribution of blood since the ability to contract the muscles of the lower limbs, which is lost due to paralysis following injury, promotes improvements in cardiorespiratory measures, including, but not limited to, cardiac output[80, 181, 182]. Accordingly, persons with SCI have been found to have lower stroke volumes and cardiac outputs than their able-bodied counterparts[69, 97], which is in agreement with the findings of this study for paraplegics and tetraplegics and was seen during the orthostatic challenge (Figure 13). Thus, elevated oxygen extraction may serve as a compensatory response and has the potential to enhance cardiorespiratory response to exercise in persons with SCI. Future studies examining arterio-venous oxygen extraction are warranted to support the findings of this study and determine whether whole-body exercise promotes greater improvements in oxygen extraction in comparison to arm exercise alone. It has been postulated that peripheral oxygen extraction may be elevated due to the activation of a greater volume of muscle mass[79, 183]. Additionally, a lower oxygen extracting capacity has been reported for the arms[184-187] and even following training, only marginal improvements in oxygen extraction by the arms have been observed. In contrast, it has been demonstrated in several studies that exercise in the population with SCI that incorporates the lower extremities helps to promote enhancements in oxygen extraction[42, 77, 78, 88], in addition to improvements in cardiac output[42, 77, 78]. Similarly, it has been found that following training in able-bodied individuals, exercising muscle may require less blood flow for the same submaximal exercise intensity as a result of an increase in arterio-venous oxygen difference[188]. The lower oxygen extraction for the arms is associated with a lower oxygen conductance in the upper extremities compared with the lower extremities. Accordingly, for a given oxygen demand, a greater oxygen delivery is required for exercising arm than leg muscles, causing a relatively high blood flow to the upper extremities[189]. However, following endurance exercise training in the general population, an increase in total vascular conductance, and the associated delivery of more blood to exercising muscles, has been found to be primarily responsible for enhancing oxygen extraction capabilities[190]. The result of this is a larger pressure gradient for enhancing the delivery of available oxygen to exercising muscle[181]. Thus, it can be postulated that exercise training incorporating the lower extremities in persons with SCI may help to promote enhancements in central as well as peripheral physiological adaptations[181].

Participants reported ratings of perceived exertion that indicated they perceived exercise to be very difficult at the highest power output they attained, suggesting they had exercised to volitional fatigue. This also indicates that participants subjectively experienced greater levels of strain with increasing intensity during exercise[191] as measured by the scale. Able-bodied individuals tended to report greater ratings of perceived exertion at the completion of peak exercise testing. In agreement with the cardiovascular measures collected during the peak exercise tests, able-bodied individuals also subjectively illustrated a greater work capacity in comparison to persons with SCI by reporting higher levels of strain expressed by greater ratings of perceived exertion. Accordingly, this scale has been found to correlate and relate to a variety of physiological measures, and has been proven to be a valid measure of exercise intensity[192].

In agreement with previous findings[193], able-bodied individuals were found to have higher arterial compliance than persons with SCI. Inactivity resulting from paralysis and the loss of supraspinal sympathetic vascular control have been reported to be potential factors for poor arterial compliance[194]. Furthermore, arterial stiffness is associated with cardiovascular disease, specifically atherosclerotic burden[193] and arterial compliance decreases as the severity of atherosclerosis increases[195].

Participation in exercise has been shown to increase arterial compliance[196] and arterial compliance has also been found to increase following an acute bout of exercise[197]. Decreased arterial compliance and increased arterial stiffness may be the result of a variety changes to arterial structure including smooth muscle hypertrophy, replacement of viable cells with connective tissue, and increased cross-linking of connective tissue[198]. Exercise training, or moderate physical activity may help to modify these changes in several ways: 1) an increase in arterial pressure and heart rate may produce forces on the large conducting vessels which may cause them to deform. The resulting stretch from occasional periods of increased deformation of the large blood vessels may combat some of the connective tissue cross-linking[198], 2) vasodilation of skeletal muscle increases greatly during exercise, and at least some of this is propagated upstream to the large conducting vessels[198], and 3) an increase in pulsatile flow in the aorta during exercise may lead to a greater production of vasodilating factors[199-201], including nitric dioxide, which relaxes vascular smooth muscle in conducting arteries[198]. However, arterial compliance was not found to increase following exercise in participants with SCI in this study and several reasons may be postulated to explain this. A change in body composition following injury with a propensity towards muscle wasting and fat accumulation[38] is common following SCI and along with decreased physical activity following injury, increases the risk for cardiovascular disease[38, 193]. Improvement in arterial compliance following an acute bout of exercise was demonstrated in obese individuals who were placed on a energy-restricted diet to promote weight loss[202]. It has been demonstrated in previous studies that weight loss improves arterial compliance[203, 204]. Accordingly, perhaps individuals with SCI in this study were not found to have improved arterial compliance following exercise as a result of greater fat accumulation subsequent to injury. That is, perhaps a change in body composition with an increase in lean muscle mass and reduction in fat may help to improve arterial compliance in this population. Additionally, it has been shown in a previous study that small artery compliance increases after an acute bout of exercise only after six months of exercise training[197]. Accordingly, exercise training may be required to help improve arterial compliance following acute bouts of activity in persons with SCI.

While findings of the current study show that acute forms of exercise do not help improve arterial compliance in persons with SCI, it is still important to note that exercise rehabilitation has been found to lead to marked health benefits in persons with SCI, and improve exercise tolerance[67]. Additionally, since arterial compliance is a measure of cardiovascular health[67], helping individuals with SCI to lead more physically active lifestyles is important.

8 LIMITATIONS AND FUTURE CONSIDERATIONS

The small sample size for both groups of participants limited the strength of some statistical findings of the present study and may limit the generalizability of the findings. However, despite this small sample size, significant results were still found for several important cardiovascular and cardiorespiratory measures in response to the orthostatic challenge and peak exercise, respectively. Differences between groups of participants were also revealed. Several studies examining exercise response in individuals with SCI have had sample sizes ranging from five to eight participants[28, 29, 41, 77, 79, 205, 206] and have found statistical significance and drawn upon both statistically and clinically significant results to explain their outcomes. This is similar for studies investigating orthostatic hypotension in persons with SCI, where several studies have sample sizes ranging from five to eight[50, 63, 109, 207] participants. Furthermore, within the group of participants with SCI, the number of individuals with paraplegia and tetraplegia (n=3 for both groups, respectively) is also small and likely limited the ability to find more significant results and make more generalizations about differences between these two groups. However, differences in autonomic function and control following injury were reflected in numerous findings, keeping in agreement with the fact that exercise capacity and response are different between these individuals. This highlights the importance of understanding variations in cardiovascular response to different stresses that are encountered since they may affect performance, whether during exercise, or another type of cardiovascular stress, such as an orthostatic challenge in persons with SCI.

Ventilation, and thus, end-tidal or arterial, carbon dioxide were not measured during the orthostatic challenge and, therefore, the influence of chemoreceptor sensitivity and the retention of carbon dioxide on cerebral blood flow dynamics were not assessed during this test. For future consideration, measurement of ventilation would provide more information about cerebral autoregulation during the sit up test in both able-bodied individuals and persons with SCI. It is currently unknown if the orthostatic challenge employed in this study would lead to hyperventilation which has been seen previously during head-up tilt. This has been found to alter the partial pressure of carbon dioxide and transcranial Doppler recordings of mean flow velocity in normal subjects[208]. Measuring ventilation is an important consideration for future studies since the partial pressure of carbon dioxide appears to be the most important contributing factor to cerebral blood flow regulation[209, 210]. Numerous studies have examined cerebral blood flow during an orthostatic challenge and there are both investigations that do[118, 171], and do not[172, 211] include methods to measure carbon dioxide to assess its influence on cerebral blood flow during the orthostatic stress. Additionally, while the partial pressure of carbon dioxide has been shown to regulate cerebral blood flow, it has also been illustrated that changes in cerebral blood flow are minor (3.9–4.4.% per Torr) in response to hypercapnia[212-215].

While the partial pressure of carbon dioxide during an orthostatic challenge in individuals with SCI has been examined[55], there are no current investigations that explore this during an orthostatic challenge following an acute bout of steady state exercise in persons with SCI. Additionally, there are only a limited number of studies that have examined the effects of exercise on orthostatic hypotension[11, 63], so further investigation is warranted.

While persons with SCI in this investigation included their legs passively into hybrid exercise, it was observed that passive inclusion of the lower limbs for able-bodied individuals was a challenge. Even though activity of the legs during hybrid exercise was monitored via electroymyogram, and verbal feedback was provided to participants to encourage no active movement of the legs, visual inspection of electromyogram data indicated that able-bodied participants had difficulty minimizing active muscle contraction. Thus, it is difficult to definitively conclude that passive inclusion of the legs during hybrid exercise in this investigation promotes greater cardiorespiratory response in comparison to arm exercise alone in able-bodied persons, but the findings of this study support the idea that whole-body exercise promotes greater aerobic capacity and performance in both groups of participants. Furthermore, it was illustrated in this study that passive inclusion of the lower limbs during exercise in persons with SCI promotes greater cardiorespiratory response in comparison to arm exercise alone.

Finally, only individuals with chronic SCI were included in this study. Accordingly, it would be beneficial to study the effects of an acute bout of steady state exercise on response to an orthostatic challenge in persons with acute SCI, as tolerance to orthostatic stress has been found to change with increasing time since injury[50].

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