THE EFFECTS OF EXERCISE TRAINING ON CARDIOVASCULAR REGULATION IN INDIVIDUALS WITH SPINAL CORD INJURY

By

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Abstract

Introduction. Individuals with spinal cord injury (SCI) are prone to severe cardiovascular dysfunction and an increased risk of mortality from various cardiovascular diseases. The underlying mechanisms responsible for the increased cardiovascular risk are not precisely understood, however, the reduced activity levels that accompany SCI certainly contribute. Unfortunately, muscular paralysis (partial or complete) limits the exercise options for individuals with SCI and the role of exercise rehabilitation as a means of reversing cardiovascular risk is not fully understood in this population.

Recently developed methods may be particularly useful in evaluating the effects of exercise on the cardiovascular health and function in individuals with SCI. Specifically, power spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV) have become commonly used, non-invasive methods used to quantify the autonomic control of the cardiovascular system. Clinically, measures of HRV and BPV have particular value as relatively decreased cardiac vagal predominance has been associated with an increased risk of cardiovascular mortality, and increased BPV is associated with end organ damage. In addition, Doppler ultrasound imaging techniques allow for the determination of arterial dimension and function. As such, these imaging techniques may be used to determine arterial blood flow and vascular compliance; the latter referring to the ability of the vessel to expand and recoil during changes in intravascular pressure. Clinically, these measures are also of value as reductions in blood flow contribute to thrombus formation, in addition to delayed wound healing and an increased risk of pressure sore formation, while reductions in arterial compliance are a

contributing factor to vascular damage, and the associated risks of thrombosis, myocardial infarction and stroke.

The primary purpose of this thesis was to examine the effects of exercise training on resting measures of HRV, BPV and arterial dimension and function in individuals with SCI. A secondary purpose, was to determine the effects of exercise training on the ability to tolerate orthostatic stress in individuals with SCI. Although the first training study in this thesis used arm ergometry and resistance training as the exercise stimulus, the principle mode of exercise training that was used was body-weight supported treadmill training (BWSTT) as it may be particularly well suited as a cardiovascular stimulus in the SCI population. Specifically, BWSTT is an upright exercise that involves the legs, and may be performed without the risks that are commonly associated with functional electrically stimulated (FES) exercise such as burns to the skin, stimulation-induced pain and autonomic dysreflexia. It was hypothesized that BWSTT would result in i) positive changes in the autonomic regulation of the cardiovascular system, as indicated by measures of HRV and BPV, and ii) positive changes in arterial dimension and function, as indicated by Doppler ultrasound measures. Regarding the effects of exercise training on orthostatic tolerance, previous work has provided some evidence that exercise training confers an enhanced ability for individuals with SCI to respond to cardiovascular stress. On the other hand, it was also reasonable to hypothesize that potential training-induced reductions in sympathetic outflow and arterial resistance would decrease the ability to tolerate postural stress in individuals with SCI.

Methods. Short-term, continuous ECG and blood pressure (Finapres) recordings were taken before and after exercise training in individuals with SCI and used to

determine measures of HRV and BPV, respectively. In addition, Doppler ultrasound imaging was performed on the femoral and carotid arteries, before and after exercise training, in order to determine vascular dimension and function. All testing was conducted in the resting supine position and during an orthostatic stress (60° head-up tilt).

Results. 1. Measures of heart rate variability (HRV) and blood pressure variability (BPV) were found to be reproducible in individuals with SCI, regardless of the level of injury. As such, clinicians and researchers may be encouraged to use these measures to determine the effectiveness of various interventions on the cardiovascular health in the SCI population. **2.** Individuals with incomplete tetraplegia were found to retain the ability to make positive changes in cardiac sympathovagal balance following 3 months of combined arm ergometry and resistance exercise training. No exercise-induced changes were noted in orthostatic tolerance. **3.** The results of the third study demonstrated that individuals with incomplete tetraplegia can make positive adaptations to the autonomic regulation of the cardiovascular system following 6 months of BWSTT as indicated by measures of HRV and BPV. In addition, these adaptations occurred without an accompanying tendency to become less tolerant of orthostatic stress. **4.** The results of the fourth study showed that individuals with motor-complete SCI may experience favourable vascular changes following 4 months of BWSTT. Although there were no significant exercise-induced changes in measures of HRV and BPV, the results suggested that favourable changes in both these measures may occur in individuals who experience a substantial heart rate (HR) response to this type of training. Greater HR responses were elicited in those who were more orthostatically intolerant and had greater muscle

spasticity. Finally, BWSTT was found to worsen orthostatic intolerance in individuals with tetraplegia, but not in those with paraplegia.

Conclusions. Individuals with SCI retain the ability to make positive changes in cardiovascular regulation with exercise training, as indicated by measures of HRV and BPV, as well as by Doppler ultrasound measures of arterial function. Individuals with less severe SCI (ASIA C and D injuries) may be particularly well suited for BWSTT as a means to promote cardiovascular improvement. Specifically, individuals with spared motor function (ASIA C injuries) made positive adaptations in measures of HRV and BPV after 6 months of BWSTT, and further, due to the spared sensory ability, these individuals may not be able to tolerate FES exercise. Individuals with motor-complete SCI may experience positive vascular changes with BWSTT, regardless of the HR elicited during this form of exercise. In addition, those with high muscle spasticity and a susceptibility to orthostatic intolerance may experience positive adaptations in measures of HRV and BPV.

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ABBREVIATIONS

ASIA	American Spinal Injury Association
BP	Blood pressure
BPV	Blood pressure variability
BWSTT	Body-weight supported treadmill training
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FES	Functional electrically stimulated
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
HUT	Head-up tilt
LF	Low frequency
LF:HF	Low frequency to high frequency ratio
MAP	Mean arterial pressure
NE	Norepinephrine
SBP	Systolic blood pressure
SCI	Spinal cord injury

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Chapter 1

Review of Literature

1. Introduction and clinical perspectives

1.1 Epidemiology of spinal cord injury

Spinal cord injury (SCI) is a particularly abrupt and life-altering condition that has an extremely wide range of physiological and psychological consequences. Epidemiological studies have estimated the incidence of SCI in Canada and the United States to be approximately 35/million and 40/million, respectively (Sekhon and Fehlings, 2001). While these rates may seem relatively innocuous at first, they translate to approximately 1,000 newly injured Canadians and 12,000 newly injured Americans each year, and further, a combined prevalence of approximately 250,000 individuals (Sekhon and Fehlings, 2001). When considering the effects of a SCI on one's family and friends, the number of people currently coping with the consequences of SCI in Canada and the United States alone, is staggering.

With respect to injury severity, studies have shown that approximately 55% of individuals with SCI have incomplete injuries, leaving 45% with complete injuries (Appendix A) (Sekhon and Fehlings, 2001). Moreover, approximately 40% of those people living with SCI have tetraplegia (cervical injuries), while 60% have paraplegia (injuries at, or below the first thoracic level) (Sekhon and Fehlings, 2001). Considering the possible combinations of injury level and injury severity, individuals with SCI present, as a group, with an extremely varied array of abilities and disabilities in terms of both function and health.

1.2 Morbidity and mortality after spinal cord injury

Causes of mortality in the SCI-population have changed dramatically in the last few decades, largely due to improved bladder care, and the reduction in corresponding deaths due to urinary complications (Frankel et al., 1998). Likewise, improved care of both acutely and chronically injured individuals has greatly increased the life expectancy in the SCI population, which continues to approach that of the able-bodied (Frankel et al., 1998). In particular, individuals with complete tetraplegia, complete paraplgia and all those with ASIA D injuries, have life expectancies of 70%, 84% and 92% compared to the healthy, able-bodied population, respectively (Yeo et al., 1998).

As a result of these shifting mortality rates, heart disease has emerged as the number two killer in individuals with SCI (Frankel et al., 1998). A more detailed examination of mortality in the SCI-population was provided by DeVivo et al. (1993), who tabulated the various causes of death, and their corresponding standardized mortality ratios (SMR), in a cohort of 9,135 individuals following their first 12 years after injury (all of whom survived the first 24 hours). Non-ischemic heart disease ranked as the second most common cause of death in the SCI population, although specific risks differed widely across injury types. Specifically, those with incomplete paraplegia showed a similar risk compared to the able-bodied population, while those with complete tetraplegia exhibited an increased risk of approximately 23-fold. Ischemic heart disease was the fifth most common cause of death in the SCI population, and again, specific risks depended on the type of injury; ranging from a similar risk as the able-bodied population in people with incomplete paraplegia to a 2.6-fold increase in risk in people with

complete tetraplegia. In addition, individuals with SCI, regardless of injury type, also exhibited an increased relative risk for other cardiovascular diseases such as 'diseases of the pulmonary circulation' and 'diseases of the arteries'.

It has yet to be determined if the increased risk of cardiovascular mortality after SCI is due primarily to the injury per se, or the general decrease in activity that is characteristic of this population. However, studies have begun to show exercise-induced decreases in various indices of cardiovascular risk in individuals with SCI (Bauman et al., 1992; Brenes et al., 1986).

In addition to an increased risk of cardiovascular mortality, individuals with SCI are also prone to various cardiovascular abnormalities, which may or may not be life-threatening, but certainly limit independence and function, and adversely affect quality of life. One such condition is known as orthostatic intolerance, which can be defined as an acute or progressive decline in mean arterial pressure (MAP) of more than 10 to 15 mmHg in the upright position (Blackmer, 1997). Symptoms of orthostatic intolerance may include light-headedness, dizziness, visual changes and possibly syncope (Braddom, 1996). The causes of othostatic intolerance following SCI are discussed in detail below, however, in general, this condition is thought to stem from the sympathetic decentralization that is characteristic of SCI, and the resulting inability to vasoconstrict below the level of injury during upright posture.

The role of exercise rehabilitation as a means of reversing the cardiovascular consequences associated with SCI is not fully understood. Traditional rehabilitation for individuals with SCI has focussed primarily on increasing mobility, function and social

reintegration, and thus, the potential for improvement in cardiovascular health of this population is currently unknown.

2. Neural control of the cardiovascular system

2.1 Neural control of the heart

Cardiac muscle represents somewhat of a unique tissue in the body as it may contract rhythmically on its own, without neural influence. This intrinsic beat of the heart has been shown to be approximately 100-110 beats per minute in the healthy human adult (Katona et al., 1982). Quite obviously however, there are many instances such as during physical or emotional stress, when the heart rate greatly exceeds the intrinsic beat, and conversely, there is a great deal of time at rest when the heart rate is substantially lower than the intrinsic beat. These deviations in heart rate are largely due to neural influences from the autonomic nervous system. Specifically, the autonomic nervous system consists of two divisions; the parasympathetic limb, which is chiefly inhibitory and acts to reduce heart rate, and the sympathetic limb which is primarily excitatory and acts to raise both heart rate and contractility. Sympathetic innervation in general, is provided by fibres that originate mainly in the intermediolateral cell column of the spinal cord, between the first thoracic to the second lumbar levels (T_1-L_2)(Strack et al., 1988). In the specific case of cardiac sympathetic innervation, the heart receives input from fibres that originate between the spinal segments of T1-T4 (Hockman et al., 1987).

Parasympathetic innervation to the heart is provided by the vagus nerve which does not descend in the spinal cord, but rather exits the central nervous system from the brainstem. Specifically, preganglionic parasympathetic fibres originate in the dorsal

motor nucleus of the medulla oblongata and exit in the vagus nerve. The vagus nerve (left and right) then forms three pairs of vagal cardiac nerves, which in turn, synapse with postganglionic fibres that terminate primarily in the SA and AV nodes (Hockman, 1987) (Figure 1; page 42).

2.1.1 Neural control of the heart after spinal cord injury

While paralysis and immobility may be the most obvious consequence of SCI, injured individuals are also prone to serious autonomic dysfunction due to the disconnection between higher centres and the autonomic fibres that originate in the spinal cord. For example, individuals with SCI at or above the high thoracic level (T1-T4) are prone to severe alterations in cardiac autonomic control (Bunten et al., 1998; Grimm et al., 1995; Grimm et al., 1997; Inoue et al.,1990; Inoue et al., 1995; Wang et al., 2000) as the cell bodies of preganglionic sympathetic fibres may be damaged themselves, and/or simply disconnected from supraspinal influence. In contrast, the parasympathetic fibres that innervate the heart are provided by the vagus nerve, and thus, they are spared from damage during SCI. Theoretically, therefore, individuals with SCI suffer from a unique imbalance of neurocardiac control. The nature and extent of this imbalance however, is yet to be fully understood, and will be further discussed and investigated below.

2.1.2 Heart rate variability as a measure of autonomic control of the heart

The analysis of heart rate variability (HRV) has become a common, non-invasive method used to measure the autonomic control of the heart (Akselrod et al., 1981; Kamath et al., 1993; Malik and Camm, 1995). This method is based on the principle that even during constant resting conditions, the heart does not beat with perfect metronome-

like regularity. Further, an analysis of the temporal variability between successive heart beats (specifically, between successive R-R intervals obtained from an electrocardiogram) can be used to estimate the relative predominance of cardiac sympathetic outflow and cardiac parasympathetic outflow (or vagal outflow), over a given period of time.

From a biochemical perspective, the techniques that are used to analyze HRV take advantage of the fact that the sympathetic and parasympathetic nervous systems use different neurotransmitters to exert their influence on the heart, and further, that different mechanisms are used to terminate the effects of each neurotransmitter. For example, the postganglionic parasympathetic fibres release acetylcholine (ACh) which i) acts relatively quickly to decrease heart rate (latencies to onset of 50-100 ms), and ii) is rapidly hydrolized by the abundance of cholinesterase located at the SA and AV nodes (Hockman, 1987; Warner and Cox, 1962). In contrast, the postganglionic sympathetic fibres release norepinephrine (NE) which i) acts relatively slowly to increase heart rate (1 to 3 seconds latency), and ii) has its effects more slowly terminated mainly by the presynaptic reuptake of this neurotransmitter, and to a lesser extent its diffusion out of the synaptic cleft into the surrounding extracellular fluids (Hockman 1987; Warner and Cox, 1962). Therefore, the parasympathetic system may exert a beat-to-beat influence on cardiac control, while the sympathetic system cannot alter cardiac behaviour within one cardiac cycle. There are several methods that can be used to analyze HRV depending on whether the variability of the successive R-R intervals is expressed in the time or frequency domain (Task Force, 1996). Unlike time domain analysis, which is primarily

only an index of vagal outflow, power spectral analysis of HRV, serves as an estimate of both parasympathetic and sympathetic cardiac regulation. For this reason, power spectral analysis was the method used in the present investigations, and therefore, will be the only method discussed in this review.

In brief, when successive R-R intervals are plotted against time a complex but reproducible signal is typically produced in normal healthy subjects. This complex signal (referred to as a tachogram), is in fact, the summation of several distinct signals, each oscillating at a distinct frequency (Figures 2 & 3; pages 43 & 44). Mathematical analysis of this complex signal can then be used to determine the relative predominance of each frequency over a given period of time. In normal healthy individuals at rest, the successive R-R intervals primarily oscillate around two distinct frequencies; a low frequency oscillation (LF; 0.04-0.15 Hz; center frequency: 0.1 Hz) and a high frequency oscillation (HF; 0.15-0.40 Hz; center frequency: 0.25 Hz) (Kamath and Fallen, 1993). The relative predominance, or power, of the LF and HF oscillations can then be quantified and graphically represented in a power spectrum (Figure 4; page 45). Various investigations, utilizing either biochemical blocking agents (Pomeranz et al., 1985) or maneuvers known to provoke certain autonomic responses (Montano et al., 1994), have shown that the HF oscillation corresponds to the parasympathetic outflow to the heart, while the LF oscillation corresponds to both the sympathetic and parasympathetic outflow of the heart, although it is much more indicative of the former. Thus, the LF:HF ratio has become an acceptable and reproducible estimation of cardiac sympathovagal balance (Malik and Camm et al., 1995). Although NE and Ach exert the effects of the

sympathetic and parasympathetic nervous systems, respectively, it is important to note that the actual cause of HRV (i.e., the mechanism behind the continuous shifts in sympathetic and parasympathetic predominance) is due to the effects of respiration on intrathoractic pressure. Specifically, during inhalation the diaphragm descends and intrathoracic pressure decreases. This decrease in pressure is then sensed by baroreceptors which in turn, cause a reflex increase in HR via an enhanced sympathetic outflow. In contrast, during exhalation the diaphragm ascends causing an increase in intrathoracic pressure and a baroreceptor-mediated decrease in HR via an enhanced parasympathetic outflow. Thus, respiration is critical to the production of HRV and accordingly, studies will either evaluate HRV during spontaneous breathing or paced breathing (via a metronome) usually at a frequency of 12-15 breaths per minute (Task Force, 1996). While paced breathing at 15 breaths per minute acts to fix the center frequency of the HF power at the typical value of 0.25 Hz, this manipulation does not represent the natural resting condition of the individual being examined. As the present studies sought to examine the effects of exercise on HRV during the normal resting state, all HRV testing sessions were performed during spontaneous breathing conditions.

2.1.3 Heart rate variability as a predictor of cardiovascular risk

Several investigations have noted the predictive power of HRV for the risk of mortality from various cardiovascular diseases. In particular, there appears to be an association between an increased risk of cardiovascular mortality and indices of reduced cardiac vagal outflow and/or increased cardiac sympathetic predominance obtained from HRV analysis.

One of the earliest large-scale studies that investigated the predictive power of HRV, examined 808 patients who had recently (11 ± 3 days prior) suffered a myocardial infarction (MI) (Kleiger et al., 1987). A time domain measure of HRV (SDNN; the standard deviation of all normal RR-intervals) was measured at baseline via 24-hour Holter monitor recordings, and patients were followed–up for a mean of 31 months. The investigators reported that 127 of the 808 patients died during the follow-up period, and the relative risk of all-cause mortality was 5.3 times greater in the group with low HRV (SDNN < 50ms) compared to the group with high HRV (SDNN > 100 ms). Further, HRV remained a significant predictor of all-cause mortality after adjusting for several other clinical variables. As SDNN is representative of vagal outflow to the heart, Kleiger and colleagues (1987) suggested that the shift away from cardiac vagal predominance and toward cardiac sympathetic predominance was associated with an increased risk of mortality. Other similar studies have also shown that decreases in time domain measures of HRV, and thus decreased vagal predominance, are associated with an increased risk of sudden cardiac death in post-MI patients (Algra et al., 1993; Myers et al., 1986).

Although the majority of studies that have examined HRV and cardiovascular risk have utilized time domain measures of HRV, there are also a small number of studies that have employed frequency measures. As mentioned, frequency domain measures may be advantageous as they allow for the estimate of both sympathetic and parasympathetic outflow to the heart. For example, studies by Lombardi et al., (1987, 1992) have shown an increase in the LF:HF ratio in patients who recently suffered acute MI compared to healthy age-matched controls. This shift in cardiac autonomic balance toward a

sympathetic predominance was evident from short term ECG (Lombardi et al., 1987) as well as 24-hour ambulatory Holter recordings (Lombardi et al., 1992). Similar results were also shown by Ajiki et al., (1993) in patients with cardiomyopathies. Although such results have established an altered HRV in cardiac patients, they unfortunately do not associate specific values of the LF:HF ratio with corresponding relative increases in cardiovascular risk. However, a study conducted by Lanza and colleagues (1997), determined frequency domain measures of HRV in patients with unstable angina within 12 hours of admission to hospital, and related these measures to risk of in-hospital cardiac events (death or MI). Results showed that the LF:HF ratio was significantly higher in patients with subsequent cardiac events than in those without (2.12 ± 1.4 vs. 1.48 ± 0.5, respectively; $p=0.01$), and further, LF:HF ratios greater than 1.3 were significantly associated with an odds ratio of 2.7 for major cardiac events. Unfortunately, differences in HRV measurement techniques between laboratories restrict the general clinical use of any specific value for the LF:HF ratio as a critical point for cardiovascular risk. Nevertheless, several investigations have shown cardiovascular disease to be characterized by a shift in cardiac sympathovagal balance away from vagal predominance and towards a sympathetic predominance, as indicated by HRV measures (Vybiral and Glaeser, 1995; Singer and Oriz, 1995). Accordingly, some experts have suggested that HRV may be a better predictor of mortality than commonly used clinical measures such as left ventricular ejection fraction, wall motion abnormalities and exercise capacity (Singer and Ori, 1995).

The predictive power of HRV has primarily been observed in individuals with established cardiac disease or after acute MI (Malik and Camm, 1995). Whether HRV measures can predict future cardiovascular risk in apparently healthy individuals is still open to some question. For example, animal studies have examined HRV before and after induced MI. The results of such work has shown no difference in pre-MI HRV, between animals shown to be susceptible or resistant to ventricular fibrillation during exercise stress tests in the post MI state (Hull et al., 1990). However, human studies have shown an association between autonomic dysfunction and cardiovascular mortality in certain special populations free of concurrent cardiovascular disease. For example, diabetics with autonomic neuropathy (free of coronary artery disease), were shown to have mortality rates approximately three times greater than diabetics with normal autonomic function, and further, of those in the former group that died, almost 30% experienced sudden cardiac death (Ewing et al., 1980). Likewise, infants that subsequently died of sudden infant death syndrome (SIDS) were characterized by a shift toward cardiac sympathetic predominance, as determined by power spectral analysis of HRV, compared to infants that survived (Gordon et al., 1984). Thus, HRV may serve as a valid predictor of cardiovascular and all-cause mortality in a variety of populations with or without previous cardiovascular disease.

2.1.4 Heart rate variability in individuals with spinal cord injury

In recent years, several studies have employed the analysis of HRV to determine the autonomic control of the heart in individuals with SCI. Findings in this area remain somewhat equivocal.

Initial work conducted by Inoue et al. (1990) examined frequency domain measures of HRV in individuals with chronic, neurologically complete SCI (C6-C7) and age-matched, healthy able-bodied controls during supine rest. While control subjects displayed both the LF and HF components of HRV, the individuals with SCI only exhibited the HF component. Further, comparisons of HF power between the two groups showed a non-significant reduction in those with SCI compared to the able-bodied controls. These data suggested that the sympathetic innervation to the heart is completely ablated in individuals with complete tetraplegia, although the parasympathetic innervation to the heart is intact and distinctly dominant during resting conditions. However, subsequent work by Inoue and colleagues (1995), which included a wider range of injury types and a larger sample of subjects, found somewhat different results. Specifically, 6 of 15 individuals with chronic, complete tetraplegia (C6-C7) exhibited both the LF and HF components of HRV during supine rest. The investigators hypothesized, however, that the LF component shown in the individuals with SCI was simply reflex sympathetic outflow caused by stimuli from the periphery (bladder or bowel distension or spasms from the limbs) rather than cardiac sympathetic innervation originating from higher centers.

In contrast, the results from studies conducted by Grimm and colleagues (1995, 1997) have shown that there is some maintenance of cardiac sympathetic innervation following even complete cervical SCI, and further, a normal preservation of cardiac autonomic balance between the sympathetic and parasympathetic limbs. These investigators (Grimm et al., 1997) examined individuals with chronic complete

tetraplegia (above C7), chronic incomplete tetraplegia (above C7), chronic complete paraplegia (below T7) and age-matched able-bodied control subjects, during supine resting conditions and various 'provocative maneuvers' (60° head-up tilt, cold pressor test and isometric jaw contractions). The results of these investigations showed that both the LF and HF components of HRV were present in individuals with SCI, although the power of each component appeared to be inversely proportional to the level and severity of the injury. There were no differences observed between any group for the LF:HF ratio, indicating a maintenance of sympathovagal balance to the heart regardless of the type of injury sustained. Because of the preservation of the LF:HF ratio, the investigators concluded that the withdrawal of cardiac sympathetic tone that results from cervical SCI causes a compensatory reduction of cardiac vagal tone in an attempt to maintain cardiac sympathovagal balance. This conclusion was also drawn by Wang and colleagues (2000), who also found a maintenance of sympathovagal balance in individuals with tetraplegia. Thus, despite the sparing of the vagus nerve, individuals with SCI may experience a reduction in parasympathetic outflow to the heart. This may be a particularly discouraging scenario for individuals with SCI, since a withdrawal of cardiac vagal tone is associated with increased cardiac mortality in other populations (Malik and Camm, 1995).

2.2 Neurovascular control

The autonomic nervous system also plays a major role in the control of blood pressure via the innervation of the systemic vasculature. Specifically, adrenergic neurons originating between the first thoracic and second lumbar levels of the spinal cord

eventually synapse with, and innervate the entire arterial tree down to the arterioles. This adrenergic innervation exerts a constrictor effect that increases the resistance of the vessels. As mean arterial blood pressure is the product of cardiac output and total peripheral resistance, adrenergic vasoconstriction is vital to the maintenance of blood pressure at rest and in response to cardiovascular challenge. In fact, in circumstances such as upright posture, when ventricular filling pressure is limited and rises in cardiac output are prevented, only peripheral vasoconstriction can maintain blood pressure (Rowell, 1986).

Autonomic control of the vasculature differs importantly from that of the heart as there is no evidence of parasympathetic outflow to the vessels, and increases and decreases in sympathetic outflow are responsible for neurogenic vasoconstrictor and vasodilator effects, respectively. Adrenergic nerve terminals primarily release norepinephrine which acts on α-receptors on the vessel wall to cause vasoconstriction. The adrenergic nerves are not completely quiescent at rest and exert a resting sympathetic tone. Increases in sympathetic outflow above this basal tone constrict the vessel and increase resistance, while withdrawal of sympathetic outflow below this basal level cause a relative "passive" vasodilation (Calendar, 1954). It is important to note, that although some evidence exists for sympathetic cholinergic vasodilators, they do not appear to play an important role in human circulation. (Rowell, 1986)

2.2.1 Neurovascular control after spinal cord injury

Because the sympathetic fibres originate in the spinal cord, they too may be damaged during SCI or simply disconnected from the influences of higher centers. Thus,

individuals with SCI within or above the thoracic level will likely experience some deficit in terms of neurovascular control. The partial or complete loss of sympathetic outflow to the vasculature after SCI is believed to contribute to the resting hypotension that is often observed in this population, and more notably, to their inability to maintain arterial pressure during upright posture (orthostatic intolerance). As the large splanchnic vascular bed is particularly involved in the neurovascular maintenance of blood pressure, individuals with injuries above T6 (the origin of adrenergic outflow to the splanchnic vasculature) may have more exaggerated deficits. In addition, those with injuries at the high thoracic or cervical level suffer from both cardiac sympathetic denervation as well as considerable vascular denervation, and often present the greatest impairments in cardiovascular regulation (Munakata et al., 2001).

2.2.2 Blood pressure variability as a measure of neurovascular control

Resting values of arterial blood pressure are not perfectly stable, and like heart rate, systolic and diastolic blood pressure values appear to be characterized by slight beat-to-beat variations that have physiological significance. Specifically, when beat-to-beat values of systolic or diastolic blood pressure are plotted against time, a complex but reproducible signal is obtained. Power spectral analysis of this signal may then be performed in order to determine which of a wide range of frequencies are relatively predominant. Studies conducted on normal healthy humans have shown that beat-to-beat values for systolic and diastolic blood pressures typically oscillate around two distinct frequencies. Similar to heart rate variability, low frequency (LF) variations in blood

pressure, also known as the Mayer waves, oscillate around 0.1 Hz (0.04-0.15 Hz), and high frequency (HF) variations in blood pressure oscillate around 0.25 Hz (0.15-0.40 Hz).

Several studies have investigated the physiological correlates of the LF and HF components of BPV. On the most basic level, the LF components of both systolic and diastolic blood pressure have been shown to positively correlate with the LF:HF ratio of HRV, and thus, have been associated with sympathetic outflow to the cardiovascular system (Laitinen et al., 1999). These correlations, although significant, are relatively small and therefore sympathetic outflow to the heart per se, may not contribute as much to the LF components of BPV as the sympathetic outflow to the vasculature. Accordingly, more invasive studies have shown increases in the LF component of BPV during nitroglycerin infusion, coronary occlusion and exercise, each of which is associated with increased sympathetic outflow to the peripheral vessels (Rimoldi et al., 1990), and a decrease in the LF component of BPV during α-adrenergic blockade (Parati et al., 1995). Finally, a significant correlation has been shown between direct measures of muscle sympathetic nerve activity (MSNA) at the peroneal nerve and the LF component of BPV over a wide range of blood pressures evoked by either nitroprusside or phenylephrine infusion (Pagani et al., 1997). The physiological correlate of the HF component of BPV is not as analogous to the HF component of HRV, as there is no vagal outflow to the vasculature. The HF components of BPV have therefore been assumed to represent the mechanical effects of respiration which may act directly on the pressure gradients of the intrathoracic vessels (Pagani et al., 1986). It is important to note that spectral components of BPV are not simply reflections of the spectral components of

HRV. For example, since blood pressure is the product of cardiac output and vascular resistance, it may be argued that increases in the LF component of BPV may simply reflect increases in cardiac output caused by an increased sympathetic outflow to the heart, rather than a legitimate sympathetically-induced increase in peripheral resistance. However, several studies have shown a clear distinction between the spectral components of BPV and HRV. Specifically, both the LF and HF components of BPV have been observed in heart transplantation patients who concurrently showed virtually absent components of HRV (Hughson et al., 1995). Similar results have been shown during cardiac autonomic blockade via the combined administration of atropine and propranolol (Saul et al., 1991).

2.2.3 Blood pressure variability and risk of cardiovascular disease

Several studies have shown an association between increased BPV and the risk of cardiovascular disease (Miao and Su, 2002; Parati et al., 1987; Parati et al., 1992; Siche et al., 1995). Although the majority of research in this area has been cross-sectional, a longitudinal study conducted by Frattola and colleagues (1993), has provided evidence of the cause and effect relationship between increases in blood pressure variability and organ damage, and further, has shown that the deleterious effects of increased blood pressure variability are independent from the effects of increases in blood pressure. Specifically, Frattola et al. (1993) recorded 24 hour ambulatory blood pressure measures in 73 hypertensive patients, from which "among half-hour standard deviation" (a time domain measure of BPV) was calculated. Patients were also divided into quartiles based on their 24-hour mean arterial pressure (MAP). At follow-up, approximately 7 years

later, measures of end-organ damage (as indicated by several ECG and chest x-ray measures) were determined. The results showed that for any given quartile of MAP, those patients with lower values of BPV determined at the initial exam had a lower severity of end-organ damage at follow-up, especially for measures of left ventricular hypertrophy. Moreover, this relationship held true even at the lowest quartile of MAP which was approximately 80-85 mmHg.

Perhaps the best evidence that increased BPV is likely associated with increased end-organ damage, even in the absence of hypertension, may come from the sinoaortic denervated (SAD) rat model. In this model, rats are subject to surgical destruction of the carotid and aortic baroreceptor afferents, and in the chronic condition are characterized by an increase in BPV but a normal average blood pressure (Miao and Su, 2002). SAD rats have been shown to develop both aortic and left ventricular hypertrophy, both of which have been shown to correlate positively and significantly with BPV (Miao and Su, 2002; Sasaki et al., 1994). In terms of disease progression, the vascular thickening typically precedes the cardiac hypertrophy, and is caused by smooth muscle cell growth and collagen accumulation (Lacolley et al., 1995).

In each of the above mentioned studies, however, the relationship between BPV and cardiovascular disease was determined via time domain measures of BPV. Although there seems to be a strong link between time domain measures of BPV and end-organ damage, there is a paucity of literature regarding this relationship when frequency domain measures of BPV are considered. However, one study conducted by Siche et al. (1995) examined the LF power of systolic and diastolic BPV in hypertensive subjects

with and without left ventricular hypertrophy, and healthy age-matched controls. Although BPV was lower in the controls than in the hypertensive subjects without cardiac hypertrophy, Siche and colleagues showed that among those with hypertension, left ventricular hypertrophy was associated with *decreased* LF power of BPV. Although this may seem to contradict the consistent findings from SAD rats regarding the positive correlation between end organ damage and BPV, it is possible that in progressively hypertensive conditions, the LF component of BPV may initially increase but then continue to decline as the disease becomes severe. This late reduction in LF power has been shown in HRV measures in patients with advanced chronic heart failure (Malliani et al., 1991). In contrast to the results from Siche et al., (1995), more recent work provides indirect evidence supporting the protective effect of reductions in the LF component of BPV. Taylor and colleagues (2003) examined frequency domain measures of BPV before and after exercise training in a cohort of 17 older adults with hypertension, who were otherwise healthy. Nine of these individuals performed low-intensity isometric handgrip exercise for 10 weeks, while 8 served as non-exercising controls. Following the training protocol, those who exercised had significantly greater reductions in systolic and mean arterial pressures than the controls, accompanied by significantly greater reductions in LF power of systolic BPV. Although the investigators did not measure indices of end organ damage, their results are suggestive of an association between reductions in LF power of BPV and protection from cardiovascular disease.

2.2.4 Blood pressure variability after spinal cord injury

The effects of SCI on BPV remains a poorly understood and controversial area. Initial work conducted by Inoue et al. (1991) observed an intact HF component but an absent LF component of systolic BPV individuals with complete tetraplegia. These investigators concluded that the LF oscillation in blood pressure, or Mayer waves, are dependent upon the connection between supraspinal centres and the preganglionic sympathetic fibres, and that this connection is completely disrupted in individuals with complete SCI. Subsequent studies, however, have found the existence of Mayer waves in individuals with complete SCI (Guzzetti et al., 1994; Koh et al., 1994; Munakata et al., 2001), although the power of these oscillations may be reduced with higher injury levels (Munakata et al., 2001). Munakata and colleagues determined BPV measures in individuals with either high-level SCI (C4-T3) or low-level SCI (T4-T12), and able-bodied controls matched for age and sex. Mayer waves were apparent in all but one individual in the high-SCI group, although the power of the Mayer waves (LF power) in this group was considerably reduced compared to the low-level SCI group and the able-bodied controls (by approximately 50% and 65%, respectively). In addition, the power of the LF component tended to decrease during 60° head-up tilt in the high-level SCI group, whereas it significantly increased in the other two groups.

3. Vascular structure and cardiovascular regulation in the able-bodied and after spinal cord injury

In addition to the losses of neurocardiac and neurovascular control, individuals with SCI are also prone to structural changes to the cardiovascular system that may further contribute to their increased risk of cardiovascular disease.

3.1 Vascular dimensions

Several studies have established a direct relationship between physical activity and the luminal size of the conducting arteries that supply the active muscle (Dinenno et al., 2001; Huonker et al., 1996; Sinoway et al., 1986). In particular, chronic increases or decreases in arterial blood flow cause corresponding increases or decreases in resting luminal diameters (Langille and Bendeck, 1990; Masuda et al., 1989). Thus, it is not surprising that the arteries supplying paralysed musculature in individuals with SCI are substantially atrophied compared to those in able-bodied individuals. For example, the luminal diameter of the common femoral artery in individuals with SCI has been found to be only 70% and 60% of that found in sedentary and endurance trained able-bodied individuals, respectively (Schmidt-Truckass et al., 2000). Accordingly, resting femoral artery blood flow may be reduced by approximately 50% in individuals with SCI compared to the able-bodied (Nash et al., 1996). Importantly, the reductions in resting femoral artery blood flow that are commonly observed in individuals with paraplegia are not accompanied by reductions in resting cardiac output, and therefore, reductions in peripheral blood flow cannot be simply attributed to central deficits (Taylor et al., 1993a). In fact, Nash and colleagues (1997) reported similar values for resting femoral artery

blood flow between individuals with paraplegia and tetraplegia. As the latter group is characterized by a lower resting cardiac output, the deficiency in lower extremity blood flow after SCI appears to be independent of central deficits.

3.2 Vascular resistance

Vascular resistance, a major determinant of blood flow, is under neurovascular and humoral control as well as local control via such factors as myogenic regulation and metabolites released by the tissues (Rowell, 1986). With respect to neurovascular control, tonic levels of sympathetic outflow to the vessels result in a basal level of constriction and vascular resistance (Calendar, 1954). On this basis alone, it would seem natural that SCI would result in a decreased peripheral vascular resistance due to the disconnection between higher centres and the preganglionic sympathetic fibres. Interestingly however, a recent study (Hopman et al., 2002) has shown SCI to be associated with increases in peripheral vascular resistance, although the area remains somewhat equivocal.

Earlier research in both animals (Pollock et al., 1979; Rodionov et al., 1981) and humans (Lynn and Barcroft, 1950) has shown that sympathectomy, at least in the hours and days that follow, is associated with a decreased vascular resistance, and as such it may seem reasonable to expect similar decreases in vascular resistance after SCI. However, the sympathectomy model differs from SCI in two very important ways. First, unlike sympathectomy, SCI is characterized by the preservation of spinal sympathetic reflexes which may provide some residual vascular resistance, and second, SCI is also associated with immobility and extreme muscular atrophy below the level of injury (Castro et al., 1999). The profound muscular atrophy and inactivity in the paralysed limbs

may be accompanied by vascular changes that would be expected to cause increases in vascular resistance. Such vascular changes include a reduction in vessel diameters (Schmidt-Truckass et al., 2000), and capillary density (Martin et al., 1992), and perhaps a reduction in nitric oxide release (Nash et al., 1997). The acute phase of SCI may therefore be associated with decreases in vascular resistance, but in the following weeks and months, the resolution of spinal shock as well as the progression of muscular and vascular atrophy, may override the diminution of neurovascular control and thus, result in increased vascular resistance below the level of injury.

Nevertheless, there remains a certain amount of discrepancy in the literature regarding this issue, as both increases (Hopman et al., 2002; Walden et al., 1991) and decreases (Karlsson et al., 1998) in peripheral vascular resistance have been found to accompany SCI. Differences in findings may be accounted for by the injury level of the participants as well as their exercise habits. In a study conducted by Karlsson et al. (1998), leg vascular resistance was found to be reduced by approximately 40% in individuals with complete lesions (C7-T4), but no data were provided on their exercise habits. In contrast, Hopman and colleagues (2002) found leg vascular resistance to be increased by approximately 3-fold in a sedentary group of individuals with complete injuries between T4 and T12.

Clinically, increased vascular resistance and decreased peripheral blood flow are problematic for individuals with SCI as they may contribute to delayed wound healing (Walden et al., 1991) and an increased risk of pressure sore (Walden et al., 1991) and thrombus formation (Mammen, 1992; Nash et al., 1996).

3.3 Vascular compliance

Arterial compliance refers to the degree to which its internal diameter may deform in response to alterations in intravascular pressure, and is related to the elastic properties of the vessel wall. Functionally, vessel compliance acts to convert intermittent blood flow from the heart to a more steady flow throughout the circulation. Further, the ability to deform allows the vessel to withstand pulsatile increases in blood volume without experiencing undue increases in stress (Arnett et al., 1994). Arterial compliance can be expressed as the change in vessel diameter per change in arterial pressure from diastole to systole, and it is determined by both structural and functional aspects of the vessel wall. Specifically, arterial compliance is governed by the elastic content of the arterial wall, endothelial function, and smooth muscle properties (Arnett et al., 1994). Stiffness of the vessel will therefore increase with the proportion of collagen in relation to elastin, as well as with smooth muscle tone or hypertrophy (Arnett et al., 1994). As the vessel stiffens it loses its ability to expand during systole and recoil during diastole, resulting in increased systolic pressures and decreased diastolic pressures. Thus, increases in pulse pressure are often used as indirect measures of arterial stiffness. Likewise, when all else is equal, blood will travel more quickly through a stiffer vessel, and thus, increases in pulse wave velocity may be indicative of lower arterial compliance. More direct measures of vessel elasticity, however, are afforded by the coupling of imaging techniques and blood pressure measurements, such that changes in vessel diameter per unit change in blood pressure can be more directly determined.

The relationship between arterial compliance and cardiovascular risk has recently gained a great deal of attention (Kingwell, 2002; Safar, 2001; Seals, 2003). The chronic elevations in systolic blood pressure that accompany vessel stiffening may cause vascular damage leading to atherosclerosis and thus, an increased risk of thrombosis, myocardial infarction and stroke (Seals, 2003). In addition to vascular damage, decreases in arterial compliance may have a deleterious effect on the heart. As mentioned, vessel stiffness causes the ejected pressure wave to travel more quickly through the arterial system, and as a result, the reflected pressure wave returns prematurely to the heart. Normally, the reflected pressure wave returns just after aortic valve closure, in early diastole, and causes a relative increase in diastolic pressure and coronary perfusion. In contrast, prematurely reflected pressure waves arrive at the heart during systole, and therefore increase the pulsatile load on the heart. In this way, vessel stiffness increases the demand on the heart while decreasing coronary perfusion (Mitchell, 1999).

Finally, a reduction in arterial compliance may reduce the effectiveness of the arterial baroreceptors that respond to stretch. Chronic reductions in the cardiovagal arm of the baroreflex arc may, as previously discussed, increase susceptibility to ventricular fibrillation and sudden cardiac death (Seals, 2003).

In accordance with findings of vascular and cardiac damage that result from increases in vessel stiffness, several studies have established the reduction in arterial compliance as an independent risk for cardiovascular mortality. The relationship between vessel stiffness and cardiovascular risk has been demonstrated in both hypertensive (Fang et al., 1995) and normotensive (Benetos et al., 1998) individuals when considering either

the aorta (Blacher et al., 1999) or carotid artery (Blacher et al., 1998) or more peripheral vessels such as the brachial artery (Millar et al., 1999).

Presently, there is a paucity of literature regarding the effects of SCI on arterial compliance. However, one study conducted by Schmidt-Truckass et al. (2000) did find a significantly reduced compliance of the femoral and carotid arteries in individuals with chronic paraplegia compared to sedentary and trained able-bodied individuals (reductions of 40% and 70% in the femoral artery, and 38% and 50% in the carotid artery, respectively). Schmidt-Truckass and colleagues did not determine if the reduced arterial compliance in those with SCI was associated with impaired central hemodynamics, although they did determine that there was no associated increase in intima-media thickness.

4. Cardiovascular response to orthostatic stress in the able-bodied and after spinal cord injury

The maintenance of upright posture, be it active (standing) or passive (head-up tilt), may seem effortless, however, it requires a complex response from the cardiovascular system that may be impaired after SCI. If left unopposed, the effect of gravity would cause an excessive displacement of blood downward and away from the heart, and as a result venous return and cardiac output would be insufficient to prevent syncope. The able body therefore responds to orthostatic stress with a baroreceptor-mediated sympathetic response causing vasoconstriction of the splanchnic vascular bed, as well as skeletal muscle, kidney, and skin vasculature, and an increase in cardiac contractility (Rowell, 1986). Vagal withdrawal may also cause an increase in heart rate,

and veno-arteriolar reflexes may also add to the existing vasoconstriction. As a result of this complex dynamic, total peripheral resistance is increased and although venous return, stroke volume and cardiac output are somewhat decreased, excessive reductions are prevented. Importantly, by these adaptations, mean arterial pressure is maintained or even slightly increased during postural stress (Rowell, 1986). During active standing, the tone in the postural muscles may also act to maintain venous return and mean arterial pressure, however, during passive upright posture such as head-up tilt, this mechanism is not a significant factor (Amberson, 1943). It is important to note that peripheral vasoconstriction plays a larger role in maintaining mean arterial pressure during postural stress than the increases in heart rate and contractility. For example, autonomic blockade of the heart has been shown to further decrease cardiac output during head-up tilt, but has no effect on mean arterial pressure (Tyden, 1977).

As stated previously, SCI is characterized in part by a disconnection of preganglionic sympathetic fibres from higher centres, and as a result, individuals with SCI may have difficulty coping with postural stress. The degree of orthostatic intolerance, however, may be dependent on the level and severity of the SCI.

In individuals with paraplegia, a disconnection between higher centres and sympathetic preganglionic neurons may be expected in the lower limbs, and depending on the lesion level, in some portion of the viscera. Despite this deficit however, individuals with paraplegia exhibit the normal hemodynamic response to postural stress (Houtman et al., 2000; Kooner et al., 1988; Theisen et al., 2000). For example, Houtman et al. (2000), found individuals with complete paraplegia (T4-T8) to exhibit the normal

slight rise in mean arterial pressure when subjected to 70° head-up tilt, which did not differ significantly from that exhibited in an able-bodied control group. The maintenance of blood pressure was particularly interesting in this injured group, since a compromised control of sympathetic outflow to the splanchnic vascular bed and the adrenal medulla, in addition to the leg vasculature, could be expected. Further, the maintenance of mean arterial pressure could not have been attributed to the spared sympathetic outflow to the heart, as both stroke volume and cardiac output decreased in the normal fashion upon postural stress. Rather, increases in total peripheral resistance, despite the sympathetic decentralization, were found to be the likely cause of the maintained mean arterial pressure.

The mechanisms accounting for the noted increases in peripheral resistance during orthostatic stress in individuals with paraplegia are not fully understood. In a study conducted by Theisen and colleagues (2000), individuals with both high (T5-T9) and low (T10-T12) paraplegia exhibited the normal rise in mean arterial blood pressure upon postural stress, and in both groups there was evidence of lower limb vasoconstriction via a venoarteriolar reflex. In addition, there is evidence to suggest a lesser degree of venous "pooling" in the lower limbs of individuals with paraplegia compared to the able-bodied during an equivalent orthostatic stress (Raymond et al., 1999). This may be due to vascular atrophy, a reduction in venous compliance and an increase in resistance to venous flow that prevents excessive venous "pooling" of blood (Hopman et al., 1994; Martin et al., 1992; Olive et al., 2003).

It is somewhat confusing that individuals with tetraplegia do not show the normal hemodynamic response to orthostatic stress (Houtman et al., 2000; Kooner et al., 1988). Unlike the able-bodied and individuals with paraplegia, those with tetraplegia exhibit a significant reduction of mean arterial pressure during postural stress, accompanied by greater increases in heart rate (likely via vagal withdrawal), greater decreases in stroke volume, and thus a similar reduction in cardiac output (Houtman et al., 2000). Further, unlike the able-bodied and individuals with paraplegia, those with tetraplegia exhibit reductions in total peripheral resistance during postural stress. While the absence of tilt-induced increases in vascular resistance may seem intuitive due to the sympathetic decentralization, it is unclear why individuals with tetraplegia and individuals with high paraplegia (above T6) display differing responses to postural stress. Both groups presumably have a compromised sympathetic innervation to the lower limb vessels as well as the splanchnic vascular bed, and as stated, both show similar and significant reductions in cardiac output during head-up tilt despite the putative intact sympathetic innervation to the heart in those with mid to high-thoracic paraplegia alone. Further, there is evidence for an intact venoarteriolar reflex as well as spinal sympathetic reflexes in individuals with tetraplegia during postural stress (Skagen, 1983). It is possible that norepinephrine spillover from the heart that is expected in individuals with paraplegia but not tetraplegia, may lead to increases in total peripheral resistance and the maintenance of mean arterial pressure during postural stress. Still, this proposed mechanism may be too slow to account for the orthostatic tolerance that has been observed in individuals with paraplegia. Thus, future research is needed to determine mechanisms behind the normal

hemodynamic response in individuals with high-level paraplegia and the abnormal response in those with tetraplegia during orthostatic stress.

5. The effects of exercise training on cardiovascular regulation

5.1 Heart rate variability

In the able-bodied population it is well established that aerobic exercise training is associated with increased cardiac vagal outflow, as illustrated by the frequently observed training-induced bradycardia at rest, and enhancements of heart rate variability measures indicative of resting cardiac parasympathetic tone (De Meersman, 1993a; De Meersman 1993b, Dixon et al., 1992; Melanson and Freedson, 2001; Seals and Chase, 1989). With respect to frequency domain measures of heart rate variability, cross sectional studies have shown significantly lower LF:HF ratios in aerobic athletes compared to healthy sedentary controls (Dixon et al., 1992). In addition, longitudinal studies have shown training-induced decreases in the LF:HF ratio in able-bodied individuals, be they healthy (Tulppo et al., 2003) or suffering from cardiac disease (Malfatto et al., 2002; Taylor et al., 2003). For example, individuals with heart failure experienced a 36% reduction in the LF:HF ratio after six months of low-intensity (40-50% VO_{2max}) exercise training (Malfatto et al., 2002), while healthy middle-aged individuals showed reductions in the LF:HF ratio of approximately 25% after 8 weeks of moderate intensity exercise training (Tulppo et al., 2003).

Unfortunately, it can only be speculated that such shifts in cardiac autonomic balance actually conferred a reduced risk of cardiovascular mortality in the trained individuals. However, work in animals has shown an association between the training-

induced shift towards cardiac vagal predominance and a reduced risk of cardiac mortality. Specifically, in a study conducted by Hull et al. (1994), dogs without MI, but at high risk as indicated by the occurrence of ventricular arrhythmia during acute ischemia, completed six weeks of daily exercise. Following the training program, the dogs exhibited a significant increase in heart rate variability, indicative of vagal predominance, which was accompanied by the disappearance of ventricular fibrillation during a new trial of myocardial ischemia during an exercise stress test.

Currently, there are no published studies that have examined the effects of exercise training on heart rate variability measures in individuals with SCI. Thus, it has yet to be determined if the damage that is sustained to the autonomic nervous system during SCI precludes the achievement of positive exercise-induced adaptations in this population. Such adaptations would be particularly desirable in individuals with SCI, as they have been identified as a group with increased risk of cardiovascular disease (DeVivo et al., 1993). If the body does in fact, strive to maintain cardiac autonomic balance after SCI (Grimm et al., 1995; Grimm et al., 1997; Wang et al., 2000), then it is possible that the depressed sympathetic limb may prevent exercise-induced enhancements in parasympathetic outflow to the heart. On the other hand, if the observed reductions in cardiac vagal tone after SCI are coincidental to the sympathetic damage, and simply a reflection of generally lower activity levels in this population, then perhaps exercise-induced enhancements in cardiac autonomic control may be expected.

5.2 Blood pressure variability

The literature is relatively scarce with respect to the effects of exercise training on measures of blood pressure variability, and what does exist is somewhat equivocal. In a cross-sectional study conducted by Shin et al., (1995) athletes (VO_{2max} > 55 ml/kg/min) were found to have lower LF:HF ratios for heart rate variability compared to non-athletes (VO_{2max} < 45 ml/kg/min), but the groups did not differ significantly in terms of blood pressure variability measures. In contrast, more recent longitudinal studies have found exercise-induced decreases in the LF component of blood pressure variability in both the healthy population (Portier et al., 2001) and in those with hypertension (Taylor et al., 2003). Specifically, older adults with hypertension reduced the LF power of systolic blood pressure variability by nearly 30% after 10 weeks of low intensity handgrip training (Taylor et al., 2003), while marathon runners were found to have an approximate 17% reduction in LF power of systolic blood pressure variability after the training portion of their season (Portier et al., 2001). Thus, exercise-induced changes in blood pressure variability may be possible in a wide spectrum of people, regardless of initial blood pressure, age or fitness levels. Again, however, it is inconclusive whether these changes in blood pressure variability were actually associated with a reduced risk of cardiovascular mortality, although such a hypothesis would be reasonable considering the data from other experiments (Frattola et al., 1993).

It is currently unknown if individuals with spinal cord injury can experience training-induced improvements in blood pressure variability, or if the sympathetic decentralization that is characteristic of this population would prevent such changes. On a

positive note, the fact that Portier and colleagues (2001) observed training-induced changes in blood pressure variability in endurance athletes, suggests that the lower baseline blood pressures and sympathetic activity that are also common after high SCI may not prevent this population from similar training-induced improvements in blood pressure variability. Further, data from SAD rats, as previously mentioned, suggests that reductions in blood pressure variability are associated with a decreased risk of cardiovascular mortality even in those with relatively low baseline blood pressures (Miao and Su, 2002; Sasaki et al., 1994).

5.3 Vascular properties

In the able-bodied population, exercise training has long been associated with positive adaptations in the properties of the peripheral vasculature. Several cross-sectional studies have shown an association between activity and the luminal size of large conductance arteries such as the femoral artery (Dinenno et al., 2001; Schmidt-Truckass et al., 2003; Wijnen et al., 1991), as well as an improved arterial compliance (Tanaka et al., 2000; Vaitkevicius et al., 1993). Longitudinal studies have provided further evidence for a cause and effect relation between exercise training and improved vascular properties. For example, three months of aerobic exercise (primarily walking) was found to significantly increase femoral artery lumen diameter by 9% (Dinenno et al., 2001), and carotid artery compliance by 25% (Tanaka et al., 2000) in middle-aged men. While the former investigation showed no corresponding training-induced increase in resting muscle blood flow, other studies have shown such an adaptation (Sinoway et al., 1986).

Recently, investigations have begun to show that individuals with SCI are capable of making similar exercise training-induced adaptations in vascular properties. In a study conducted by Gerrits et al. (2001), individuals with SCI of varying levels and severities performed functional electrically stimulated leg cycle ergometry (FES-LCE) for six weeks. Following the training protocol, Doppler ultrasound measures revealed significant exercise-induced increases in femoral artery diameter of 8%, and resting mean inflow volume of 37%. In addition, resting femoral artery velocity index (an estimate of arterial resistance) displayed a significant decrease of 8%. No changes were noted, however, in the carotid artery. Similarly, Hopman et al. (2002), showed an approximate 30% increase in leg blood flow, and an approximate 30% decrease in leg vascular resistance after six weeks of FES-LCE in individuals with complete SCI. Finally, perhaps the most notable exercise-induced changes were shown in a study by Nash et al. (1997) involving 12 individuals with complete paraplegia. Following the 32 sessions of electrically stimulated ambulation exercise, the participants in that study showed a significant 33% increase in femoral artery cross-sectional area, accompanied by a significant 56% increase in resting femoral artery blood flow. To date, there are no published studies describing the effects of exercise on vascular compliance in individuals with SCI, despite the fact that recent work has demonstrated this population to show increased arterial stiffness in the femoral and carotid arteries compared to sedentary able-bodied controls (Schmidt-Truckass et al., 2000).

6. Body-weight supported treadmill training as a means of improving cardiovascular regulation in individuals with spinal cord injury

In the last decade, body-weight supported treadmill training (BWSTT) has shown promise as a means of enhancing and even restoring gait in individuals with incomplete spinal cord injury (SCI) (Barbeau et al., 1993; Protas et al., 2001; Wernig et al. 1992; Wernig et al. 1995; Wernig et al. 1999). Improvements in ambulatory capacity following BWSTT have included a greater weight bearing capacity, increases in walking speed and endurance and an enhanced gait pattern during BWSTT (Barbeau et al. 1998), and in some cases, an increased ability to walk over ground (Wernig et al., 1995).

In brief, BWSTT entails suspending an individual, with the use of a harness, above a motorized treadmill. Counterbalances, attached to the harness via a pulley system allow any percentage of the individual's body weight to be supported while therapists assist in the production of gait (Appendix B). To date, there are no published studies regarding the effects of BWSTT on cardiovascular regulation in individuals with SCI. Such research is certainly warranted since the SCI population has an increased risk of many types of cardiovascular disease and mortality (DeVivo et al., 1993), and further, BWSTT may be a particularly promising means of improving cardiovascular health and fitness in this group. BWSTT is an upright exercise that utilizes the large leg muscles, and thus may provide a greater cardiovascular challenge than more traditional forms of aerobic training for individuals with SCI such as arm ergometry. Further, the supporting or partial supporting of an individual's body weight allows a prolongation of exercise duration, which may be required to realize maximal cardiovascular benefit. Finally,

although FES cycling (Gerrits et al., 2001; Hopman et al., 2002) and FES ambulation (Nash et al., 1997) have shown a great deal of promise as exercise training stimuli, they both have disadvantages that are avoided in BWSTT. First, exercise involving electrical stimulation carries the risks of pain (in those with spared sensory function) and burns to the skin and autonomic dysreflexia (Jacobs and Nash, 2001), which are not concerns in BWSTT. Second, as FES ambulation requires the use of a walker it may not be a viable option for many individuals with SCI who lack the required trunk, arm and hand strength, and in fact, this training modality has only been shown of benefit in individuals with complete paraplegia. As BWSTT uses a harness as a means of supporting body weight and maintaining upright posture, individuals of all injury types may perform this mode of exercise. In contrast, the somewhat passive limb movement involved in BWSTT may not provide the same cardiovascular stimulus as either arm ergometry or electrically stimulated exercise, and therefore, may not result in equal cardiovascular benefits. Thus, further research investigating the effects of BWSTT on cardiovascular regulation in individuals with SCI is certainly warranted.

Summary

Individuals with SCI are susceptible to an array of physiological and psychological consequences, many of which stem form the damage sustained to the autonomic nervous system during injury. One such consequence is the altered control of the cardiovascular system and the increased risk of various cardiovascular diseases. However, while epidemiological studies have certainly established the increased risk of cardiovascular mortality and dysfunction that accompanies SCI, the mechanisms that

account for these consequences have yet to be fully understood. In recent decades, various techniques have been established that may help to uncover the full effects of SCI on cardiovascular regulation. In particular, power spectral analysis of HRV and BPV may be used to determine the autonomic control of the cardiovascular system, while Doppler ultrasound techniques may be used to determine the dimension and function of the peripheral vessels.

The importance of exercise rehabilitation for individuals with SCI is becoming increasingly clear as a means of improving the function and the quality of life of this population. Still, there is much that remains unknown regarding the role of exercise training as a means of decreasing the risk of cardiovascular disease in individuals with SCI. In addition, the exercise options that currently exist for individuals with SCI are limited, and the modalities that are available have various shortcomings that either restrict their effectiveness or their suitability to certain injury types. For example, arm ergometry may be an effective means of improving central cardiovascular fitness in individuals with sufficient arm function, but it is ineffective in reversing the peripheral vascular deficits that accompany SCI. Further, FES exercise may be very effective in improving cardiovascular health after SCI, however, this method may not be tolerated by many due to the associated risks of pain, skin irritation and autonomic dysreflexia. As an alternative, BWSTT may be an effective and well-tolerated means of reversing central and peripheral cardiovascular deficits in individuals with complete and incomplete SCI.

Objectives and hypotheses of the present thesis

The remainder of this thesis is organized into 5 chapters. The first 4 are presented in a format suitable for submission to a scientific journal and each, in general, addresses the issues of cardiovascular regulation after SCI and the effects of exercise training as a means of improvement. The final chapter serves as a general discussion and suggests ideas for future research. The purpose and objectives of the following 4 chapters are outlined below.

Chapter 2: *Reproducibility of heart rate variability and blood pressure variability in individuals with spinal cord injury*

Measures of HRV and BPV have become commonly used indices of neurocardiac and neurovascular control and valid predictors of cardiovascular risk. The use of these measures may therefore, have clinical value to the SCI population as a means to assess autonomic damage after injury and the resulting propensity toward cardiovascular mortality and dysfunction, as well as assessing potential changes in autonomic regulation that may result from exercise or drug therapies. The purpose of this study was to test the day-to-day reproducibility of frequency domain measures of HRV and BPV obtained from short-term recordings in individuals with SCI. It was hypothesized that despite the autonomic dysfunction that accompanies SCI, measures of HRV and BPV would be reproducible in this population.

Chapter 3: *The effects of exercise training on heart rate variability in individuals with SCI*

In the able-bodied population the effects of exercise training on the autonomic control of the heart are well-established, as several investigations have shown exercise-induced changes in HRV indicative of increased parasympathetic tone. However, it is currently unknown if individuals with SCI retain the ability to make exercise-induced changes in cardiac autonomic control. The purpose of this pilot study was to examine the effects of 3 months of arm ergometry and resistance training on resting measures of HRV in individuals with incomplete tetraplegia. It was hypothesized that individuals with SCI would respond to exercise training with a relative shift towards cardiac vagal predominance at rest.

Chapter 4: *The effects of body-weight supported treadmill training on heart rate variability and blood pressure variability in individuals with SCI*

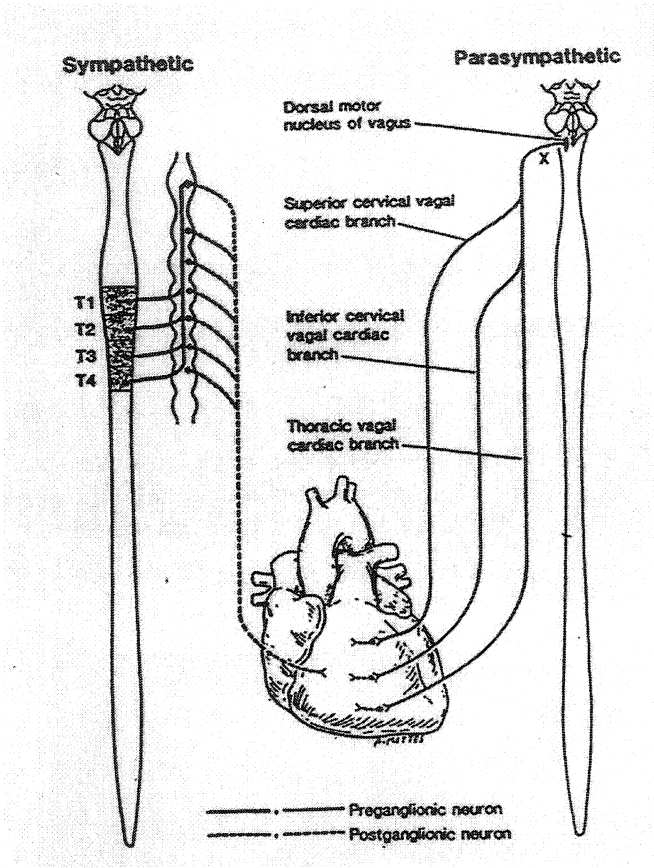
BWSTT has shown promise as a means of enhancing ambulation in individuals with incomplete SCI, however, the cardiovascular benefits that may be conferred with this mode of exercise have not been investigated. BWSTT may also have particular promise in this respect as it is an upright exercise that utilizes the large leg muscles, and further, it may not carry the risks associated with FES exercise. The purpose of this study was to examine the effects of a 6-month BWSTT program on measures of HRV and BPV in individuals with incomplete tetraplegia. It was hypothesized that individuals with SCI would respond to exercise training with a relative shift towards cardiac vagal predominance and decreases in BPV at rest. Further, it was hypothesized that these

positive adaptations would not come at the cost of a decreased tolerance of postural stress.

Chapter 5: *The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI*

BWSTT has shown promise as a means of improving ambulation in individuals with incomplete SCI, however, individuals with motor-complete SCI have not shown the same improvements and are therefore, generally excluded from this form of therapy. This exclusion may be unfortunate as BWSTT may be an ideal means to improve the cardiovascular health and function of these individuals. The purpose of this study was to examine the effects of a 4-month BWSTT program on measures of cardiovascular regulation in individuals with motor-complete SCI. It was hypothesized that BWSTT would result in an increased size, and a decreased resistance of the common femoral artery as well as a corresponding increase in resting femoral artery blood flow. In addition, increases in femoral artery compliance were expected, as were modest positive changes in measures of HRV and BPV. Finally, due to the more severe sympathetic decentralization that often accompanies motor-complete SCI, it was hypothesized that changes in femoral resistance would also result in an increased susceptibility to orthostatic intolerance.

Figure 1. Autonomic Innervation of the Heart



From Hockman, 1987.

Figure 2. R-R intervals

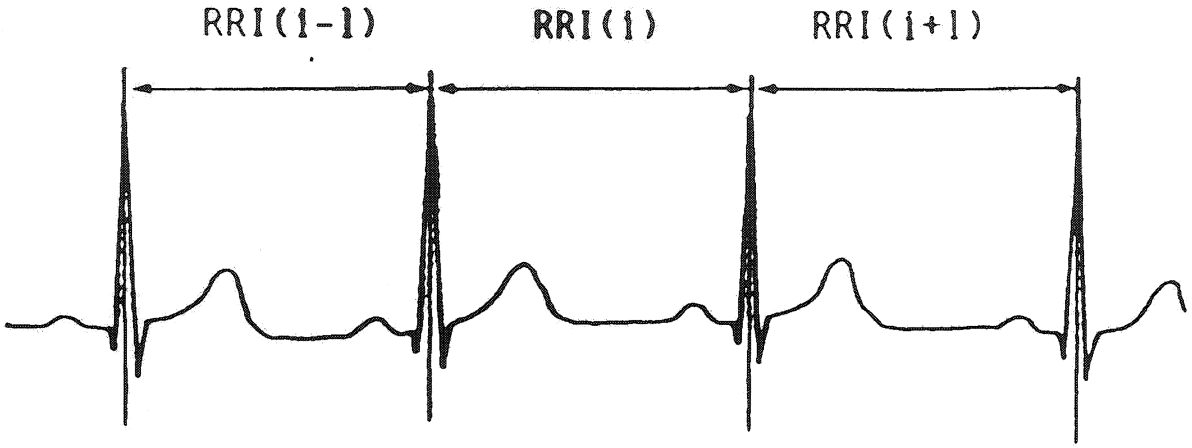


Figure 3. Tachogram obtained from an individual (male, age 24) with incomplete tetraplegia (C5, ASIA C, 24 years post injury, i.e. injured at birth) during supine resting conditions.

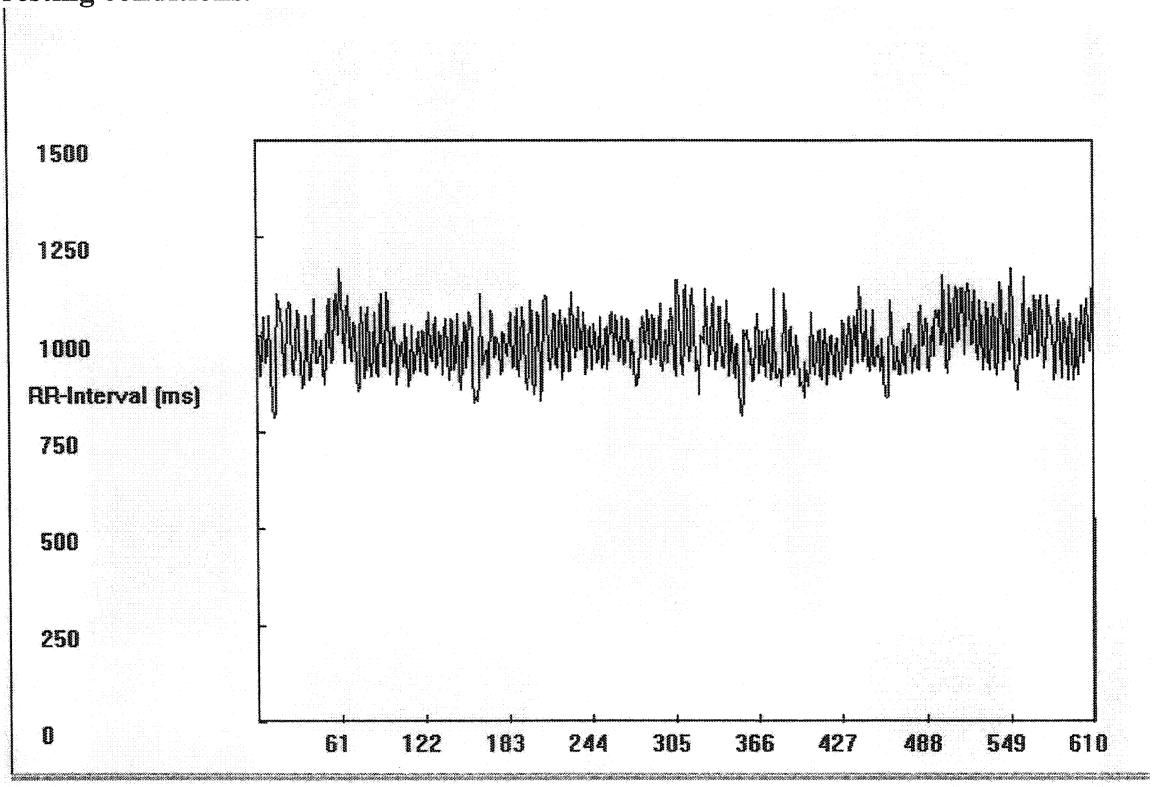
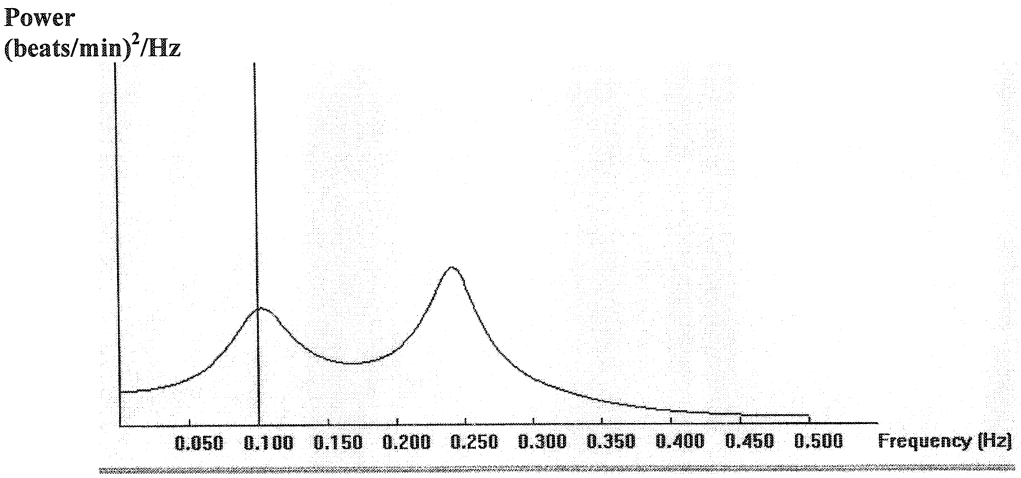


Figure 4. Power Spectrum obtained from an individual (male, age 24) with incomplete tetraplegia (C5, ASIA C, 24 years post injury, i.e. injured at birth) during supine resting conditions.



HR: 61.7 beats/min

LF Power: 4895 $(beats/min)^2$

HF Power: 6655 $(beats/min)^2$

LF:HF ratio 0.74

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Chapter 2

Reproducibility of heart rate variability and blood pressure variability in individuals with spinal cord injury

PREPARED FOR:

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Abstract

The purpose of this study was to examine the day-to-day reproducibility of resting heart rate variability (HRV) and blood pressure variability (BPV) measures in individuals with spinal cord injury (SCI). Ten individuals (6 male, 4 female; age 35.9 ± 13.2 yrs) with chronic (5.4 ± 7.7 yrs post injury) SCI (C4-T12; ASIA A-C) participated. On two separate occasions within a two-week period, 10-minute supine electrocardiogram (ECG) and Finapres blood pressure recordings were obtained from each participant during spontaneous breathing. Computer software identified RR-intervals and beat-to-beat values of systolic and diastolic blood pressure, and subsequently calculated frequency domain measures of HRV and BPV (Low frequency (LF) power, High frequency (HF) power, and the LF:HF ratio). Intraclass correlations coefficients were then calculated as an index of day-to-day reproducibility, and analyses were conducted on all participants grouped together, as well as on the group of individuals with tetraplegia only. For HRV, measures of heart rate, LF, and LF:HF were found to be highly reproducible with intraclass correlation coefficients ranging between 0.82 to 0.88, however, reproducibility of HF was found to be poor (all participants: 0.53, tetraplegia: 0.66). Measures of blood pressure and systolic BPV also showed high reproducibility, with intraclass correlation coefficients ranging between 0.72-0.93. Measures of diastolic BPV were somewhat less reproducible, but still generally good. Thus, despite the autonomic dysfunction that commonly follows SCI, the measures of HRV and BPV may still be used as reproducible indices of autonomic cardiovascular regulation in this population.

Introduction:

Power spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV) have become commonly used, non-invasive methods to quantify the autonomic control of the cardiovascular system (Akselrod et al., 1981; Kamath et al., 1993; Pagani et al., 1997; Parati et al., 1995). With respect to HRV, successive R-R intervals obtained from electrocardiogram (ECG) recordings have been shown to oscillate around two main frequencies. Various investigations have determined that the high frequency oscillation, centred around 0.25 Hz (HF_{HR}; 0.15-0.40 Hz) corresponds to parasympathetic outflow to the heart via the vagus nerve (Pomeranz et al., 1985). The low frequency oscillation, centred around 0.1 Hz (LF_{HR}; 0.04-0.15) has been shown to correspond to both the sympathetic and parasympathetic outflow to the heart, although it is much more indicative of the former (Montano et al., 1994; Pomeranz et al., 1985). Thus, the LF:HF ratio of HRV has become an accepted measure of cardiac sympathovagal balance.

Beat-to-beat variations in systolic and diastolic blood pressure (SBP, DBP) have also been shown to oscillate around two main frequencies, although the physiological correlates of these oscillations differ importantly compared to the frequency measures of HRV. The LF oscillation of systolic and diastolic BPV (LF_{SBP}, LF_{DBP}; 0.04-0.15 Hz), also referred to as Mayer waves, has been shown to correspond to neurovascular control via the sympathetic nerves (Pagani et al., 1997; Parati et al., 1995). The HF oscillation (HF_{SBP}, HF_{DBP}; 0.15-0.40 Hz) is not thought to have a direct autonomic correlate, as there is no vagal outflow to the vasculature. The HF components of BPV are therefore thought

to represent the mechanical effects of respiration which may act directly on the pressure gradients of the intrathoracic vessels (Pagani et al., 1986).

Measures of HRV and BPV have been shown to be valid and independent predictors of all cause, and cardiac mortality. In general, shifts in HRV away from vagal predominance and toward sympathetic predominance increase the risk of cardiovascular events (Algra et al., 1993; Kleiger et al., 1987; Lanza et al., 1997), and increases in BPV are associated with increases in end organ damage (Frattola et al., 1993; Miao and Su, 2002). Conversely, exercise training and increases in aerobic fitness are associated with i) shifts toward cardiac parasympathetic predominance, as commonly noted by decreases in the LF:HF ratio (Malfatto et al., 2002; Tulppo et al., 2003), and ii) decreases in the LF component of BPV (Taylor et al., 2003). Thus, measures of HRV and BPV are attractive means to evaluate changes in cardiovascular health and fitness in response to various interventions including exercise training. The true efficacy of HRV and BPV measures in this respect, however, hinge largely on their day-to-day reproducibility, and as such several investigations have been published in this area in both healthy individuals (Marks and Lightfoot, 1999; Dimier-David, 1994) and those with cardiovascular disease (Freed et al., 1994). For example, the reproducibility of frequency domain measures of HRV derived from short-term (5 min) ECG recordings was recently determined by Marks and Lightfoot (1999) in young healthy women. The intraclass correlations between days showed a good reproducibility for the frequency domain measures in general, with the reproducibility of the LF:HF ratio exhibiting particularly high values. Likewise, Freed and colleagues (1994), showed frequency domain measures of HRV to be highly

reproducible in a group of older adults with cardiovascular disease, while others have found high reproducibility for frequency domain measures of BPV obtained from short term (5 min) finger plethysmography (Finapres) recordings in young healthy men and women (Dimier-David et al., 1994).

Individuals with spinal cord injury (SCI) may suffer from severe alterations in the autonomic control of the cardiovascular system, as the preganglionic sympathetic fibres that originate in the spinal cord (T1-L2) may be damaged during trauma, or simply disconnected from the influence of higher centers. Individuals with mid-thoracic injuries (T6) likely suffer from some loss of adrenergic innervation to the blood vessels of the abdomen and lower limbs, while those with cervical and high thoracic injuries may also have varying degrees of compromised cardiac sympathetic innervation (Strack et al., 1988). Studies examining HRV and BPV in individuals with SCI have verified this reduction in sympathetic tone (Grimm et al., 1997; Inoue et al., 1991; Wang et al., 2000). Interestingly, parasympathetic outflow to the heart has also been shown to be compromised after SCI, and some have suggested that the reductions in cardiac sympathetic outflow that accompany SCI may cause compensatory reductions in cardiac vagal outflow in order to maintain autonomic balance (Grimm et al., 1997; Wang et al., 2000). Regardless of the mechanism, reductions in cardiac parasympathetic tone may be problematic for individuals with SCI, as vagal withdrawal has been associated with cardiac events, and individuals with SCI have been shown to be at increased risk of cardiovascular mortality (DeVivo et al., 1993). The reduction in sympathetic tone is also

problematic as it contributes to the reduced exercise capacity, as well as the orthostatic intolerance that is often observed in individuals with high SCI (Houtman et al., 2000).

The use of HRV and BPV measures may, therefore, be of particular interest in the SCI population, as they may be used to assess autonomic damage after injury and the resulting propensity toward both orthostatic intolerance, and possibly the risk of cardiovascular disease. Further, the effectiveness of various exercise or drug interventions designed to alleviate such deficits in the SCI population may be evaluated via HRV and BPV measures. However, before such evaluations can be made, the reproducibility of HRV and BPV must be determined in individuals with SCI. Thus, the purpose of the present study was to test the day-to-day reproducibility of frequency domain measures of HRV and BPV obtained from short-term recordings in individuals with SCI.

Methods:

Participants

Ten individuals (6 male, 4 female; age 35.9 ± 13.2 yrs.) with chronic SCI (C4-T12; ASIA A-C; 5.4 ± 7.7 yrs. post injury) were included in the present investigation. Participants were recruited from an out patient spinal cord injury clinic located at Chedoke Hospital in Hamilton, Ontario, and the severity and level of injury were determined by neurological examination conducted by a qualified physician. Participants were only included if they were at least six months post injury and were free of any coincident cardiac disease. This investigation was approved by the McMaster Research

Ethics Board (MREB), and all participants provided written informed consent in accordance to MREB guidelines. Participant characteristics are summarized in Table 1.

Protocol

Continuous recordings of ECG and BP data were obtained from each participant on two separate occasions (Day 1 and Day 2) within a 14-day period, and no two sessions for any participant were less than one week apart. Day 1 and Day 2 sessions were conducted at the same time of day (approximately 12:30-2:30 pm), and participants were instructed to abstain from caffeine and cigarette smoking for at least 12 hours prior to testing. All participants were also two hours post-prandial, and had abstained from exercise for at least 24 hours at the time of data collection. Medications were not interrupted for data collection, however, medications and dosages were identical on Day 1 and Day 2 for each participant.

Upon entering the laboratory, each participant was asked to empty his or her urine bag, then transferred onto a table and fitted with a Polar heart rate monitor and a finger plethysmograph (Finapres) cuff (Ohmeda 2300, Madison, WI). Participants lay quietly for 10 minutes prior to the 10-minutes of data collection, which took place in a dark, quiet, temperature controlled room. Data were recorded during supine rest and spontaneous breathing, and participants were asked to remain awake, and as still and quiet as possible during the recording sessions. Anti-embolic stockings and abdominal binders were not worn by any of our participants during the data collection session.

ECG and BP data acquisition

ECG and blood pressure signals were sampled at 500 Hz using a 12 bit analog-digital converter (CODAS, DATAQ Inc., Akron, OH). The signals were continuously and simultaneously displayed on an IBM computer using WINDAQ data acquisition software (Dataq Instruments). The HR and BP recordings were saved on the computer's hard drive and transferred to a separate computer equipped for HRV and BPV analysis.

Data analysis

Computation of HRV and BPV

A customized software program (MATLAB) (Kamath et al., 1998), was used to identify a stable and noise independent fiducial point on all R-waves for each recording, as well as beat-to beat values of systolic and diastolic blood pressure. An RR-interval tachogram, as well as separate SBP and DBP tachograms, were then generated from the continuous ECG and blood pressure data, respectively. All tachograms were then inspected for ectopic beats which were subsequently removed using a linear interpolation algorithm (Kamath et al., 1998). When files were found to contain excessive ectopic beats (>5/min), the investigator visually inspected the tachogram for a sufficiently long period of relatively ectopic-free segments of HR and BP data for further analysis. Beat-to-beat heart rate and blood pressure variability signals were then computed, and resampled at 2 Hz using linear interpolation to obtain equally sampled time series. For each data set, 4 record lengths of 128 sec were selected automatically for power spectral analysis. The mean value of the heart rate and blood pressure signals were removed and the equally sampled HRV and BPV signals were fed through a second order high pass

Butterworth filter with a cut-off of 0.02 Hz. Power spectra were then computed from the filtered HRV an BPV signals using previously described software (Kamath et al., 1998). The data analysis software used allowed the investigator to accept or reject any of the 4 power spectra produced for each data set. Thus, the investigator could reject power spectra showing a fusion of the LF and HF peaks, which sometimes, albeit rarely, occurred during spontaneous breathing. Final frequency domain measures represent the average of all accepted record lengths. Oscillations ranging between 0.04-0.15 Hz were designated as LF while oscillations between 0.15-0.40 Hz were designated as HF. Peak values of the LF and HF components were identified from the HRV and BPV power spectra and expressed as $(beats/min)^2/Hz$, and $(mmHg)^2/Hz$, respectively. The power of the LF and HF components were calculated by integrating the area under each curve and expressed as $(beats/min)^2$ and $mmHg^2$. LF:HF ratios and mean heart rate were also calculated by the MATLAB program. Systolic, diastolic and mean arterial pressures (MAP = (SBP+2DBP)/3) were determined directly from the raw data tracings collected by the WINDAQ data acquisition software.

Statistical analysis

One-way analysis of variance (ANOVA) with repeated measures on the time factor were used to determine significant within-subject differences between Day 1 and Day 2 for each variable. Statistical significance was set at $p<0.05$ and throughout the text, data are presented as means ± standard deviation. Intraclass correlation coefficients (R) were computed to determine test:retest reproducibility. All statistical analyses were conducted on the entire group of participants as a whole (n=10), and separately on the

subset of individuals with tetraplegia (n=6), as the latter may be expected to have greater autonomic dysfunction due to the compromised sympathetic innervation to the heart. In one participant with paraplegia (DP), Day 2 measures of BP were not recorded due to technical problems. Therefore, data pertaining to BP and BPV correspond to n=9 when all participants are grouped together, and n=6 for those with tetraplegia.

Results:

HR and HRV measures

No significant differences were observed between days for any of the HR or HRV measures. In general, intraclass correlation coefficients showed a high reproducibility for HR, LF power and the LF:HF ratio (range: 0.82-0.88). Measures of HF power, however, showed poor reproducibility (all participants: 0.53, tetraplegia: 0.66; Table 2).

BP and BPV measures

No significant differences were observed between days for SBP, DBP or MAP, and further, intraclass correlation coefficients showed these measures to have good reproducibility, especially for the SBP and MAP measures (range: 0.72-0.93; Table 3).

No significant differences were observed between days for any of the BPV measures, and in general, intraclass correlation coefficients showed these measures to be reproducible. Specifically, measures of systolic BPV were highly reproducible when considering either all of the participants, or just those with tetraplegia (range: 0.79-0.92). Measures of diastolic BPV, although generally good, appeared to be somewhat less reproducible compared to the systolic BPV measures, especially when all participants were grouped together (Table 4).

Discussion:

The main finding of the current study is that frequency domain measures of heart rate and blood pressure variability were generally reproducible in our group of individuals with SCI. In addition the reproducibility was evident when all participants were considered as a whole, or when individuals with tetraplegia were considered separately. Thus, it would appear that sympathetic decentralization, or partial decentralization, does not adversely affect the stability HRV or BPV measures. As a standard, other investigators have suggested that reproducibility be considered "good" if intraclass correlation coefficients range between 0.60 and 0.81, and "almost perfect" if they exceed 0.81. In the present study, only HF power of HRV and the LF:HF_{DBP} ratio fell below this standard of reproducibility with intraclass correlation coefficients of 0.53 and 0.51, respectively. In addition, measures of systolic blood pressure variability appeared to be somewhat more reproducible than measures of diastolic blood pressure variability. Nonetheless, measures of heart rate and blood pressure variability in our investigation were generally found to have high day-to-day reproducibility.

As a comparison, Marks and Lightfoot (1999) showed frequency domain measures of HRV in healthy able-bodied individuals to be similarly reproducible, with intraclass correlation coefficients of 0.82, 0.67 and 0.86 for LF power, HF power and the LF:HF ratio, respectively. Similar to our results, Marks and Lightfoot (1999) also showed HF power to be somewhat less reproducible than LF power and the LF:HF ratio. The mechanisms behind such a discrepancy are unclear, and can only speculated upon. It is well established that the rate of respiration has influence over the centre frequency and

the amplitude of the HF power component (Brown et al., 1993). This being the case, it may be argued that the spontaneous breathing performed of our participants may have varied somewhat from day to day, and resulted in less reproducibility of the HF power. However, this explanation is highly unlikely for several reasons. First, although respiratory rate was not measured in the present investigation, our data analysis software did allow for inspection of individual power spectra based on ~2.5 min periods, and thus, it was possible to reject data that corresponded to obvious fusion of LF and HF peaks that occurs with lower breathing rates. Accordingly, the centre frequency of the HF component was virtually identical from Day 1 to Day 2 (0.21 ± 0.03 vs. 0.21 ± 0.03 Hz, respectively), and there were no significant differences in the HF power between days (Table 2). Second, in the study by Marks and Lightfoot (1999), participants performed paced breathing at 10-12 breaths/min on both days of testing and yet the HF component still showed a lower reproducibility than the LF component and the LF:HF ratio. It may be more likely that the poor reproducibility of HF power was due to the physiological state of the participants. In particular, in both investigations the participants were tested in the resting supine position and in the absence of any external auditory or visual stimuli. In this state, the parasympathetic system should predominate. It is possible, therefore, that the relative inactivity of the sympathetic system in the resting state is associated with a correspondingly low amount of variation. However, it should be noted, that while the participants in the study by Marks and Lightfoot (1999) certainly displayed vagal predominance (LF:HF of approximately 0.5), the participants in the present study exhibited substantial sympathetic activity despite their resting supine state (LF:HF ratio

of approximately 1.25-1.45). Thus, further research is required to determine the cause of the relatively low reproducibility of HF power. It is of interest to note that the HF power of BPV did not appear to be any less reproducible than the LF power or the LF:HF ratio, and as stated, HF power of BPV is thought to represent the mechanical effects of respiration on the pressure gradients of the intrathoracic vessels (Pagani et al., 1986). This may support the argument that the relatively low reproducibility of the HF component of HRV is unlikely to be due to mechanisms related to breathing, but rather due to mechanisms involving the vagal outflow to the heart per se.

Our findings regarding the reproducibility of BPV measures are more difficult to compare to the able-bodied population. Specifically, studies have shown frequency domain measures of BPV to be highly reproducible in healthy individuals (Cloarec-Blanchard et al., 1997; Dimier-David et al., 1994), but as intraclass correlations were not used in those investigations direct comparisons to the present study are not possible.

It is important to note that individuals with SCI above T6 may exhibit large and sudden increases in blood pressure in response to noxious stimuli below the level of the injury; a condition referred to as autonomic dysreflexia. Thus, individuals with SCI are certainly prone to a specific variation in blood pressure that is not experienced by the able-bodied population. Autonomic dysreflexia is most commonly provoked by bladder distension (Karlsson, 1999), and thus, our participants were required to empty their urine bags, and void their bladders if possible, before data were recorded. Likewise, individuals with SCI are susceptible to muscle spasticity, which may cause increases in blood pressure and heart rate. However, data were always recorded under the supervision of the

experimenter, and no participant was either seen to experience muscle spasticity during the testing sessions or report the experience of muscle spasticity when asked afterwards. Thus, although individuals with SCI are prone to physiological conditions that may periodically disturb heart rate and blood pressure, our findings strongly suggest that measures of HRV and BPV show day-to-day reproducibility in individuals with SCI when proper precautions are taken.

There are important clinical implications to the present investigation. As stated, individuals with SCI have been shown to have an increased risk of cardiovascular mortality compared to the able-bodied population (DeVivo et al., 1993). Further, the risk of certain cardiovascular diseases, as well as the reduction of risk from various drug or exercise therapies, may be predicted via the analysis of HRV and BPV measures (Algra et al., 1993; Frattola et al., 1993; Kleiger et al., 1987; Lanza et al., 1997; Miao and Su, 2002). Individuals with relatively high SCI are also prone to orthostatic intolerance, due in part to autonomic dysfunction, and measures of HRV and BPV may reflect susceptibility to this condition (Grimm et al., 1997). Thus, reliable analysis of autonomic function via HRV and BPV measures may be particularly applicable and valuable to the SCI population. The findings of the present study show for the first time, that clinicians may use short-term measures of HRV and BPV in individuals with SCI without fear of undue day-today variations, provided that simple precautions such as bladder voiding or urine bag emptying are considered.

There are also important physiological implications that are suggested by the present investigation. Specifically, there has been some debate as to the presence of LF

power of HRV and BPV (Mayer waves), in individuals with SCI. While some have found LF power in individuals with SCI and acknowledged it as physiologically meaningful (Grimm et al., 1997), other have argued that the observed LF power in individuals with SCI is simply due to sympathetic reflexes in response to stimuli below the level of injury (Inoue et al., 1995). The findings of the present study help to confirm the presence of LF power of HRV and BPV in individuals with SCI, and further, the reproducibility of these measures suggest that they are not simply the result of random stimuli, but rather, that they are physiologically relevant.

There were limitations in the present study that should be acknowledged. In particular, blood pressure data was collected with the use of a Finapres device, and blood pressure values obtained with this method may differ slightly from those obtained intra-arterially. However, studies have shown only a minimal discrepancy between the blood pressure values obtained with these two methods (2 to 3 mmHg), and further, studies have shown the Finapres to be a reliable measure of blood pressure (Parati et al., 1989).

The other notable limitation to the present study is that medications were not interrupted for the testing sessions. However, of the several medications taken by our participants, the only ones that may reasonably have affected our measures were baclofen, ditropan and detrol, which were taken for their antispastic properties. Baclofen, which was taken orally by 7 of our 10 participants, is prescribed for the treatment of muscle spasticity. Although this medication has been shown to have adverse and generally depressive effects on the cardiovascular system, the incidence of these effects are very low, usually transient and only associated with the start of treatment (CPS,

2003). Further, it may have been unethical and ill-advised to interrupt the baclofen treatment of our participants as serious side effects, including anxiety and tachycardia, are associated with abrupt baclofen withdrawal (CPS, 2003). Ditopan, which was taken by 3 of our 10 participants, and Detrol, taken by 1 of our participants, are prescribed for the treatment of bladder spasms. The incidence of cardiovascular side effects with Ditropan and Detrol usage is very rare, and in the case of the former, may not differ from placebo (CPS, 2003). Colace (stool softener), Fosamax (bone density medication) and Celexa (antidepressant) were also taken by some our participants, (3, 3 and 2 of 10, respectively), but these medications are not associated with cardiovascular side effects (CPS, 2003). Further, it should be emphasized that the medications taken by our participants, as well as the times of administration and dosages, were identical on Day 1 and Day 2. Thus, even if the medications did affect the absolute values of blood pressure or heart rate, such effects would have been identical on both testing days, and the reproducibility of our measures would not have been confounded.

Conclusions:

The present investigation is the first to show that HRV and BPV may be used as reproducible indices of autonomic regulation of the cardiovascular system in individuals with SCI, provided that precautions such as bladder emptying are addressed. In addition, the reproducibility of HRV and BPV measures in individuals with SCI suggests that the previously observed indices of sympathetic outflow in this population, such as LF power and the LF:HF ratio, are not simply the result of random stimuli below the level of injury, but rather, that they are physiologically relevant. Thus, measures of HRV and BPV may

be used by clinicians to assess autonomic function, and perhaps the risk of cardiovascular morbidity and mortality in individuals with SCI.

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Table 1. Participant characteristics

Participant	Sex	Age	Lesion Level	ASIA Clasification	Years Post Injury
1	M	57	C6	B	6
2	F	20	C6	C	1.5
3	F	26	C4	B	4.5
4	M	30	C6	B	1.5
5	M	51	T12	A	4.5
6	M	38	C5	B	0.5
7	F	45	T3	A	4.5
8	M	28	T5	A	3
9	F	45	T9	A	26.5
10	M	19	C4	B	1

Table 2. Reproducibility of heart rate and heart rate variability measures

	Day 1	Day 2	R
All participants (n=10)			
HR	59.1 ± 11.1	59.1 ± 12.2	0.88*
LF power	6517 ± 1330.2	6030 ± 1209.6	0.84*
HF power	4965 ± 1231.5	5156 ± 1116.3	0.53
LF:HF	1.45 ± 0.57	1.27 ± 0.45	0.82*
Tetraplegia (n=6)			
HR	52.8 ± 8.5	54.3 ± 13.7	0.88*
LF power	6462 ± 1355.4	6210 ± 1285.1	0.82*
HF power	4823 ± 1317.1	5550 ± 1119.4	0.66
LF:HF	1.49 ± 0.61	1.22 ± 0.46	0.82*

N.B. HR: Heart rate (beats/min); LF power: Low frequency power, HF: High frequency power $(\text{beats/min})^2$. LF:HF: Low frequency to High frequency ratio. R: Intraclass correlation coefficient. Day 1 and Day 2 data are expressed as means ± S.D. * denotes significant intraclass correlation ($p<0.05$).

Table 3. Reproducibility of blood pressure measures

	Day 1	Day 2	R
All participants (n=9)			
SBP	**109.1 ± 24.9**	**112.2 ± 24.1**	**0.93***
DBP	**55.5 ± 13.8**	**50.7 ± 14.4**	**0.72***
MAP	**73.3 ± 16.3**	**71.2 ± 14.6**	**0.92***
Tetraplegia (n=6)			
SBP	**111.4 ± 16.2**	**109.9 ± 17.7**	**0.87***
DBP	**56.0 ± 10.8**	**55.0 ± 14.7**	**0.73***
MAP	**74.4 ± 11.3**	**73.0 ± 13.1**	**0.88***

N.B. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, and MAP: Mean arterial pressure (mmHg). R: Intraclass correlation coefficient. Day 1 and Day 2 data are expressed as means ± S.D. * denotes significant intraclass correlation ($p<0.05$).

Table 4. Reproducibility of blood pressure variability measures

	Day 1	Day 2	R
SYSTOLIC			
All participants (n=9)			
LF_{SBP}	160.9 ± 47.7	165.6 ± 49.0	0.92*
HF_{SBP}	93.3 ± 47.0	88.8 ± 48.4	0.92*
$LF:HF_{SBP}$	2.61 ± 1.90	3.30 ± 3.07	0.79*
Tetraplegia (n=6)			
LF_{SBP}	162.3 ± 58.5	170.7 ± 54.3	0.93*
HF_{SBP}	91.9 ± 57.5	83.8 ± 53.5	0.94*
$LF:HF_{SBP}$	2.99 ± 2.26	3.73 ± 3.58	0.80*
DIASTOLIC			
All participants (n=9)			
LF_{DBP}	186.2 ± 24.1	195.2 ± 21.0	0.71*
HF_{DBP}	67.5 ± 23.9	59.0 ± 20.4	0.71*
$LF:HF_{DBP}$	3.95 ± 2.39	3.99 ± 1.67	0.51
Tetraplegia (n=6)			
LF_{DBP}	181.3 ± 25.5	194.0 ± 24.4	0.87*
HF_{DBP}	72.8 ± 25.1	60.2 ± 23.7	0.87*
$LF:HF_{DBP}$	3.35 ± 1.78	4.03 ± 2.00	0.89*

N.B. LF: Low frequency power, and HF: High frequency power $mmHg^2$, LF:HF: Low frequency to High frequency ratio. R: Intraclass correlation coefficient. Day 1 and Day 2 data are expressed as means ± S.D. * denotes significant intraclass correlation ($p<0.05$).

Chapter 3

The effects of exercise training on heart rate variability in individuals with SCI

PREPARED FOR:

ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION

Abstract

The purpose of this study was to examine the effects of three months of twice-weekly exercise training on the autonomic regulation of the heart in individuals with incomplete tetraplegia. Five individuals (4 male, 1 female; age 33.0 ± 9.5 yrs.) with chronic SCI (C4-C5; ASIA B-D; 10.1 ± 9.7 yrs. post injury) were included in the investigation. Ten-minute electrocardiogram (ECG) recordings were collected in both the resting supine position and during orthostatic stress (60° head-up tilt), before and after three months of twice-weekly combined resistance and arm ergometry training. Testing was conducted at the same time of day pre and post-training in a dark quiet room during spontaneous breathing. Customized computer software was used to identify RR-intervals and subsequently calculate frequency domain measures of heart rate variability (Low frequency (LF) power, High frequency (HF) power and the LF:HF ratio) as well as mean heart rate (HR). There were no significant changes in resting HR, LF power or HF power following the three months of exercise training. However, there was a significant reduction in the resting LF:HF ratio (pre: 1.96 ± 0.73, post: 1.21 ± 0.44; $p<0.05$), due to the combined effects of a 14.9% decrease in LF power and a 25.8% increase in HF power (both non-significant). There was no effect of training on the LF:HF ratio or HR response during 60° head-up tilt. These findings suggest that individuals with incomplete tetraplegia retain the ability to make positive changes in the autonomic regulation of the heart with exercise training.

Introduction:

The regulation of heart rate (HR) is influenced, in large part, by the sympathetic and parasympathetic divisions of the autonomic nervous system. In healthy able-bodied individuals, HR may be increased above its intrinsic pace via input from cardiac sympathetic fibres that originate from the upper thoracic portion of the spinal cord (T1-T4) (Hockman, 1987), or lowered below its intrinsic pace via parasympathetic fibres carried in the vagus nerve. It is the balance of these two neural limbs that, in large part, determines the HR at rest and in response to physical and/or mental stress.

The analysis of heart rate variability (HRV) has become a common, non-invasive method used to measure the autonomic control of the heart (Akselrod et al., 1981; Kamath et al., 1993; Malik and Camm, 1995). Specifically, successive R-R intervals obtained from the electrocardiogram (ECG) have been shown to oscillate around two distinct frequencies. The high frequency (HF; approximately 0.25 Hz at rest) oscillation corresponds to the respiratory sinus arrhythmia and reflects parasympathetic outflow to the heart, while the low frequency (LF; approximately 0.1 Hz) oscillation corresponds to both the sympathetic and parasympathetic outflow to the heart, although it is much more indicative of the former. Power spectral analysis allows for the quantification of these two oscillations, and accordingly, the LF:HF power ratio has become an accepted index of cardiac sympathovagal balance (Malik and Camm, 1995; Pagani et al., 1986). Finally, work in our laboratory has shown HRV to be a reproducible measure in individuals with tetraplegia (Ditor et al., 2003).

Individuals with spinal cord injury (SCI) at or above the high thoracic level (T1-T4) are prone to severe alterations in cardiac autonomic control (Bunten et al., 1998; Grimm et al., 1997; Inoue et al., 1991; Wang et al., 2000), due to the disconnection that results between higher centers and the preganglionic sympathetic fibres originating in the spinal cord. The implications of this autonomic disturbance are yet to be fully understood, and the results of investigations into HRV after SCI have been somewhat equivocal. For example, some investigations into HRV after SCI have shown a complete absence of LF power in individuals with complete tetraplegia, suggesting that the sympathetic innervation to the heart is completely ablated in this population (Inoue et al., 1990, 1991). In contrast, more recent studies have shown a partial preservation of LF power in individuals with SCI, although the degree of conservation seems to be inversely proportional to the level and severity of the injury (Grimm et al., 1995, 1997). Despite this partial preservation, however, those with complete tetraplegia failed to show the normal increase in LF:HF ratio (i.e. the normal shift toward cardiac sympathetic predominance) in response to various cardiovascular challenges (Grimm et al., 1995, 1997). This deficit in the sympathetic innervation to the heart is clinically relevant since i) it contributes to orthostatic intolerance; a common sequelae after SCI that limits independence and quality of life, and ii) it reduces maximal exercise capacity, which likely contributes to the increased risk of cardiovascular disease in individuals with SCI.

In addition to this sympathetic dysfunction, the parasympathetic control of the heart may also be impaired following SCI despite the sparing of the vagus nerve. Specifically, it has been suggested that the withdrawal of cardiac sympathetic tone that

results from SCI causes a compensatory withdrawal of cardiac parasympathetic tone in order to maintain autonomic balance (Grimm et al., 1997; Wang et al., 2000). Such a compensation, however, may be problematic for individuals with SCI since reductions in resting parasympathetic tone have been shown to be an independent risk factor for death in other populations (Gleiger et al., 1987; Kleiger et al., 1987).

In the able-bodied population the effects of exercise training on the autonomic control of the heart are well-established, as several investigations have shown exercise-induced changes in HRV indicative of increased parasympathetic tone (DeMeersman, 1993a, 1993b; Taylor et al., 2003). It has yet to be determined, however, if the same exercise-induced adaptations can be achieved in individuals with high-level SCI (i.e. at or above T_1-T_4). If the body does in fact strive to maintain cardiac autonomic balance after SCI, as others have suggested (Grimm et al., 1997; Wang et al., 2000), then the compromise to the sympathetic system in this population may preclude the normal exercise-induced enhancements of cardiac parasympathetic tone. Conversely, the decreased parasympathetic tone that has been shown to accompany SCI may only be a reflection of the reduced activity levels in this population, in which case exercise-induced enhancements in resting parasympathetic tone may be expected. Since individuals with SCI have been shown to be at an increased risk of cardiovascular mortality (DeVivo et al., 1993), it is of particular interest to examine the potential for exercise-induced enhancements in autonomic function in this population. Finally, it is unclear if exercise training may promote a more effective sympathetic innervation of the heart in individuals with SCI during times of cardiovascular stress. The fact that adrenoceptor density and

sensitivity are altered following SCI (Arnold et al., 1995), suggests a possible plasticity in the cardiac sympathetic control that may respond favourably to exercise training. If so, exercise training may also partially reverse the propensity to orthostatic intolerance that is common in those with high thoracic or cervical SCI.

The purpose of the present study was therefore, to examine the effects of a three month exercise training program on the resting autonomic control of the heart (as determined by power spectral analysis of HRV) in individuals with incomplete tetraplegia. A secondary purpose was to examine the effects of the exercise training program on cardiac autonomic control during orthostatic stress.

Methods:

Participants

Five individuals (four male, one female; age 33.0 ± 9.5 yrs.) with chronic SCI (C4-C5; ASIA B-D; 10.1 ± 9.7 yrs. post injury) were included in the present investigation. These individuals were recruited from an outpatient clinic for individuals with SCI at Chedoke Hospital, Hamilton, Ontario, Canada. Participants were only included if they were at least one year post injury and were free of any coincident cardiac disease. Participants were also required to be free of any musculoskeletal condition that would contraindicate exercise training. This investigation was approved by the McMaster Research Ethics Board (MREB), and all participants provided written informed consent in accordance to MREB guidelines. Participant characteristics are summarized in Table 1.

ECG data acquisition

The ECG data were recorded at baseline and following three months of exercise training. Pre and post-testing sessions were conducted at the same time of day (approximately 12:30-2:30 pm), and participants were instructed to abstain from caffeine and cigarette smoking for at least 12 hours prior to testing, and all participants were two hours post-prandial at the time of data collection. Medications were not interrupted for ECG data acquisition, however, participants were asked to not change their medications during the course of the investigation. All post-testing sessions were conducted at least 24 hours after the participants' final exercise training session in order to ensure a true resting condition for the ECG data recording.

ECG data were collected with the participants in both the supine resting position and during an orthostatic stress (60° head-up tilt). Upon entering our laboratory, participants were fitted with a heart rate monitor and were transferred onto a tilt table in a dark, quiet, room. In an attempt to achieve steady state resting conditions, participants were asked to lie quietly for 10 minutes before any data were recorded. Participants then remained still and quiet during a 10-minute period of supine rest, a five minute period of 20° head-up tilt, a five minute period of 40° head-up tilt, and finally, a 10-minute period of 60° head-up tilt. HR data were only recorded however, during the 10-minute supine condition and the 10-minute 60° head-up tilt condition, and participants breathed spontaneously during the entire testing session. Participants were asked not to sleep during the ECG data collection and although they were not disturbed during the testing sessions, none had any problems remaining awake. Anti-embolic stockings and

abdominal binders were not worn by any of our participants during the ECG data collection session and each participant was asked to empty his or her urine bag before ECG data were recorded.

Polar heart rate monitors were used to collect the ECG data. When necessary, participants were assisted in putting on the heart rate monitors which were worn around the chest approximately one inch below the nipple line. ECG signals were sampled at 500 Hz using a 12 bit analog-digital converter (CODAS, DATAQ Inc., Akron, OH). The signals were continuously displayed on an IBM computer using WINDAQ data acquisition software (Dataq Instruments). The ECG recordings were saved on the computer's hard drive and transferred to a separate computer equipped for HRV analysis.

Data Analysis

A customized software program (MATLAB) (Kamath et al., 1998), was used to identify a stable and noise independent fiducial point on all R-waves for each recording. An RR-interval tachogram was then generated from the continuous ECG data. All tachograms were then inspected for ectopic beats which were subsequently removed using a linear interpolation algorithm (Kamath et al., 1998). When files were found to contain excessive ectopic beats (>5/min), the investigator visually inspected the tachogram for a sufficiently long period of relatively ectopic-free segments of HR data for further analysis. Beat-to-beat heart rate variability signals were then computed, and then resampled at 2 Hz using linear interpolation to obtain equally sampled time series. For each data set, 4 record lengths of 128 sec were selected automatically for power spectral analysis. The mean value of the heart rate was removed and the equally sampled

HRV signals were fed through a second order high pass Butterworth filter with a cut-off of 0.02 Hz. A 10^{th} order autoregressive model was then applied to the filtered HRV signal. The data analysis software used allowed the investigator to accept or reject any of the 4 power spectra produced for each data set. Thus, the investigator could reject power spectra showing a fusion of the LF and HF peaks, which sometimes, albeit rarely, occurred during spontaneous breathing. Final frequency domain measures represent the average of all accepted record lengths. Oscillations ranging between 0.04-0.15 Hz were designated as LF while oscillations between 0.15-0.40 Hz were designated as HF. Peak values of the LF and HF components were identified from the HRV power spectra and expressed as $(beats/min)^2/Hz$. The power of the LF and HF components were calculated via integrating the area under each curve and expressed as $(beats/min)^2$. LF:HF ratios and mean heart rate were also calculated by the MATLAB program.

Testing of arm ergometry performance

Participants performed three six-minute steady-state workloads (WL) on Monarch™ arm ergometers. Borg ratings (Borg, 1970) of perceived exertion (RPE) of one, two and four on a 10-point scale were used to determine the intensity of the three workloads; an acceptable alternative for exercise prescription in populations without a normal HR response to exercise (McLean et al., 1995). HR was determined for each WL (via a Polar heart rate monitor) and WL/HR (W/beats/min) was calculated. The index of arm ergometry performance was thus defined, pre and post-training, as the ((WL/HR)x100) for the highest attained WL, where HR was less than 100 beats/minute (Hicks et al., 2003). HR's less than 100 beats/minute were only considered when

calculating the arm ergometry performance index in order to prevent the confounding results that otherwise may have been caused by the compromised sympathetic outflow to the heart in our participants.

Testing of muscle strength

Muscle strength testing was conducted on a multi-station wheelchair accessible weight training system (Equalizer Exercise Machines, Red Deer, Alberta) or unilateral wall pulleys (Sammons Preston, Mississauga, Ontario). Right and left one repetition maximums (1 RM's) were determined for each participant for chest press, elbow flexion and shoulder flexion maneuvers. The index of muscle strength was thus defined as the composite score (in kg), for all of the six 1 RM's (right and left chest press, right and left elbow flexion and right and left shoulder flexion).

Training intervention

The training intervention involved a twice-weekly, supervised exercise training program that combined arm ergometry and resistance training. Participants began each exercise session with a warm-up (wheeling around an indoor track). This was followed by the aerobic portion of their training session which consisted of arm ergometry for 15-30 minutes at an intensity of approximately three to four on the 10-point Borg scale (Borg, 1970) of RPE. Participants who lacked sufficient grip strength to pedal independently had their hands strapped to the arm ergometer handles. Initially, participants performed two bouts of arm ergometry of 5-10 minutes each, which was gradually increased to two 15-20 minutes bouts as training progressed. As the participants and trainers noted decreases in RPE or HR over time at any given WL, the

duration and/or WL was progressively increased as individually tolerated by the participants.

The resistance training was performed on wall pulleys, free weights and the Equalizer weight machine. Training initially consisted of two sets of each exercise at 50% of the 1 RM, and progressed to three sets of each exercise at 70-80% of the 1 RM after the first four weeks. Workloads were increased as individually tolerated by the participants. A wide variety of exercises were available for each of the following muscle groups: forearm, biceps, triceps, deltoids, back, chest, abdominals and leg flexors and extensors; although not all participants exercised the lower extremities. Two exercises for each and all possible muscle groups were performed each training session and exercises were varied each workout.

Statistical analysis

Changes in resting HRV indices and exercise performance measures over time were determined via one-way analysis of variance (ANOVA) with repeated measures on the time factor. Two-way ANOVA's (condition x time) were used to determine exercise training-induced changes in cardiac autonomic control in response to orthostatic stress. Tukey HSD post-hoc analyses were used as required to determine specific differences between means. Statistical significance was set at $p<0.05$ and throughout the text and figures, data are presented as means ± standard deviation.

Results:

Program compliance

All five participants completed the three months of exercise training without incident. The program compliance rate (expressed as the percentage of available sessions attended) was 77.5% and there were no episodes of autonomic dysreflexia or musculoskeletal injuries as a result of the exercise training.

The effects of exercise training on resting HRV measures

There was a significant 38.3% decrease in the resting LF:HF ratio after three months of exercise training (pre: 1.96 ± 0.73, post: 1.21 ± 0.44; p=0.047) (Table 2). This reduction of the LF:HF ratio was due to both a non-significant 14.9% decrease in resting LF power (p=0.18) and a non-significant 25.8% increase in resting HF power (p=0.26) (Table 2). There were, however, no changes in resting HR as a result of the three-month exercise-training program (Table 2).

The effects of exercise training on HRV measures during orthostatic stress

Two of the five participants experienced autonomic dysreflexia during the 60° head-up tilt testing (possibly due to urinary catheter blockage), and therefore, HRV during orthostatic stress was only measured in three participants. In these three participants there was only a non-significant increase in the LF:HF ratio during 60° head-up tilt (p=0.17), and there was no exercise-induced change in the response to this postural stress. There was no main effect for condition on LF power, but there was a trend for a condition by time interaction (p=0.07). There was no main effect for condition on HF power, and no condition by time interaction. There was a significant increase in HR upon

60° head-up tilt (p=0.01), but no exercise-induced change in this response to postural stress (Table 2).

Changes in arm ergometry performance and muscle strength following exercise training

There was a significant increase arm ergometry performance after three months of exercise training (pre: 3.2 ± 2.2 vs. post: 7.5 ± 2.8 ((W/beats/min)x100); p=0.047) (Figure 1). However, there was no change in the composite strength score after three months of exercise training (pre: 72.3 ± 39.5 vs. post: 71.2 ± 37.8 kg; p=0.86) (Figure 1).

Discussion:

The effects of exercise on resting HRV

This study is the first to demonstrate that, despite the disrupted sympathetic outflow to the cardiovascular system that follows SCI, individuals with incomplete tetraplegia do retain the ability to make positive changes in the resting autonomic control of the heart as a result of exercise training. This was evidenced by the 38.3% reduction in resting LF:HF ratio (indicative of a shift towards increased vagal modulation) that was shown after three months of twice weekly combined resistance and aerobic training. Specifically, the participants in the present study experienced a reduction of the LF:HF ratio from an initial value of 1.96 ± 0.73 to a final value of 1.21 ± 0.44, the latter of which is comparable to values obtained from our lab for sedentary able-bodied individuals (1.60 ± 0.85), but still higher than the values obtained from our lab for able-bodied aerobic athletes (0.86 ± 0.16) (Dixon et al., 1992). It is also important to note that the participants in this study did present symptoms indicative of sympathetic

decentralization, and that the investigators were not simply assuming such a deficit based on the participants' lesion levels. For example, all participants had self-reported experiences with both autonomic dysreflexia and/or orthostatic hypotension at some point in their post-injured lives (beyond six months post injury). Further, the participants' average training HR's during arm ergometry over the three month course of exercise training were 88, 95, 82, 105, and 110 beats/min, despite corresponding average training RPE's of 6, 4.5, 5, 4 and 6.5, respectively (4 corresponding to "somewhat severe", and 7 corresponding to "very severe"), on the 10 point Borg scale.

The clinical relevance of the exercise-induced improvements in resting autonomic regulation are substantial since lower LF:HF ratios may be associated with increased cardiovascular health. For example, individuals in various cardiovascular disease states such as essential hypertension (Guzzetti et al., 1988), idiopathic dilated cardiomyopathy (Ajiki et al., 1993), and sudden cardiac death (Malik and Camm, 1995), present elevated LF:HF ratios compared to healthy age-matched controls. Further, the training-induced bradycardia that is experienced by aerobic athletes is attributed to a predominantly parasympathetic outflow to the heart which has been verified by various indices of HRV (Levy et al., 1998; Seals and Chase, 1989), including a lower LF:HF ratio in comparison to the sedentary population (Dixon et al., 1992). Thus, our data suggest that despite their compromised sympathetic outflow to the cardiovascular system, individuals with incomplete tetraplegia retain the ability to shift towards an autonomic profile that is thought to be cardioprotective, and away from an autonomic profile that is associated with cardiovascular disease, following exercise training. The clinical relevance of this

finding is further emphasized by the fact that heart disease is a leading cause of death in individuals with SCI (DeVivo et al., 1993). More specifically, in a study of 9,135 individuals with spinal cord injury, non-ischemic heart disease (including rhythm disorders) was found to be the number two killer in persons with incomplete tetraplegia, and further, this group had a significant four-fold increased risk of death due to non-ischemic heart disease compared to the able-bodied population (DeVivo et al., 1993). It is reasonable to suggest that these rhythm disorders result from the altered autonomic outflow to the heart that is experienced after high thoracic and cervical injuries. In fact, other investigators have observed that the onset of these rhythm disorders occur too early post-injury to be caused by mere inactivity, and therefore, are more likely due to autonomic disturbances (Groah et al., 2001). Thus, the findings of the present study may greatly emphasize the importance of exercise training as a means of preventing non-ischemic heart disease in individuals with incomplete tetraplegia.

It is difficult to speculate on the mechanisms that were responsible for the observed decrease in the resting LF:HF ratio. Our participants experienced a 25.8% increase in resting HF power and a 14.9% decrease in resting LF power (both statistically non-significant). Therefore, it is not clear if the observed shifts in autonomic balance were due primarily to enhancements of cardiac vagal tone or a withdrawal of cardiac sympathetic tone. The fact that parasympathetic outflow to the heart normally predominates at rest suggests that the former was the principal adaptation. However, as LF power reflects both sympathetic and vagal outflow to the heart, enhancements of vagal outflow alone would tend to increase both HF and LF power. Since the participants

in the present study also experienced a 14.9% decrease in resting LF power, a withdrawal of resting sympathetic outflow to the heart also likely contributed to the observed decrease in resting LF:HF ratio. This would be a particularly interesting adaptation considering the partial damage that our participants sustained to the sympathetic nervous system, and further research is warranted to determine if in fact, declines in resting cardiac sympathetic tone contributed to the reduction that was observed in the resting LF:HF ratio.

With respect to the exercise stimulus responsible for the observed changes in sympathovagal balance, it is noteworthy that our participants showed improvements in arm ergometry performance following the three months of exercise training, but made no improvements in strength. The lack of strength gains were likely due to the very modest intensity at which our exercise regimen began. Strength training was initiated at fairly low intensities, as we were particularly concerned about the possibility of overuse injuries in our participants, which can lead to serious functional loss for those who are dependent on their upper limbs for wheelchair propulsion. Thus, the improvements in cardiac autonomic balance that were realized by the participants in the present study were likely the result of the aerobic portion of our training protocol.

A somewhat unexpected finding of the present study was the lack of a decrease in resting heart rate following the three month exercise training program, despite the reductions that were noted in the LF:HF ratio. While this may seem counterintuitive, as a training-induced bradycardia may have been expected, it confirms previous observations that HR and indices of HRV do not always change in parallel with exercise training, i.e.

exercise training may evoke changes in resting HR without evoking changes in resting HRV (Boutcher et al., 1995), and vice versa (Melanson and Freedson, 2001; Portier et al., 2001). Thus, the examination of resting HR alone may not be sufficient in detecting changes made in the sympathovagal balance of the heart.

Previous research investigating the autonomic control of the heart in individuals with incomplete tetraplegia has shown that this population does retain some amount of both sympathetic and vagal outflow to the SA node although each may be reduced in comparison to the outflow observed in age-matched able-bodied controls (Grimm et al., 1995, 1997). The reduction in LF power found in the above studies was attributed, quite obviously, to the sympathetic disruption caused by SCI, while the reduction in HF power may be more difficult to interpret. Some (Grimm et al., 1995, 1997; Wang et al., 2000), have hypothesized that the SCI-induced reduction in cardiac sympathetic tone results in a compensatory reduction in cardiac parasympathetic tone in order to maintain a normal sympathovagal balance to the heart (as evidenced by the lack of a difference in the LF:HF ratio between individuals with SCI and able-bodied controls). This conclusion may be problematic for individuals with SCI because it implies that the level of cardiac vagal tone is limited by the damage to the sympathetic nervous system. The findings from the present study, however, seem to contradict the hypothesis of a compensatory reduction in cardiac vagal tone. Specifically, the reductions that were observed in the LF:HF ratio after exercise training suggest that the body does not strive to maintain any specific autonomic balance after SCI, and that the damaged sympathetic nervous system does not preclude enhancements in vagal outflow or adaptations in sympathovagal

balance. An alternative explanation for the relatively low HF power observed by others (Grimm et al., 1995,1997; Wang et al., 2000) in people with incomplete tetraplegia may, therefore, simply be that these individuals were less active than their corresponding able-bodied controls, as is commonly the case in individuals with SCI. While inactivity would normally be expected to cause elevated LF:HF ratios, the damage to the sympathetic system may have acted to concurrently lower LF power, resulting in a relatively normal autonomic balance.

There are two notable limitations of the present study which detract from the findings of exercise-induced changes in resting LF:HF ratio; first, the lack of a non-exercising control group, and second, the fact that medications were not interrupted for the testing sessions. However, although no formal control group was included in the present study, data from our lab has shown the LF:HF ratio to be unchanged before and after three months of sedentary living in a group of three individuals with SCI (1.00 ± 0.30 vs. 1.19 ± 0.26, respectively; $p>0.05$). Differences in the level and severity of injury between these three sedentary individuals and our current group of exercising participants prevented us from using the former group as legitimate non-exercising controls. For example, all of the participants in the present study had tetraplegia, and only one had functional muscle strength (Table 1). In contrast, the level of injury ranged from C8-T4 in the three sedentary individuals with SCI, and two of three had ASIA D injuries with functional walking ability. Still, the consistency of the LF:HF ratio before and after three months of sedentary living in these three individuals does emphasize that the changes in

HRV that were observed in the present study were in fact, brought about by exercise training, rather than the effect of time.

With respect to the medications that our participants were taking, the only ones that may reasonably have affected our measures were baclofen and ditropan, which were taken for their antispastic properties. Baclofen, which was taken orally by 4 of our 5 participants, is prescribed for the treatment of muscle spasticity. Although this medication has been shown to have adverse, and generally depressive, effects on the cardiovascular system, the incidence of these effects are very low, usually transient and only associated with the start of treatment (CPS, 2003). Further, it may have been unethical and ill-advised for us to interrupt the baclofen treatment of our participants as serious side effects, including anxiety and tachycardia, are associated with abrupt baclofen withdrawal (CPS, 2003). Ditopan, which was taken by 2 of our 5 participants is prescribed for the treatment of bladder spasms. The incidence of cardiovascular side effects with Ditropan usage have been shown to be rare, and may not differ from placebo (CPS, 2003). Finally, it should be emphasized that the medications taken by our participants, as well as the times of administration and dosages, were identical during pre and post testing sessions.

The effects of exercise on HRV during orthostatic stress

In contrast to the changes that were observed in the LF:HF ratio at rest following three months of exercise training, there were no exercise-induced changes observed the LF:HF ratio during 60° head-up tilt. Despite the small sample size we had for this measure (n=3), such a finding suggests that exercise training did not enhance the ability

of our participants to withstand, or respond to an orthostatic stress. However, there was a strong trend for a condition by time interaction for LF power. Thus, it appears that there was a greater relative increase in LF power in response to 60° head-up tilt after the training program compared to the pre-trained response. By itself, this observation of potential changes in LF power is difficult to interpret since this component of HRV contains elements of both cardiac sympathetic and parasympathetic outflow. However, increases in LF power occurring in concert with decreases in HF power may be interpreted as increases in cardiac sympathetic tone per se. This may suggest that the 3-month exercise training program resulted in greater relative increases in cardiac sympathetic outflow in response to orthostatic stress. Although the changes we observed in LF power were not statistically significant, similar exercise-induced changes in the response to cardiovascular stress have been found by others (Bloomfield et al., 1994).

Conclusions

The findings of the present study demonstrate that individuals with incomplete tetraplegia retain the ability to bring about positive changes in the resting autonomic outflow to the heart after three months of twice-weekly exercise training. These findings are clinically relevant because shifts towards an increased vagal modulation of the heart are associated with decreased cardiovascular risk, and further, these findings refute the hypothesis that the degree of vagal outflow to the heart is limited by the compromised sympathetic outflow to the heart in individuals with SCI.

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Figure Captions:

Figure 1

Changes in composite strength scores (kg) (white bars) and the index arm ergometry performance ((W/beats/min)x100) (black bars) following three months of exercise training. * denotes significant increase from pre-trained value ($p<0.05$).

Figure 1.

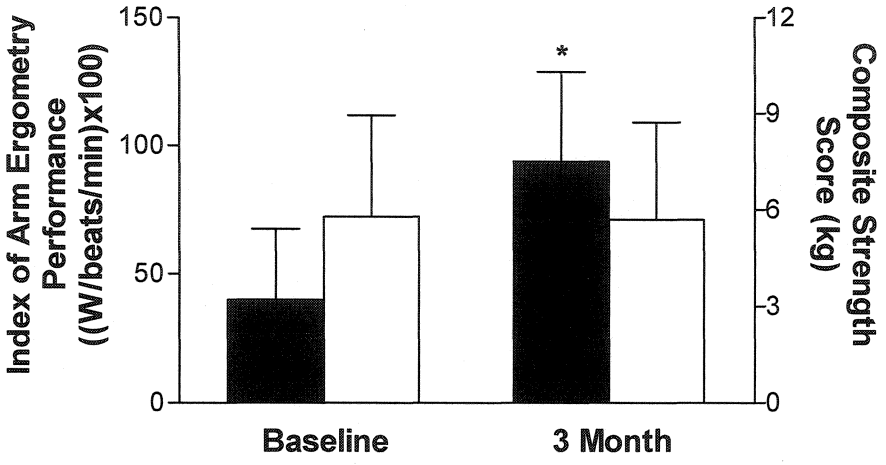
Index of Arm Ergometry Performance ((W/beats/min)x100)
150
100
50
0
12
9
6
3
0
Composite Strength Score (kg)
*
Baseline
3 Month

Table 1. Participant Characteristics

Participant	Sex	Age	Lesion Level	ASIA Score	Years Post-Injury
1	M	27	C4	C	2.5
2	M	35	C5	D	3.5
3	F	20	C4	C	3.5
4*	M	40	C5	B	23
5*	M	43	C4	C	18

* denotes participants that were excluded from HRV analysis during 60° head-up tilt due to autonomic dysreflexia.

Table 2. The effects of exercise on HR and HRV measures at rest and during orthostatic stress

	Pre-training		Post-training	
	Supine	**60° HUT**	**Supine**	**60° HUT**
HR	55.7 ± 10.4	85.3 ± 6.1*	53.7 ± 9.7	83.2 ± 2.7^{+}
LF	7042 ± 666.8	6783 ± 518.0	5991 ± 1591.0	7079 ± 896.2
HF	4238 ± 1324.0	3337 ± 1678.2	5330 ± 1419.5	3594 ± 2582.3
LF:HF	1.96 ± 0.73	2.42 ± 1.10	1.21 ± 0.44*	2.67 ± 1.46

Note: HR, mean heart rate (beats/min); LF, low frequency power ((beats/min)^2); HF, high frequency power ((beats/min)^2); LF:HF, low frequency to high frequency power ratio. * denotes significantly different from pre-trained supine condition ($p<0.05$); $^{+}$ denotes significantly different from post-trained supine condition ($p<0.05$).

Values are means ± S.D.

Chapter 4

The effects of body-weight supported treadmill training on heart rate variability and blood pressure variability in individuals with SCI

PREPARED FOR:

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Abstract

The purpose of this study was to examine the effects of a 6-month body-weight supported treadmill training (BWSTT) program, at a frequency of 3 sessions per week, on the autonomic regulation of heart rate (HR) and blood pressure (BP) in individuals with incomplete tetraplegia. Eight individuals (6 male, 2 female; age 27.6 ± 5.2 yrs.) with chronic SCI (C4-C5; ASIA B-C; 9.6 ± 7.5 yrs. post injury) were included in the present investigation. Ten minute HR and finger arterial pressure (Finapres) recordings were collected in both the resting supine position and during orthostatic stress (60° head-up tilt), before and after the 6-month BWSTT program. Testing was conducted in a dark, quiet room during spontaneous breathing. Customized computer software was used to calculate frequency domain measures of heart rate variability (HRV; LF power, HF power and LF:HF ratio) and blood pressure variability (BPV; LF_{SBP} and LF_{DBP}), which were used as indices of neurocardiac and neurovascular control, respectively. There was a significant reduction in HR (61.9 ± 6.9 vs. 55.7 ± 7.7 beats/min; $p=0.05$) and LF:HF ratio (1.23 ± 0.47 vs. 0.99 ± 0.40; $p<0.05$) after the BWSTT program, indicating a shift towards cardiac vagal predominance. In addition, although there was no change in BP, there was a significant reduction in LF_{SBP} (183.1 ± 46.8 vs. 158.4 ± 45.2 $mmHg^2$; $p<0.01$), indicating a reduction in sympathetic outflow to the vasculature. There were no significant effects of training on measures of HRV and BPV during 60° head-up tilt. These findings suggest that individuals with incomplete tetraplegia retain the ability to make positive changes in the autonomic regulation of the cardiovascular system with

BWSTT, and further, the general reductions in sympathetic tone do not result in increased orthostatic intolerance.

Introduction:

The incidence of spinal cord injury (SCI) in Canada and the United States has been estimated at 35/million and 40/million, respectively. While these rates may seem relatively innocuous, they translate to approximately 1,000 newly injured Canadians and 12,000 newly injured Americans each year, and a combined prevalence of approximately 250,000 individuals (Sekhon and Fehlings, 2001). Roughly half of these individuals have incomplete injuries, and as such, have retained some motor and/or sensory function below the level of injury (Sekhon and Fehlings, 2001).

In the last decade, body-weight supported treadmill training (BWSTT) has shown promise as a means of enhancing and restoring gait recovery in individuals with incomplete spinal cord injury (SCI) (Barbeau et al., 1993; Protas et al., 2001; Wernig et al. 1992; Wernig et al. 1995; Wernig et al. 1999). Improvements in ambulatory capacity following BWSTT have included a greater weight bearing capacity, increases in walking speed and endurance and an enhanced gait pattern during BWSTT (Barbeau et al. 1998), and in some cases, an increased ability to walk over ground (Wernig et al., 1995). To date, however, there are no published studies regarding the effects of BWSTT on the cardiovascular health and function of individuals with SCI, despite the fact that i) cardiovascular health and function are major health issues in the SCI population, and ii) BWSTT may hold particular promise as a means of improving such health issues.

Specifically, cervical SCI has been associated with an increased risk of mortality from several cardiovascular diseases including both ischemic and non-ischemic heart disease (DeVivo et al., 1993). However, the factors accounting for this increased risk are

not fully understood, and accordingly, there is much to be determined regarding the potential for cardiovascular improvement in individuals with SCI. BWSTT is an upright exercise that utilizes the large leg muscles, and thus, may provide a greater cardiovascular challenge than more traditional forms of aerobic training for individuals with SCI, such as arm ergometry. Further, the supporting, or partial supporting, of one's body weight allows a prolongation of exercise duration, which may be required to realize maximal cardiovascular benefit. Finally, although functional electrical stimulation (FES) has been shown to confer cardiovascular benefit in individuals with SCI (Nash et al., 1997), it may not be practical for individuals with incomplete injuries due to the pain associated with this technique (Jacobs and Nash, 2001).

Recently developed methods may be particularly useful in evaluating the effects of BWSTT on the cardiovascular health and function in individuals with SCI. Specifically, power spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV) have become commonly used, non-invasive methods used to quantify the autonomic control of the cardiovascular system (Akselrod et al., 1981; Kamath et al., 1993; Pagani et al., 1997; Parati et al., 1995). With respect to HRV, successive R-R intervals obtained from electrocardiogram (ECG) recordings have been shown to oscillate around two main frequencies. The high frequency oscillation, centred around 0.25 Hz (HF_{HRV}; 0.15-0.40 Hz) corresponds to parasympathetic outflow to the heart via the vagus nerve (Pomeranz et al., 1985), while the low frequency oscillation, centred around 0.1 Hz (LF_{HRV}; 0.04-0.15) has been shown to correspond to both the sympathetic and parasympathetic outflow to the heart, although it is much more indicative of the former

(Montano et al., 1994; Pomeranz et al., 1985). Thus, the LF:HF ratio of HRV has become an accepted measure of cardiac sympathovagal balance. Similarly, the LF oscillation of systolic and diastolic BPV (LF_{SBP}, LF_{DBP}; 0.04-0.15 Hz), also referred to as Mayer waves, has been shown to correspond to neurovascular control via the sympathetic nerves (Pagani et al., 1997; Parati et al., 1995). The HF oscillation of BPV (HF_{SBP}, HF_{DBP}; 0.15-0.40 Hz) is not associated with neurovascular control, but rather, it is thought to represent the mechanical effects of respiration which may act directly on the pressure gradients of the intrathoracic vessels (Pagani et al., 1986).

Measures of HRV and BPV have been found to have significant clinical value, as relative reductions in cardiac vagal predominance have been associated with an increased risk of cardiovascular mortality (Gleiger et al., 1987; Kleiger et al., 1987), and increased BPV and enhanced Mayer waves are associated with end organ damage (Frattola et al., 1993; Miao and Su, 2002). In the able-bodied population, exercise training has been shown to promote changes in HRV and BPV consistent with increases in cardiac vagal predominance, and a general reduction of sympathetic outflow to the cardiovascular system (DeMeersman 1993; Taylor et al., 2003). It is currently unclear if individuals with SCI are capable of experiencing the same exercise-induced enhancements in HRV and BPV, or if such changes are prevented by the unique autonomic disturbance that is often caused by the injury. Preliminary work from our lab (Ditor et al., unpublished observations) suggests that individuals with incomplete tetraplegia may experience increases in cardiac vagal predominance following an arm ergometry training protocol, however, that work did not include measures of BPV, and as mentioned, autonomic

adaptation may be more effectively examined via BWSTT. Further, as individuals with cervical SCI are characterized by an inability to tolerate postural stress (Houtman et al., 2000) it is of interest to determine what effects BWSTT may have on such orthostatic tolerance. There is some evidence that exercise training may confer an enhanced ability for individuals with SCI to respond to cardiovascular stress, as indicated by a relatively greater sympathetic response from rest to maximal arm-ergometry exercise following 6 months of FES-cycle training (Bloomfield et al., 1994). On the other hand, it is possible that potential training-induced reductions in sympathetic outflow, although beneficial to long-term cardiovascular health, may decrease the ability to tolerate postural stress, especially in light of the sympathetic decentralization that is characteristic of many with SCI.

The purpose of the present study was to determine the effects of a 6-month BWSTT training regimen, at a frequency of 3 times per week, on measures of resting HRV and BPV in individuals with incomplete cervical SCI. A secondary purpose, was to investigate the effects of the BWSTT regimen on the autonomic response to orthostatic stress in individuals with SCI, as determined by changes in HRV and BPV measures.

Methods:

Participants

Eight individuals (6 male, 2 female; age 27.6 ± 5.2 yrs.) with chronic SCI (C4-C5; ASIA B-C; 9.6 ± 7.5 yrs. post injury) were included in the present investigation. Although 11 individuals were initially recruited for the study, one participant did not complete all 6 months of BWSTT. Of the 10 individuals that did complete all 6 months, 2

were excluded from the final analysis due to problems regarding testing sessions, i.e. technical problems regarding data acquisition and non-compliance to the testing requirements. Although there was no formal control group was included in the present investigation, our lab has obtained data from a group of 3 individuals (3 male; age 37.0 ± 4.6 yrs.) with SCI (C8 ASIA D; T1 ASIA C; T4 ASIA D; 13.0 ± 10.5 yrs. post injury) before and after 3 months of sedentary living. Statistical analyses were not made between our exercising participants and the sedentary group, however, the data from these 3 individuals has been provided as an informal comparison. All 14 individuals were recruited from an outpatient SCI clinic at Chedoke Hospital, Hamilton, Ontario, Canada. Participants were only included if they were at least one year post injury and were free of any coincident cardiac disease. Participants were also required to be free of any musculoskeletal condition that would contraindicate exercise training. This investigation was approved by the McMaster Research Ethics Board (MREB), and all participants provided written informed consent in accordance to MREB guidelines. Participant characteristics are summarized in Table 1.

ECG and blood pressure data acquisition

Continuous recordings of HR and blood pressure (BP) data were obtained from each participant at baseline and after 6 months of BWSTT. In general, testing sessions occurred between 12:30pm and 7:00pm, however, for any given participant the clock time for pre and post testing sessions never deviated by more than 1.5 hours. Participants were instructed to abstain from caffeine and cigarette smoking for at least 12 hours prior to testing, and were 2 hours post-prandial. All post-training testing sessions were

conducted at least 24 hours after the last bout of exercise in order to ensure a true resting condition during data acquisition. Medications were not interrupted during the study, however, medications and dosages were identical at all testing sessions for each participant. In addition, only 4 of our 8 participants were taking any medication, and of those 4, the only medications that may reasonably have affected our measures were baclofen, and ditropan, which were taken for their antispastic properties. Further, the incidence of cardiovascular side effects associated with these medications are very low, usually transient, and only associated with the start of treatment (CPS, 2003).

Upon entering the laboratory, each participant was asked to empty his or her urine bag, then transferred onto a table and fitted with a Polar HR monitor and a finger plethysmography (Finapres) cuff (Ohmeda 2300, Madison, WI). In an attempt to achieve steady state resting conditions participants lay quietly for 10 minutes prior to the start of data collection, which took place in a dark, quiet room. The testing protocol consisted of a 10-minute period of supine rest, a five minute period of 20° head-up tilt (HUT), a five minute period of 40° HUT, and finally, a 10-minute period of 60° HUT. HR and BP data were only recorded however, during the 10-minute supine condition and the 10-minute 60° HUT condition. Participants were asked not to sleep during data collection and although they were not disturbed during the testing sessions, none had any problems remaining awake. Data were recorded during spontaneous breathing and anti-embolic stockings and abdominal binders were not worn by any of our participants during the testing sessions.

HR and BP signals were sampled at 500 Hz using a 12 bit analog-digital converter (CODAS, DATAQ Inc., Akron, OH). The signals were continuously and simultaneously displayed on an IBM computer using WINDAQ data acquisition software (Dataq Instruments). The HR and BP recordings were saved on the computer hard drive and transferred to a separate computer equipped for HRV and BPV analysis.

Computation of HRV and BPV

A customized software program (MATLAB) (Kamath et al., 1998), was used to identify a stable and noise independent fiducial point on all R-waves for each recording, as well as beat-to beat values of systolic and diastolic blood pressure (SBP, DBP). An RR-interval tachogram, as well as separate SBP and DBP tachograms, were then generated from the continuous HR and BP data, respectively. All tachograms were then inspected for ectopic beats which were subsequently removed using a linear interpolation algorithm (Kamath et al., 1998). When files were found to contain excessive ectopic beats (>5/min), the investigator visually inspected the tachogram for a sufficiently long period of relatively ectopic-free segments of HR and BP data for further analysis. Beat-to-beat HRV and BPV signals were then computed, and then resampled at 2 Hz using linear interpolation to obtain equally sampled time series. For each data set, 4 record lengths of 256 points were selected automatically for power spectral analysis. The mean value of the HR and BP were removed and the equally sampled HRV and BPV signals were fed through a second order high pass Butterworth filter with a cut-off of 0.02 Hz. Power spectra were then computed from the filtered HRV an BPV signals using previously described software (Kamath et al., 1998). Final frequency domain measures

represent the average of all accepted record lengths. Oscillations ranging between 0.04-0.15 Hz were designated as LF while oscillations between 0.15-0.40 Hz were designated as HF. The data analysis software used allowed the investigator to accept or reject any of the 4 power spectra produced for each data set. Thus, the investigator could reject power spectra showing a fusion of the LF and HF peaks, which sometimes, albeit rarely, occurred during spontaneous breathing. Peak values of the LF and HF components were identified from the HRV and BPV power spectra and expressed as $(beats/min)^2/Hz$, and $(mmHg)^2/Hz$, respectively. The power of the LF and HF components were calculated via integrating the area under each curve and expressed as $(beats/min)^2$ and $mmHg^2$. LF:HF ratios and mean heart rate were also calculated by the MATLAB program. SBP and DBP were determined by ausculation over the left brachial artery at heart level and mean arterial pressure (MAP) was subsequently calculated (MAP = (SBP+2DBP)/3).

Training intervention

BWSTT apparatus

The Woodway Loco-system (Woodway USA Inc., Foster, CT) is a specialized treadmill with a built-in weight supporting system. Participants were fitted with a harness while seated in their wheelchairs and then wheeled up a ramp to the treadmill. Cables were then attached to the harness, and a pulley system was used to hoist participants into the standing position over the treadmill. Once upright, a second set of cables were used to connect participants to weight stacks located at the front of the treadmill. Weight could be added to the stacks in 8 kg increments (4 kg/stack), and when finer increments were needed, hand weights were added to the stacks. The hoisting cables were loosened once

body-weight had been counterbalanced, but remained attached to the harness at all times for safety reasons, i.e. in case of a fall, the hoisting cables would "catch" the participant almost immediately. The Woodway Loco-system allows for a range of speeds between 0.1 and 5.0 km/hr, and speed may be adjusted by 0.1 km/hr increments. Treadmill speed, as well as distance and time ambulated are displayed on a computer control panel at the side of treadmill, within view of the exerciser. Hand-rails are attached to the treadmill, and participants were allowed to use these rails for balance, but were discouraged to use them to assist in weight support. Two assistants sat at either side of the tread, and assisted participants in the gait cycle, while a third stood behind the participant and aided in weight shifting, balance and general safety. All assistants were trained to detect signs of autonomic dysreflexia and respond accordingly, however, no episodes of autonomic dysreflexia were evoked during the training sessions.

Training protocol

Participants exercised at a frequency of 3 times per week for 6 months. During the first training session an appropriate amount of body-weight support was chosen for each participant, such that he or she could just stand on the tread without buckling at the knees. Body-weight support was decreased as individually tolerated over the course of the study. For the sake of safety, initial treadmill speed was arbitrarily chosen at 0.5 km/hr, and the duration of ambulation at 15 minutes (3 bouts of 5 minutes). Speed and duration were also increased as individually tolerated over the course of the study. However, time constraints dictated a maximum duration of 60 minutes, and increases in speed were only allowed if proper gait mechanics could be maintained. When decreases in body-weight

support were made, it was not unusual for a participant to require brief periods of decreased speed or duration until he or she became more comfortable with the new weight. Likewise, increases in speed were sometimes accompanied by periods of decreased weight support and duration. The distance ambulated per session was obtained from each participant's training log, and used as an index of exercise progression over time.

Statistical analysis

The means of resting HRV and BPV measures at baseline and after 6 months of BWSTT were compared by one-way analysis of variance (ANOVA). One-way ANOVA's were also used to make comparisons between the first 3 months of training and the last 3 months of training regarding mean distance ambulated per session, speed of ambulation and mean HR during BWSTT. Two-way ANOVA's (condition x time) were used to determine exercise training-induced changes in HRV and BPV in response to orthostatic stress. Tukey HSD post-hoc analyses were used as required to determine specific differences between means. Statistical significance was set at $p \leq 0.05$ and throughout the text and figures, data are presented as means ± standard deviation.

Results:

Program compliance

All 8 participants successfully completed the 6-month BWSTT protocol. The compliance rate, calculated as (number of sessions completed/number of scheduled sessions) x 100, was 83.6 ± 9.1%. There were no episodes of autonomic dysreflexia,

musculoskeletal injury or pressure sore development in any participant during the course of the training program.

Distance ambulated per BWSTT session

There was a significant increase in distance ambulated per session when comparing the first 3 months of the BWSTT program to the last 3 months, indicating that the training protocol was indeed progressive. The increase in distance was due to an increased speed of ambulation (0.79 ± 0.32 vs. 1.08 ± 0.31 km/hr; p=0.0001), rather than duration of ambulation per session (29.6 ± 12.0 vs. 32.9 ± 9.7 min/session; p=0.09). In addition, the mean HR during BWSTT was 128.8 ± 19.0 beats/min during the first 3 months of training and 125.5 ± 24.5 beats/min during the last 3 months (p=0.41). The maintenance of HR during increases in training intensity suggests a cardiovascular training effect in our participants (Figure 1).

The effects of exercise training on resting HR and BP

There was a significant decrease in resting HR following the 6 months of BWSTT (p=0.05). However, there were no significant changes in resting SBP, DBP or MAP (Table 2).

The effects of exercise training on resting HRV and BPV measures

Regarding HRV, there was a significant reduction in the resting LF:HF ratio following the 6 months of BWSTT (p=0.01)(Table 3). The reduction in the resting LF:HF ratio was due to the significant reduction in resting LF power (p=0.009), as changes in resting HF power were not significant (p=0.63) (Table 3).

Regarding BPV, there was a significant decrease in resting LF_{SBP} following the 6

months of BWSTT (p=0.007)(Table 4). In contrast, there was only a non-significant reduction in LF_{DBP} following the training program (p=0.13) (Table 4).

Measures of resting HRV and BPV in non-exercising individuals with SCI

The group of non-exercising individuals with SCI showed no change in any measure of resting HR, HRV or BPV after 3 months of sedentary living, although they did experience a significant increase in MAP (p=0.047)(Table 5).

The effects of exercise training on resting HR and BP during orthostatic stress

There was a significant increase in HR upon 60° HUT (p=0.001), but no significant changes in SBP, DBP or MAP indicating a maintenance of BP upon postural stress. There was no effect of training on the HR or BP response to 60° HUT (Table 2).

The effects of exercise training on HRV and BPV measures during orthostatic stress

Regarding HRV, there was a significant increase in the LF:HF ratio upon 60° HUT (p=0.005), but there was no training effect on this response (p=0.50). The increase in the LF:HF ratio upon postural stress was due to a significant increase and decrease in LF power (p=0.03) and HF power (p=0.004), respectively. There was a trend (p=0.09) for a condition x time interaction for LF power, suggesting an enhanced sympathetic response to 60° HUT following training (Table 3). There were no effects of 60° HUT on measures of BPV, and no condition x time interaction (Table 4).

Discussion:

The main findings of this study have both physiological and practical relevance. From a physiological perspective, our results demonstrate that individuals with incomplete cervical SCI retain the ability to make positive changes to the autonomic

regulation of the cardiovascular system with exercise training. Specifically, this study is the first to show favorable exercise-induced changes in BPV in individuals with SCI, and further, the present findings help to confirm unpublished observations from our lab regarding positive changes in HRV measures following exercise training in individuals with incomplete tetraplegia. From a practical perspective, this study is the first to demonstrate the effectiveness of BWSTT as a means of improving cardiovascular health and regulation in individuals with incomplete SCI.

Clinically, the changes observed in this study are important as lower LF:HF ratios and LF_{SBP} have been associated with a decreased risk of cardiovascular mortality and end-organ damage, respectively (Frattola et al., 1993; Lanza et al., 1997). Further, as SCI has been shown to result in an increased risk of mortality from various cardiovascular diseases (DeVivo et al., 1993), favorable changes in HRV and BPV may be of particular interest to the SCI population.

Although concurrent reductions were observed in the resting LF:HF ratio and resting HR, the reduction that was observed in resting LF_{SBP} was not accompanied by a similar decline in resting SBP or MAP. While the lack of a change in resting BP may seem to detract from the clinical implications of the present study, it is important to note that reductions in BPV may confer a protective effect against cardiovascular disease independently of BP. For example, in a study conducted by Frattola et al. (1993), BPV was determined in 73 hypertensive patients, who were divided into quartiles based on their 24-hour MAP. Measures of end-organ damage were subsequently determined at follow-up, approximately 7 years later. The results showed that for any given quartile of

MAP, those patients with lower values of BPV determined at the initial exam, had a lower severity of end-organ damage at follow-up. Further, this relationship held true even at the lowest quartile of MAP which was approximately 80-85 mmHg. In addition, animal work using the sinoaortic denervated (SAD) rat model has provided evidence that lower BPV may confer cardiovascular benefit independently of BP. In the SAD model, rats are subject to surgical destruction of the carotid and aortic baroreceptor afferents, and in the chronic condition, are characterized by an increase in BPV but a normal average blood pressure (Miao and Su, 2002). SAD rats have been shown to develop both aortic and left ventricular hypertrophy, both of which have been shown to correlate positively and significantly with BPV (Miao and Su, 2002; Sasaki et al., 1994).

It is important to mention that the work by Frattola et al. (1993) and Miao and Su (2002), used time domain measures to demonstrate the relationship between BPV and cardiovascular risk, while the present study noted exercise-induced reductions in LF_{SBP}, a frequency domain measure of BPV. However, studies using direct measures of muscle sympathetic nerve activity (MSNA) have verified LF_{SBP} as an index of sympathetic outflow to the vasculature (Pagani et al., 1997), and thus, it would be reasonable to expect that reductions in frequency domain measures of BPV may also confer cardiovascular benefit. Still, as direct measures of cardiovascular disease progression were not measured in the present investigation, the observed decline in LF_{SBP} should be interpreted with some caution.

The exercise-induced reduction in LF:HF ratio may be a particularly encouraging finding for individuals with SCI. Previous investigators have hypothesized

that the reduction in cardiac sympathetic outflow that may result from SCI causes a compensatory reduction in cardiac vagal tone in an attempt to maintain autonomic balance (Grimm et al., 1997; Wang et al., 2000). Such a compensation would be problematic for individuals with SCI as reductions in cardiac vagal tone have been shown to be an independent risk for cardiovascular mortality (Gleiger et al., 1987; Kleiger et al., 1987). However, the observed reduction in the LF:HF ratio in the present study helps to confirm preliminary work from our lab, and suggests that cardiac autonomic balance remains receptive to change following SCI, and that favourable exercise-induced changes in autonomic balance are possible in this population.

In spite of these encouraging results, it is important to point out some potential limitations to our data. First, the participants in this study exhibited a fairly well preserved sympathetic outflow to the cardiovascular system as seen by the maintenance of MAP upon postural stress and by the relatively high HR's that were experienced during exercise training (average HR: 127.1 ± 21.3; peak HR: 147.1 ± 23.7 beats/min). Therefore, it is unclear if individuals with more severe sympathetic decentralization can bring about the same exercise-induced changes in the LF:HF ratio. However, in the present study, even those with the lowest peak HR during exercise training (participant 3, 120 beats/min; participant 5, 120 beats/min) still experienced representative decreases in the LF:HF ratio following the 6-month training protocol (participant 3, 19%; participant 5, 32%).

Second, the reduction that was observed in the LF:HF ratio was accounted for by a significant reduction in LF power, and only a non-significant increase in HF power.

Thus, the changes that were noted in cardiac autonomic balance seemed to be driven more by reductions in sympathetic tone rather than increases in vagal tone, (although LF power contains both sympathetic and vagal components, the present finding of decreased LF power in conjunction with increased or maintained HF power, strongly suggests a reduction in sympathetic outflow per se). The absence of vagal enhancement may make any associated health benefits questionable, as the majority of studies regarding HRV and cardiovascular risk have used time domain measures (Malik and Camm, 1995), and thus, have primarily commented on the cardio-protective nature of vagal outflow per se. Still, Lanza et al. (1997) did find an association between reductions in the LF:HF ratio and protection from cardiovascular mortality. Further, norepinephrine, per se, has been shown to have deleterious effects on myocardial tissue (Brouri et al., 2002; Masuda et al., 2002).

In contrast to the exercise-induced changes in resting autonomic function, the 6-month BWSTT program did not substantially affect our participants' ability to tolerate orthostatic stress. There was a trend ($p=0.09$) for a condition x time interaction for LF power, such that the change in LF power from supine to 60° HUT tended to be enhanced following the training program (again, relative increases in LF power, in the face of decreases in HF power, may be interpreted as a relative enhancement of sympathetic outflow). This would suggest that the 6-month BWSTT program resulted in a relative exaggeration of the pressor response to orthostatic stress, an observation that should be pursued in future studies. There is some evidence from previous research that exercise training might enhance sympathetic outflow in individuals with SCI. Specifically, Bloomfield et al (1994), found a relatively increased catecholamine response to maximal

arm-ergometry exercise following 6-months of FES-cycling. It is reasonable to hypothesize that the exercise-induced reduction in LF_{SBP} that we observed was accompanied by similar reductions in resting peripheral vascular resistance. Support for this hypothesis may come from work by Hopman et al., (2002), who noted decreases in vascular resistance in individuals with complete SCI after 6 weeks of FES-cycling exercise. It may follow that such a decrease in vascular resistance would necessitate a greater relative pressor response to postural stress in order to maintain MAP. Regardless, it is still interesting and relevant that none of our participants became less tolerant to postural stress after the exercise training program, as indicated by the maintained MAP during 60° HUT at post-testing. This is an encouraging finding as it suggests that individuals with incomplete SCI may retain orthostatic tolerance following an exercise training program involving the lower limbs, despite the fact that such an intervention likely decreased resting vascular resistance. However, as previously mentioned, our participants did not suffer from severe sympathetic decentralization. Thus, it remains unclear if individuals with more severe SCI may retain relative orthostatic tolerance following BWSTT.

In terms of BWSTT per se, the present study is the first to show that this exercise training modality may confer cardiovascular benefit to individuals with incomplete tetraplegia. Although cardiovascular benefit has been shown to follow FES exercise (Hopman et al., 2002; Nash et al., 1997), many individuals with incomplete SCI will find electrical stimulation excessively painful. Nevertheless, there are important disadvantages to BWSTT that warrant discussion. First, despite the findings of Wernig and colleagues

(1995), in our experience, long-term BWSTT does not confer consistent over-ground walking capabilities, even in those who eventually progress to zero body-weight support. In addition, as only walking may be mimicked during BWSTT, there are obvious limits to the speed that may be performed with this type of exercise. Further, the resources required for BWSTT restrict the duration of ambulation per training session. Thus, the progressive nature of this training technique is limited, and therefore, it may not persist to be a sufficient cardiovascular stimulus for many individuals.

Conclusions:

The present study is the first to show that individuals with incomplete tetraplegia retain the ability to make positive adaptations to the autonomic regulation of the cardiovascular system flowing 6 months of 3x-weekly BWSTT. These findings may be particularly valuable to individuals who have trouble tolerating FES exercise. Future work should examine whether individuals with more severe SCI, and thus, less motor function, may make the same cardiovascular adaptations following BWSTT despite the more passive nature of ambulation that would be expected.

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Figure Captions:

Figure 1

Distance ambulated per session (m), and mean HR during BWSTT (beats/min) over the course of the training program. * denotes significant increase in distance ambulated per session compared to the 0-3 month training period.

Figure 1.

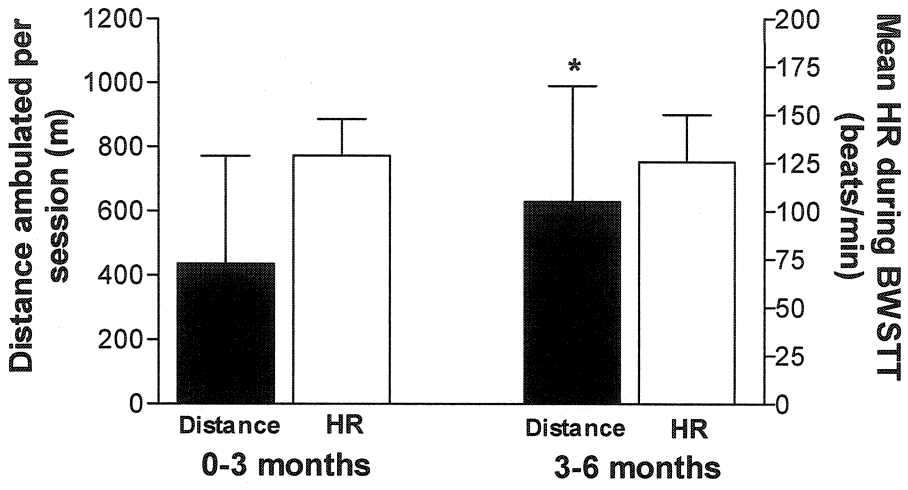
Distance ambulated per session (m)
1200
1000
800
600
400
200
0
200
175
150
125
100
75
50
25
0
Mean HR during BWSTT (beats/min)
*
Distance
HR
Distance
HR
0-3 months
3-6 months

Table 1. Participant Characteristics

Participant	Sex	Age	Lesion Level	ASIA Score	Years Post-Injury
1	M	29	C5	B	11
2	M	24	C5	C	24
3	F	20	C5	C	5
4	M	22	C5	C	4
5	M	31	C4	C	2
6	M	28	C4	C	4
7	F	33	C5	C	16
8	M	34	C4	C	11

Table 2. Measures of HR and BP during supine rest and orthostatic stress, before and after 6 months of BWSTT

	Baseline		6 months	
	Supine	HUT	Supine	HUT
HR†	61.9 ± 6.9	90.2 ± 21.4	55.7 ± 7.7 *	80.0 ± 15.7
SBP	117.0 ± 20.3	107.1 ± 15.7	114.8 ± 15.0	100.0 ± 14.2
DBP	73.3 ± 10.6	71.4 ± 11.5	71.8 ± 9.4	74.8 ± 9.4
MAP	87.8 ± 13.5	83.3 ± 12.2	86.1 ± 10.7	83.2 ± 10.2

Note: HR, mean heart rate (beats/min); SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure (mmHg); HUT, 60° head-up tilt. * denotes a significant decrease compared to supine baseline values ($p=0.05$). † denotes a main effect for condition, such that HR increased upon HUT ($p<0.01$). Values are means ± S.D.

Table 3. Measures of HRV during supine rest and orthostatic stress, before and after 6 months of BWSTT

	Baseline		6-month	
	Supine	HUT	Supine	HUT
LF †	5894 ± 815	6575 ± 706	5121 ± 1234 *	6337 ± 407
HF †	5493 ± 1472	3718 ± 1125	5642 ± 1001	4088 ± 659
LF:HF †	1.23 ± 0.47	2.06 ± 0.80	0.99 ± 0.40 *	1.64 ± 0.29

Note: LF, low frequency power; HF, high frequency power $(beats/min)^2$; LF:HF, low frequency to high frequency ratio; HUT, 60° head-up tilt. * denotes a significant decrease compared to supine baseline values ($p<0.05$). † denotes a main effect for condition, such that values of LF and LF:HF are increased, and values of HF are decreased upon HUT ($p<0.05$). Values are means ± S.D.

Table 4. Measures of BPV during supine rest and orthostatic stress, before and after 6 months of BWSTT

	Baseline		6-month	
	Supine	HUT	Supine	HUT
LF_{SBP}	183.1 ± 46.8	133.3 ± 64.4	158.4 ± 45.2 *	121.9 ± 59.4
LF_{DBP}	191.0 ± 26.4	164.5 ± 70.2	170.6 ± 34.6	161.9 ± 69.3

Note: LF_{SBP}, low frequency power of systolic blood pressure; LF_{DBP}, low frequency power of diastolic blood pressure ($mmHg^2$); HUT, 60° head-up tilt. * denotes a significant decrease compared to supine baseline values ($p<0.01$).Values are means ± S.D.

Table 5. Measures of resting HR, BP, HRV and BPV in non-exercising individuals with SCI

	Baseline	3 months
HR	64.5 ± 23.1	64.3 ± 13.9
SBP	117.0 ± 8.2	128.7 ± 10.1
DBP	70.7 ± 3.1	76.0 ± 7.2
MAP	86.1 ± 4.5	93.6 ± 7.3 *
LF	5363 ± 1413.7	6081 ± 231.0
HF	5569 ± 724.5	5513 ± 805.9
LF:HF	1.00 ± 0.30	1.19 ± 0.27
LF_{SBP}	153.2 ± 75.0	152.0 ± 76.0
LF_{DBP}	182.4 ± 58.2	182.6 ± 41.8

Note: HR, mean heart rate (beats/min); SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure (mmHg); LF, low frequency power; HF, high frequency power $(beats/min)^2$; LF:HF, low frequency to high frequency ratio; LF_{SBP}, low frequency power of systolic blood pressure; LF_{DBP}, low frequency power of diastolic blood pressure ($mmHg^2$). * denotes a significant increase compared to baseline values ($p<0.05$). Values are means ± S.D.

Chapter 5

The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI

PREPARED FOR:

SPINAL CORD

Abstract

Body-weight supported treadmill training (BWSTT) has shown promise as a means of improving ambulation in individuals with incomplete SCI. Individuals with motor-complete SCI, however, have not shown the same improvements and are usually excluded from this form of therapy. This exclusion may be unfortunate as BWSTT may be an ideal means to improve cardiovascular health and function in these individuals. The purpose of this study was to i) investigate the effects of a 4-month BWSTT program on arterial dimension and function and measures of HRV and BPV in individuals with motor-complete SCI, ii) determine if potential training-induced cardiovascular changes would be accompanied by reductions in orthostatic tolerance, and iii) to make a preliminary examination of what factors may predict cardiovascular adaptation following BWSTT in this population. Six individuals (4 male, 2 female; age 37.7 ± 15.4 yrs.) with chronic SCI (C4-T12; ASIA A-B; 7.6 ± 9.4 yrs. post injury) were included in the present investigation. Following 4 months of BWSTT there was a significant decrease in the resistance of the common femoral artery (CFA; pre: 0.98 ± 0.17, post: 0.73 ± 0.26, mmHg/ml/min; $p<0.05$), and a trend for an increase in CFA compliance at rest (pre: 0.064 ± 0.029, post: 0.106 ± 0.051, mm^2/mmHg; $p=0.07$). There were no significant changes in the resting blood flow of the CFA (pre: 101.7 ± 30.4, post: 129.2 ± 66.2, ml/min; $p>0.05$) or compliance of the common carotid artery (CCA; pre: 0.110 ± 0.039, post: 0.107 ± 0.071, mm^2/mmHg; $p>0.05$). Following the 4 months of BWSTT those with tetraplegia could no longer tolerate 60° head-up tilt, while those with paraplegia showed no reduction in orthostatic tolerance. There were no exercise-induced changes in

neurocardiac or neurovascular control as indicated by measures of heart rate variability (HRV) and blood pressure variability (BPV) when all participants were considered together. However, the results suggest that the subgroup of individuals who had a substantial heart rate (HR) response to BWSTT (n=3), may experience exercise training-induced changes in HRV reflective of a relative shift toward cardiac vagal predominance and reductions in BPV. The factors that seemed to predict this HR response to BWSTT appeared to be a greater propensity to orthostatic intolerance and a higher degree of muscular spasticity.

Introduction:

Individuals with spinal cord injury (SCI) are prone to severe cardiovascular dysfunction and an increased risk of mortality from various cardiovascular diseases (DeVivo et al., 1993). Further, the risk of cardiovascular mortality appears to be heightened in those with more severe or complete SCI (DeVivo et al., 1993; Groah et al., 2001). Although the underlying mechanisms responsible for the increased risk are not precisely understood, the loss of mobility and reduced activity levels that accompany severe SCI certainly contribute.

Unfortunately, complete muscular paralysis limits the options for exercise rehabilitation, and the current exercise strategies for individuals with complete SCI have various shortcomings that may reduce their effectiveness from a cardiovascular perspective. Although arm ergometry may provide a significant cardiovascular challenge for those with adequate arm function, it does not target the vessels of lower limbs; which contribute importantly to the increased cardiovascular risk in individuals with SCI (Mammen, 1992; Nash et al., 1996). In addition, although functional electrically stimulated (FES) exercise has shown great promise as a cardiovascular stimulus (Gerrits et al., 2001; Hopman et al., 2002; Nash et al., 1997), it carries the risk of burns to the skin, autonomic dysreflexia and bone fracture, and further, stimulated contractions may not be evoked in those with lower motor neuron injuries (Jacobs and Nash, 2001). The cardiovascular benefit of FES exercise may also be limited as individuals with SCI are more prone to muscle fatigue (Castro et al., 1999; Ditor et al., in press; Olive et al., 2003) and may only perform such exercise for relatively short durations (Olive et al., 2003).

In the last decade, body-weight supported treadmill training (BWSTT) has shown promise as a means of enhancing gait recovery in SCI individuals with partially spared motor function (Barbeau et al., 1993; Protas et al., 2001; Wernig et al. 1992; Wernig et al. 1995; Wernig et al. 1999), but not in those with motor-complete SCI who have therefore been excluded from this therapy (Beherman & Harkema, 2000; Dietz et al., 1995; Dietz et al., 1997). With respect to cardiovascular benefit, however, BWSTT may offer distinct advantages over other exercise interventions, even in individuals with motor-complete SCI. First, unlike arm ergometry, BWSTT is an upright exercise that specifically targets the lower limbs. Second, because of the passive nature of the exercise and the body-weight support, this type of training can be performed for long durations without fatigue. Finally, BWSTT may be performed in individuals with upper or lower motor neuron injuries and without the inherent risks associated with FES exercise.

From a cardiovascular perspective, the value of BWSTT may be best evaluated by measures of peripheral vascular function as well as by indices of neural control of cardiovascular regulation, as both have clinical value and may be adversely altered after SCI. Regarding the former, recent research has shown that individuals with complete SCI exhibit peripheral vascular changes that likely contribute to their increased cardiovascular risk. Specifically, studies have found the luminal diameter to be significantly reduced (Schmidt-Truckass et al., 2000), and the vascular resistance to be significantly increased (Hopman et al., 2002; Walden et al., 1991) in the femoral artery of individuals with complete SCI, and accordingly, resting femoral artery blood flow may be reduced by approximately 50% compared to that of able-bodied individuals (Nash et al., 1996).

Clinically, this reduction in blood flow has been hypothesized to contribute to thrombus formation (Mammen, 1992; Nash et al., 1996), in addition to delayed wound healing (Walden et al., 1991) and an increased risk of pressure sore formation (Walden et al., 1991). Individuals with SCI have also been shown to suffer from a reduced compliance of the femoral artery (Schmidt-Truckass et al., 2000). Arterial compliance, or the ability of an artery to expand and recoil in response to changes in intravascular pressure, is particularly important as it allows the vessel to accommodate pulsatile increases in blood volume and thus confers a protective effect against vessel wall damage (Arnett et al., 1994). Clinically, reductions in arterial compliance are thought to be a contributing factor to vascular damage, and the associated risks of thrombosis, myocardial infarction and stroke (Seals, 2003).

With respect to neural regulation, power spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV) have become commonly used, non-invasive methods used to quantify the autonomic control of the cardiovascular system (Akselrod et al., 1981; Kamath et al., 1993; Pagani et al., 1997; Parati et al., 1995). Regarding HRV, successive R-R intervals obtained from electrocardiogram (ECG) recordings have been shown to oscillate around two main frequencies. The high frequency oscillation, centred around 0.25 Hz (HF_{HRV}; 0.15-0.40 Hz) corresponds to parasympathetic outflow to the heart via the vagus nerve (Pomeranz et al., 1985), while the low frequency oscillation, centred around 0.1 Hz (LF_{HRV}; 0.04-0.15) has been shown to correspond to both the sympathetic and parasympathetic outflow to the heart, although it is much more indicative of the former (Montano et al., 1994; Pomeranz et al., 1985). Thus, the LF:HF

ratio of HRV has become an accepted measure of cardiac sympathovagal balance. Similarly, the LF oscillation of systolic and diastolic BPV (LF_{SBP}, LF_{DBP}; 0.04-0.15 Hz), also referred to as Mayer waves, has been shown to correspond to neurovascular control via the sympathetic nerves (Pagani et al., 1997; Parati et al., 1995). Measures of HRV and BPV have been found to have significant clinical value, as relatively decreased cardiac vagal predominance has been associated with an increased risk of cardiovascular mortality (Gleiger et al., 1987; Kleiger et al., 1987), and increased BPV and enhanced Mayer waves are associated with end organ damage (Frattola et al., 1993; Miao and Su, 2002). Previous work from our lab has shown positive changes in HRV and BPV following BWSTT in individuals with motor-incomplete SCI (Ditor et al., unpublished observations), however, it is unknown if individuals with motor-complete SCI may experience the same benefit, due to their more passive participation in the exercise. Our previous work also suggested that BWSTT may confer reductions in general resting sympathetic tone, without impairing orthostatic tolerance in individuals with motor-incomplete tetraplegia. However, it has yet to be determined if individuals with more severe sympathetic decentralization may respond in the same way, of if potential changes in resting autonomic tone following BWSTT may come at the cost of a decreased tolerance to postural stress.

The purpose of this study was to investigate the effects of a 4-month BWSTT program on arterial dimension and function and measures of HRV and BPV in individuals with motor-complete SCI. As a secondary purpose, we investigated the effects of BWSTT on the response to postural stress (60° head-up tilt; HUT), to

determine if potential training-induced changes in resting cardiovascular regulation would be accompanied by reductions in orthostatic tolerance. Finally, as the physiological characteristics of our participants varied widely, we aimed to make a preliminary examination of what factors may predict favourable outcomes following BWSTT in individuals with motor-complete SCI.

Methods:

Participants

Six individuals (4 male, 2 female; age 37.7 ± 15.4 yrs.) with chronic SCI (C4-T12; ASIA A-B; 7.6 ± 9.4 yrs. post injury) were included in the present investigation. Although 10 individuals were initially recruited, three participants withdrew from the study for personal reasons, and one participant could not adequately adhere to the training program due to recurrent health issues. In addition, of those that completed the training program, the three individuals with tetraplegia could not sufficiently maintain 60° HUT during post-testing to allow for complete data collection, and therefore, tilt data correspond to participants with paraplegia only. All participants were recruited from an outpatient SCI clinic at Chedoke Hospital, Hamilton, Ontario, Canada. Participants were only included if they were at least one year post injury and were free of any coincident cardiac disease. Participants were also required to be free of any musculoskeletal condition that would contraindicate exercise training. This investigation was approved by the McMaster Research Ethics Board (MREB), and all participants provided written informed consent in accordance to MREB guidelines. Participant characteristics are summarized in Table 1.

Testing protocol

Participants underwent 2 separate testing procedures at baseline and after 4 months of BWSTT. Testing session #1 consisted of Doppler ultrasound imaging of the carotid and femoral arteries. Testing session #2 consisted of continuous heart rate and blood pressure data acquisition to determine measures of heart rate variability (HRV) and blood pressure variability (BPV). For both sessions data were acquired during supine rest and during postural stress (60°HUT). In order to minimize external confounding stimuli, testing sessions were conducted on separate days, and post-testing sessions were always conducted at least 24 hours after the final training session to ensure a true resting state. In general, testing sessions occurred between 10:00am and 5:00pm, however, for any given participant the clock time at each testing session never differed by more than 2 hours at pre and post-testing. Participants were instructed to abstain from caffeine and cigarette smoking for at least 12 hours prior to testing, and were 2 hours post-prandial. Anti-embolic stockings and abdominal binders were not worn during the testing sessions, and participants were asked to empty their urine bags prior to data acquisition. Medications were not interrupted during the study, however, medications and dosages were identical at all testing sessions for each participant. In addition, the only medications that may reasonably have affected our measures were baclofen (taken by 5 participants), and ditropan (taken by 2 participants), which were taken for their antispastic properties. The incidence of cardiovascular side effects associated with these medications are very low, and often transient and only associated with the start of treatment (CPS, 2003).

Doppler ultrasound imaging

Upon entering the laboratory, participants were transferred onto a tilt table and approximately 5-10 minutes of supine rest preceded any data acquisition. The common carotid (CCA) and common femoral (CFA) arteries were then imaged during supine rest and 60° HUT, with a 3-minute period of 30° HUT separating these 2 conditions. Measurements of the CCA were made approximately 1.5 cm proximal to the bifurcation, and measurements of the CFA were made below the inguinal ligament, approximately 2 cm proximal to the bifurcation.

Arterial diameters, and mean blood velocities (MBV) were estimated by a Doppler ultrasound system, with a high-resolution (5-10 MHz) linear array probe (GE Vingmed System Five), and BP was simultaneously recorded by a Finapress cuff for subsequent determination of arterial compliance (Ohmeda 2300, Madison, WI). BP and MBV data were continuously displayed at 200 Hz and stored on a computer for later analysis with the use of customized software (Chart 4, Powerlab), and Doppler ultrasound images were stored on the system's internal hard drive for subsequent manual analysis (Echopac image analysis V = GE). The pulsed wave Doppler sample volume gate was adjusted to cover the width of the entire vessel to account for the non-uniform blood velocity distribution within the vessel. Real time images were over two cardiac cycles (cineloop), and therefore, systolic and diastolic diameters could be measured, and used to determine mean vessel diameter ((systolic +2(diastolic))/3). For each image obtained, systolic diameter was measured 3 times and averaged for a final value, and likewise for diastolic diameter. In addition, 3 images were taken for each artery and averaged. MBV

was obtained by integration of the area under the curve of the continuous MBV signal over a 1-minute period that included the time of the vessel imaging. For the femoral artery, forward blood velocity was considered positive and reverse blood velocity as negative when integrating the area under the curve of the MBV signal. The blood flow velocity of our system was calibrated against a corn-starch solution pumped through tubing (Shoemaker et al., 1996).

Femoral artery blood flow volume (FBF) was calculated as: FBF (ml/min) = MBV (cm/sec) x mean vessel cross-sectional area (CSA; cm^2) x 60; where CSA = π(mean diameter/2)^2. Femoral artery resistance (mmHg/ml/min) was calculated as: Resistance (mmHg/ml/min) = MAP/FBF. Arterial compliance (for the carotid and femoral arteries) was calculated as: Compliance (mm^2/mmHg) = (Systolic CSA (mm^2) – diastolic CSA (mm^2)) / pulse pressure (mmHg).

HR and blood pressure data acquisition for HRV and BPV measures

Continuous recordings of HR and blood pressure (BP) data were obtained from each participant at baseline and after 4 months of BWSTT. Upon entering the laboratory, each participant was transferred onto a table and fitted with a Polar HR monitor and a finger plethysmography (Finapres) cuff (Ohmeda 2300, Madison, WI). In an attempt to achieve steady state resting conditions participants lay quietly for 10 minutes prior to the start of data collection, which took place in a dark, quiet room during spontaneous breathing. HR and BP data were collected during a 20-minute period of supine rest and a 20-minute period of 60° HUT. An adjustable arm-rest was attached to the tilt table such that participants could keep their hand at heart level during 60° HUT for Finapres BP

recording. A 3-minute period of 30° HUT, with no data collection, separated the supine and 60° HUT trials. Participants were asked not to sleep during data collection and although they were not disturbed during the testing sessions, none had any problems remaining awake. Systolic, diastolic and mean arterial pressures (MAP = (SBP+2DBP)/3) were determined by automated ausculation at the left brachial artery (Dinamap pro 100V2, GE Medical Systems, Tampa, Fla) just prior to the 20-minute period of supine rest, and again, immediately upon 60 ° HUT. All subsequent single value BP data in the present study refer to these measures.

HR and Finapres BP signals were sampled at 500 Hz using a 12 bit analog-digital converter (CODAS, DATAQ Inc., Akron, OH). The signals were continuously and simultaneously displayed on an IBM computer using WINDAQ data acquisition software (Dataq Instruments). The data were then saved on the computer hard drive and and transferred to a separate computer (Daewoo AMD-K6 processor) equipped for HRV and BPV analysis.

Computation of HRV and BPV

A customized software program (MATLAB) (Kamath et al., 1998), was used to identify a stable and noise independent fiducial point on all R-waves for each recording, as well as beat-to beat values of systolic and diastolic blood pressure (SBP, DBP). An RR-interval tachogram, as well as separate SBP and DBP tachograms, were then generated from the continuous HR and BP data, respectively. All tachograms were inspected for ectopic beats which were subsequently removed using a linear interpolation algorithm (Kamath et al., 1998). When files were found to contain excessive ectopic

beats (>5/min), the investigator visually inspected the tachogram for a sufficiently long period of relatively ectopic-free segments of HR and BP data for further analysis. Beat-to-beat HRV and BPV signals were then computed, and then resampled at 2 Hz using linear interpolation to obtain equally sampled time series. For each data set, 4 record lengths of 256 points were selected automatically for power spectral analysis. The mean value of the HR and BP were removed and the equally sampled HRV and BPV signals were fed through a second order high pass Butterworth filter with a cut-off of 0.02 Hz. Power spectra were then computed from the filtered HRV an BPV signals using previously described software (Kamath et al., 1998). Final frequency domain measures represent the average of all accepted record lengths. Oscillations ranging between 0.04-0.15 Hz were designated as LF while oscillations between 0.15-0.40 Hz were designated as HF. The data analysis software used allowed the investigator to accept or reject any of the 4 power spectra produced for each 10 minute testing session. Thus, the investigator could reject power spectra showing a fusion of the LF and HF peaks, as sometimes, albeit rarely, occurred during spontaneous breathing. Peak values of the LF and HF components were identified from the HRV and BPV power spectra and expressed as $(beats/min)^2/Hz$, and $(mmHg)^2/Hz$, respectively. The power of the LF and HF components were calculated via integrating the area under each curve and expressed as $(beats/min)^2$ and $mmHg^2$.

Training intervention

BWSTT apparatus

The Woodway Loco-system (Woodway USA Inc., Foster, CT) is a specialized treadmill with a built-in weight supporting system. Participants were fitted with a harness

while seated in their wheelchairs and then wheeled up a ramp to the treadmill. Cables were then attached to the harness, and a pulley system was used to hoist participants into the standing position over the treadmill. Once upright, a second set of cables were used to connect participants to weight stacks located at the front of the treadmill which could be set at a pre-determined percentage of each participant's body weight. The Woodway Loco-system allows for a range of speeds between 0.1 and 5.0 km/hr, and speed may be adjusted by 0.1 km/hr increments. Hand-rails are attached to the treadmill, and while participants could use these rails for balance if needed, they were discouraged to use them to assist in weight support. Two trainers sat at either side of the tread, and assisted participants in the gait cycle, while a third stood behind the participant and aided in weight shifting, balance and general safety.

Training protocol

Participants exercised at a frequency of 3 times per week for 4 months. During the first training session an appropriate amount of body-weight support was chosen for each participant, such that he or she could just stand on the tread without buckling at the knees. Although participants had the opportunity to decrease body-weight support as individually tolerated, none of them were able to reduce their support over the course of the training protocol. For the sake of safety, initial treadmill speed was arbitrarily chosen at 0.5 km/hr, and the duration of ambulation at 15 minutes (3 bouts of 5 minutes). As the exercise was essentially passive, speed and duration were progressed relatively quickly in the training program. Increases in speed were largely dictated by the amount of spasticity in the legs, and the trainers' ability to move the leg through this spasticity while

maintaining proper gait mechanics and safety. Time constraints dictated a maximum duration of 60 minutes. Daily training HR's were recorded in each participant's training log, from which an average training HR could be determined over the course of the 4-month training period. Also, in order to determine the contribution of upright posture to the HR response to ambulation, HR was determined after 5 minutes of motionless upright suspension on the treadmill at baseline and after the 4 months of BWSTT. The baseline upright HR was determined on the third day of training to allow for habituation to the BWS treadmill.

Statistical analysis

One-way analyses of variance (ANOVA) with repeated measures for time were used to compare means corresponding to resting measures before and after 4 months of BWSTT, as well as to compare the HR response to BWSTT between the first 2 months of training and the last 2 months. Two-way ANOVA (condition x time) with repeated measures for time, were used to determine exercise training-induced changes in response to orthostatic stress. Tukey HSD post-hoc analyses were used as required to determine specific differences between means and Pearson r correlation analyses were performed to determine possible relationships between variables. Statistical significance was set at $p<0.05$ and throughout the text and figures, data are presented as means ± standard deviation. In order to identify factors that may predict positive outcome, participants were divided into 2 groups based on the HR response to ambulation; i.e. those who experienced an average training HR greater than 100 beats/min (responders), and those who experienced an average training HR less than 100 beats/min (non-responders). Due

to the small number of participants, however, exercise-induced changes between these two groups were not compared statistically, but only informally described.

Results:

Program compliance and safety considerations

The compliance rate ((number of sessions completed/number of scheduled sessions) x 100), of the 6 participants that successfully completed the BWSTT protocol was 83.3 ± 7.6%. In this group, 1 individual experienced frequent syncope during the training sessions, especially nearing the end of the 4-month protocol. One other participant developed a stage 1 pressure sore over a vertebrae due to irritation from the harness. The sore was detected early, covered with a clear adhesive during the subsequent training sessions and was not problematic. No episodes of autonomic dysreflexia or musculoskeletal injuries occurred in any participant during the course of the training program.

Cardiovascular response to BWSTT

There was no significant change in resting HR following the 4-month BWSTT program (Table 2), and therefore, pre and post values were averaged for the determination of the HR response to BWSTT. Likewise, there was no significant change in the average HR during BWSTT when comparing the first 2 months of training to the last 2 months, or upright HR at pre and post testing. Upright HR's were significantly higher than resting HR's ($p=0.001$), and there was a trend ($p=0.09$) for a further, but modest increase in HR from the upright position to ambulation (resting: 64.4 ± 6.3; upright: 80.0 ± 11.6; ambulation: 98.1 ± 22.3 beats/min). However, the HR response to

ambulation was extremely varied in our participants, especially in those with tetraplegia. For example, participants with paraplegia experienced an average HR increase of 37.1 ± 10.7% (range 28-49%; exercise HR: 86-106 beats/min) while those with tetraplegia experienced an average increase of 67.1 ± 39.1% (range 26-104%; exercise HR: 68-135 beats/min). The peak exercise HR that was recorded over the course of training was significantly higher than the average exercise HR ($p=0.004$; range 78-168 beats/min), suggesting that the passive nature of the movement was more likely responsible for the relatively modest HR response to ambulation, rather than sympathetic decentralization per se. Three participants experienced an average exercise HR greater than 100 beats/min (responders: DB: 135, RH: 106, TC: 103, beats/min), the other 3 experienced a much more modest HR response to ambulation (non-responders: BK: 68, DP: 86, RM: 93, beats/min). The distinction between responders and non-responders should not be confused with the distinction between those with tetraplegia and those with paraplegia (see Table 1), i.e. the HR response to ambulation was not simply a factor of lesion level. Rather, greater HR responses to ambulation seemed to occur in those with the greatest degree of muscle spasticity and in those who were the least tolerant of orthostatic stress. In particular, there was a significant correlation between the percentage change in HR from rest to ambulation, and the percentage change in MAP from rest to 60 ° HUT at baseline testing ($p=0.02$, $r = -0.89$; Figure 1).

The effects of BWSTT on resting measures of arterial dimension and function

There was no significant change in the CSA or the resting blood flow of the CFA with training ($p=0.54$, $p=0.28$, respectively)(Table 2). There was however, a significant

25.5% reduction in the resistance of the CFA following 4-months of BWSTT (p=0.04)(Table 2). Similarly, there was a trend (p=0.07) toward an increased compliance of the CFA (Table 2). There was no significant change in the compliance of the CCA (p=0.88). Finally, there were no apparent differences between responders and non-responders for exercise-induced changes in arterial dimension or function.

The effects of BWSTT on resting measures of HRV

There were no significant changes in LF power, HF power or the LF:HF ratio after 4 months of BWSTT (p=0.10, p=0.47, p=0.25, respectively)(Table 3). There was, however, a suggestion that responders may have experienced a selective, but not statistically significant, training-induced decrease in the LF:HF ratio (pre: 1.53 ± 0.67 vs. post: 1.04 ± 0.35; p=0.14), while non-responders showed no change (pre: 1.37 ± 0.08 vs. post: 1.41 ± 0.35; p=0.85) (Figure 2). The putative reduction in the LF:HF ratio among responders was due to increases in HF power (4272.0 ± 785.3 vs. 5203.4 ± 845.6, $(beats/min)^2$; p=0.03) and non-significant decreases in LF power (5845.7 ± 1727.0 vs. 4975.8 ± 868.4, $(beats/min)^2$; p=0.27).

The effects of BWSTT on resting measures of BPV

There was no change in SBP, DBP or MAP following the 4 months of BWSTT (p=0.90, p=0.62, p=0.74, respectively) (Table 4). Likewise, there were no significant training-induced changes in LF_{SBP} or LF_{DBP} (p=0.64, p=0.42, respectively)(Table 4). There was, however, a suggestion that responders may have experienced selective training-induced decreases in LF_{SBP} (responders pre: 196.3 ± 20.0, responders post: 158.5 ± 13.7, p=0.03; non-responders pre: 131.7 ± 48.7, non-responders post: 153.5 ± 79.2,

$mmHg^2$, p=0.36) and LF_{DBP} (responders pre: 206.8 ± 19.0, responders post: 174.3 ± 33.3, p=0.06 non-responders pre: 173.4 ± 8.8, non-responders post: 182.6 ± 37.2, $mmHg^2$, p=0.68; Figures 3 and 4).

The effects of BWSTT on orthostatic tolerance

Following the 4 months of BWSTT, none of the participants with tetraplegia could maintain 60° HUT long enough for the complete collection of HRV, BPV and Doppler ultrasound data, and in fact, one participant would experience syncope immediately upon being tilted to 60°. This was in direct contrast to baseline testing, when all participants could maintain 60° HUT for the full duration that was required.

There was no change in orthostatic tolerance in participants with paraplegia following the 4 months of BWSTT (MAP: pre supine: 89.8 ± 14.9, pre HUT: 91.9 ± 12.7, post supine: 83.7 ± 10.9, post HUT: 89.1 ± 1.8, mmHg).

Discussion:

The main finding of this study is that individuals with motor-complete SCI may experience positive peripheral vascular changes following 4 months of BWSTT. These changes were evidenced by the significant decrease in femoral artery resistance and the strong trend (p=0.07) for increase in femoral artery compliance in our participant group. These changes appeared to be quite robust, as the decreases in resistance and the increases in compliance were observed in 5 of our 6 participants (a separate individual in each case experienced no change). The lack of a statistically significant change in femoral compliance was likely due to our small sample size, as the effect size of this adaptation was very large (ES=1.01). The HRV and BPV data were not quite as clear and

suggested that only a select group of individuals may experience changes in these measures following BWSTT.

The effects of BWSTT on vascular dimension and function

The reduction in CFA resistance and increase in CFA compliance appeared to be independent of the HR response to exercise, as responders and non-responders showed similar changes. Thus, BWSTT may promote changes in peripheral vascular resistance and compliance in motor-complete SCI despite the relatively low HR that may be elicited. There were, however, no changes in femoral artery CSA or compliance of the CCA, and the increases in resting femoral artery blood flow were not significant. The lack of a change in compliance of the CCA may be noteworthy for two reasons. First, it may act as an informal control, and demonstrate that the increases in femoral artery compliance were not a random effect of time. Second, it suggests that although BWSTT was effective in causing local vascular effects it was not an intense enough exercise stimulus to cause systemic vascular adaptations.

From clinical perspective, the observed increase in femoral artery compliance may be encouraging for individuals with complete SCI, as the relationship between arterial stiffness and cardiovascular risk has been well established (Kingwell, 2002; Safar, 2001; Seals, 2003). Specifically, the inability of a vessel to expand and recoil with pressure changes results in damage to the vessel wall, which in turn may lead to atherosclerosis and thrombus formation (Seals, 2003). Vessel compliance also converts intermittent blood flow from the heart to a more steady flow throughout the circulation and thus, enables a more effective tissue perfusion. As individuals with complete SCI are

at an increased risk of complications due to thrombus formation, and pressure sore development due to poor tissue perfusion (DeVivo et al., 1993), exercise-induced increases in arterial compliance may be particularly desirable in this population. In addition, increased arterial compliance may have a cardioprotective effect, as vessel stiffness is associated with an increased demand on the heart and a decreased coronary perfusion (Mitchell, 1999). Although these deleterious cardiac effects are most commonly associated with aortic or carotid stiffness, there is some evidence that a reduced compliance of the more peripheral brachial artery is also associated with increased cardiac risk (Millar et al., 1999). It is therefore, possible that improved femoral compliance achieved via BWSTT may also confer a cardioprotective effect, although further research is required to examine this issue. Thus, although BWSTT may not enhance ambulation in individuals with complete SCI, it may promote clinically relevant improvements in vascular compliance and should be encouraged as a possible rehab technique in this population. The present study also found a significant reduction in femoral artery resistance, but no accompanying increase in femoral artery blood flow. However, the lack of a significant change in CFA blood flow was likely due to our small sample size, as the effect size of our changes in CFA blood flow were found to be moderate (ES=0.53). Increases in CFA blood flow would be clinically relevant as they may be expected to decrease the risk of thrombus formation and pressure sore development, and aid in wound healing ability.

The true value of BWSTT as a means of promoting positive vascular adaptation must be made in comparison to other currently available modalities for individuals with

complete SCI. First, although arm ergometry may promote central cardiovascular changes in those with sufficient arm function, this form of exercise becomes less beneficial in individuals with cervical lesions (Jacobs and Nash, 2001). Further, as leg blood flow actually decreases during arm ergometry, even in individuals with SCI (albeit to a lesser extent) (Hopman, 1994), vascular changes of the lower limbs would not be expected with this form of exercise. In contrast, FES exercise has proven to be an effective means of improving central and peripheral cardiovascular function in individuals with SCI. For example, Hopman et al. (2002) found an approximate 30% decrease in femoral artery resistance following 6 weeks of FES cycling and an approximate 30% increase in femoral artery blood flow in 9 participants with complete SCI. Similarly, in a study conducted by Gerrits et al. (2001) (n=9), 6 weeks of FES cycling was associated with significant increases in femoral artery diameter (8%) and resting mean inflow volume (37%), and a significant decrease in femoral artery resistance (8%). No changes were noted, however, in the carotid artery. Finally, Nash et al. (1997) (n=12) examined the effects of electrically stimulated ambulation exercise and found a significant 33% increase in femoral artery cross-sectional area, accompanied by a significant 56% increase in resting femoral artery blood flow. While, measures of arterial compliance were not included, the combination of stimulated contractions and upright posture may prove to be the most effective means of promoting cardiovascular adaptation in individuals who can tolerate this modality. Still, FES exercise carries the risk of skin irritation, autonomic dysreflexia and bone fracture, and as mentioned, stimulated contractions may not be evoked in those with lower motor neuron injuries (Jacobs and

Nash, 2001). Thus, BWSTT may be an effective alternative for promoting positive vascular adaptations in individuals with SCI who cannot tolerate or do not have access to FES exercise. It is of interest to note that the present study did include one participant with a lower motor neuron injury (DP), and this individual experienced substantial increases in femoral artery compliance and blood flow. Anecdotally, this participant also reported an improved temperature regulation of the legs and an improved wound healing ability. Although, these are only single case observations they are highly encouraging as BWSTT may prove to be a unique means of improving vascular function in individuals with lower motor neuron injuries. Further research is certainly warranted to investigate this possibility.

A potentially negative complication associated with the vascular adaptations to BWSTT was the increased propensity to orthostatic intolerance in the participants with tetraplegia. It should be emphasized, however, that participants were particularly susceptible to postural hypotension during the 60° HUT tests as abdominal binders and anti-embolitic stockings were not permitted. In normal daily situations that require upright posture, these supportive devices would certainly counter any exercise-induced intolerance that may result from BWSTT. In addition, the rhythmic movement of the legs, and to a lesser extent the harness that was worn, prevented syncope during the BWSTT sessions. The one participant that did experience syncope during BWSTT only did so immediately after being hoisted and before ambulation began. After a brief delay this participant was always willing and able to continue with the exercise session.

Unfortunately, the participants with tetraplegia could not withstand 60° HUT long enough at post testing to allow for data collection and therefore, the mechanism that accounted for this intolerance may only be speculated upon. In able-bodied individuals exercise training-induced decreases in orthostatic tolerance have been attributed to both cardiac adaptations and an attenuated baroreflex responsiveness (Ogoh et al., 2003; Levine et al., 1991). The former mechanism was not likely a factor in the present study, as the individual with tetraplegia who did not show a HR response to ambulation, and therefore, experienced no central adaptation, still became less tolerant of postural stress after training. It is unclear if participants actually experienced a decrease in baroreflex responsiveness, or if their impaired vasoconstrictor ability simply could not cope with the training-induced decrease in vascular resistance. The latter is certainly reasonable as FES ambulation has been shown to enhance flow mediated dilation in individuals with complete SCI (Nash et al., 1997). Regardless, despite the negative implications for resting blood flow and tissue perfusion, the increased vascular resistance that that has been shown to accompany SCI (Hopman et al., 2002) may partially protect against orthostatic intolerance. Thus, decreasing leg vascular resistance in individuals with impaired vasoconstrictor ability, likely confers an decreased ability to tolerate postural stress. This may be especially apparent in individuals with impaired constriction of the large splanchnic vascular bed as individuals with paraplegia did not become intolerant to postural stress after the 4 months of BWSTT despite the decreased resting vascular resistance of the CFA that was observed.

The effects of BWSTT on HRV and BPV

In general, BWSTT did not prove to be a major central cardiovascular stimulus for individuals with motor-complete SCI, and as such, our participants as a whole did not experience significant changes in measures of HRV and BPV. However, despite the small sample size, the results suggest that a subgroup of individuals may experience a substantial HR response to this form of exercise, despite its involuntary nature, and accordingly may experience modest changes in measures of HRV and BPV. Thus, individuals with motor-complete SCI who respond to BWSTT may experience relative increases in the vagal outflow to the heart and decreases in BPV that have been associated with decreased risk of cardiovascular mortality and end-organ damage, respectively (Frattola et al., 1993; Malik and Camm, 1995; Miao and Su, 2002). In the present study, the factors accounting for the HR response to BWSTT seemed to be the presence of muscular spasticity and a propensity to orthostatic intolerance. The relationship between postural hypotension and the HR response to BWSTT was clear and demonstrated by the significant correlation between decreases in MAP upon 60° HUT and the increase in HR from rest to ambulation. This relationship suggests that the upright nature of BWSTT is a key component to its potential benefits, as it necessitates a HR response in those intolerant of postural stress. Further support for this contention may be that recumbent passive exercise has been shown to evoke no HR response in individuals with SCI (Figoni et al., 1990). However, the upright posture did not account for the entire HR response to ambulation since HR's tended to be higher during BWSTT than during motionless upright posture ($p=0.09$). Factors accounting for this further

increase in HR may only be speculated upon. Unfortunately, measures of muscle spasticity were not conducted during ambulation, and therefore, its contribution to the HR response is more anecdotal but certainly clear during the training sessions. Further research is required to examine this issue.

The autonomic adaptations that may be achieved via BWSTT should be compared to those that may be achieved by other available forms of exercise for individuals with SCI. Such comparisons are difficult due to the scarcity of literature in this area, however, previous work from our lab has shown a 38% reduction in the LF:HF ratio following 3 months of combined resistance and arm ergometry in individuals with incomplete tetraplegia (Ditor et al., unpublished observations); a comparable change to that observed by the responders in the present study. However, the participant characteristics varied greatly between these two studies and further research is required to determine the comparative efficacy of these two training techniques. In summary, peripheral vascular changes were associated with BWSTT regardless of the HR response to ambulation. Therefore, those who do not experience substantial increases in HR during ambulation may still achieve vascular benefit from this form BWSTT, but may wish to supplement this exercise with arm ergometry in order to achieve improvements in neurocardiac control.

Conclusions:

The present study is the first to show that BWSTT causes positive peripheral vascular change in individuals with motor complete SCI. Further, these improvements in vascular function may be achieved regardless of the HR response during ambulation.

BWSTT should therefore be encouraged as a means of improving cardiovascular health in this population, especially in those who cannot tolerate or do not have access to FES exercise. Still, the recommendation should be made with the understanding that BWSTT may worsen the tendency for orthostatic intolerance in individuals with motor-complete tetraplegia. Finally, BWSTT may also cause modest improvements in measures of HRV and BPV in a select subgroup of individuals who respond to ambulation with moderate to large increases in HR. In the present study, factors associated with a substantial HR response to BWSTT seemed to be a propensity to orthostatic intolerance and muscular spasticity.

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Figure Captions:

Figure 1

Relationship between the percentage change in HR from rest to ambulation during the 4 month BWSTT program and the percentage change in MAP from rest to 60° HUT at baseline testing ($p<0.05$; $r = -0.89$).

Figure 2

Changes in the LF:HF ratio before and after 4 months of BWSTT in responders (open circles, dashed lines) and non-responders (closed circles, solid lines).

Figure 3

Changes in LF_{SBP} before and after 4 months of BWSTT in responders (open circles, dashed lines) and non-responders (closed circles, solid lines).

Figure 4

Changes in LF_{DBP} before and after 4 months of BWSTT in responders (open circles, dashed lines) and non-responders (closed circles, solid lines).

Figure 1.

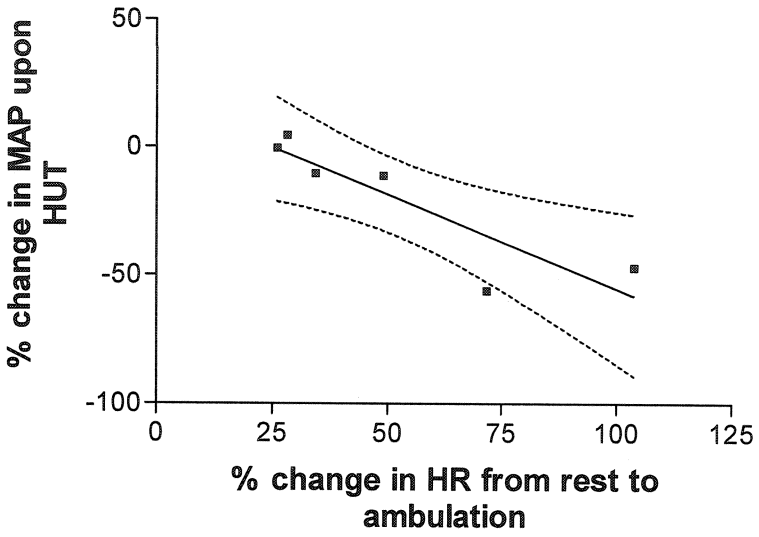
50
0
-50
-100
0
25
50
75
100
125
% change in MAP upon HUT
% change in HR from rest to ambulation

Figure 2.

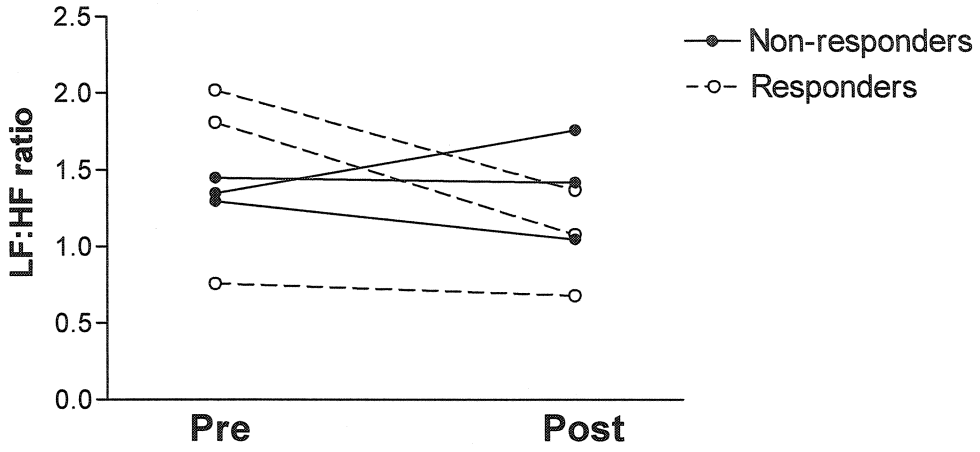
2.5
2.0
1.5
1.0
0.5
0.0
LF:HF ratio
Pre
Post
Non-responders
Responders

Figure 3.

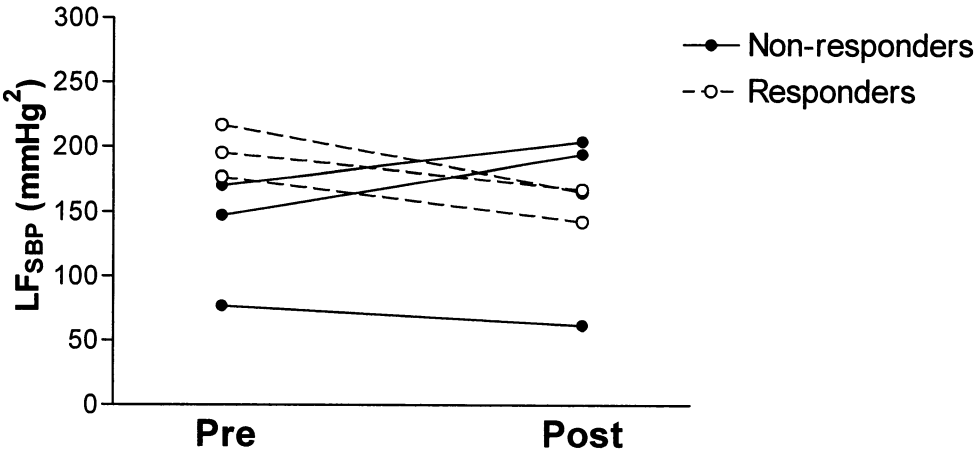
300
250
200
150
100
50
0
LFSBP (mmHg2)
Pre
Post
Non-responders
Responders

Figure 4.

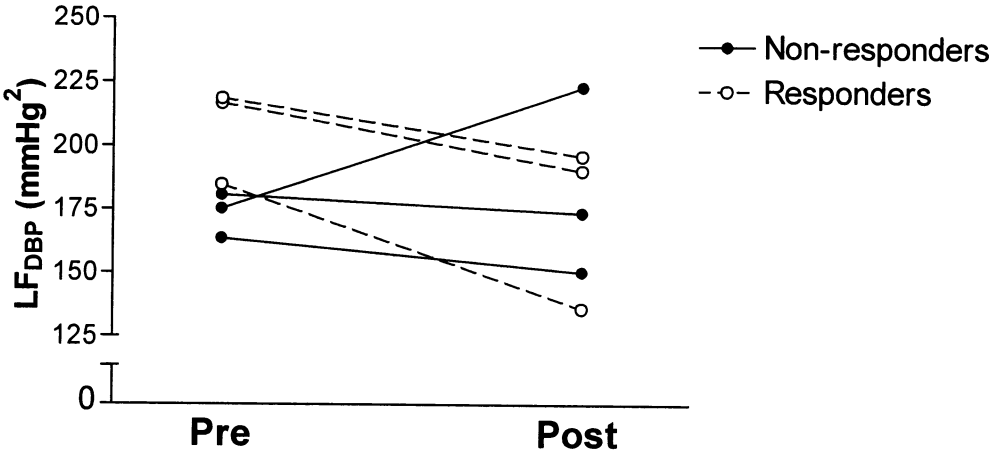
250
225
200
175
150
125
0
LF$_{DBP}$ (mmHg^2)
Pre
Post
Non-responders
Responders

Table 1. Participant Characteristics

Participant	Sex	Age	Lesion Level	ASIA Clasification	Years Post Injury
1	M	57	C6	B	6
2	F	26	C4	B	4.5
3	M	51	T12	A	4.5
4	M	28	T5	A	3
5	F	45	T9	A	26.5
6	M	19	C4	B	1

Table 2. Measures of arterial dimension and function before and after BWSTT

	Baseline	4 months
CSA_{CFA}	37.1 ± 16.2	39.5 ± 11.0
R_{CFA}	0.98 ± 0.17	0.73 ± 0.26 *
BF_{CFA}	101.7 ± 30.4	129.2 ± 66.2
$Comp_{CFA}$	0.064 ± 0.029	0.106 ± 0.051
$Comp_{CCA}$	0.110 ± 0.039	0.107 ± 0.071

Note: CSA_{CFA}, cross-sectional area of the common femoral artery (mm^2); R_{CFA}, resistance of the common femoral artery (mmHg/ml/min); BF_{CFA}, blood flow at the common femoral artery (ml/min); $Comp_{CFA}$, Compliance of the common femoral artery, $Comp_{CCA}$, Compliance of the common carotid artery (mm^2/mmHg). * denotes a significant decrease compared to baseline values ($p<0.05$). Values are means ± S.D.

Table 3. Measures of HR and HRV before and after BWSTT

	Baseline	4 months
HR	61.9 ± 9.7	66.9 ± 5.7
LF	6302 ± 1251.9	5525 ± 882.4
HF	4647 ± 664.1	4916 ± 803.9
LF:HF	1.45 ± 0.44	1.23 ± 0.37

Note: HR, mean heart rate (beats/min); LF, low frequency power; HF, high frequency power $(beats/min)^2$; LF:HF, low frequency to high frequency ratio. Values are means ± S.D.

Table 4. Measures of BP and BPV before and after BWSTT

	Baseline	4 months
SBP	114.0 ± 19.0	113.2 ± 10.1
DBP	65.7 ± 10.5	64.0 ± 7.3
MAP	81.8 ± 13.1	80.4 ± 7.4
LF_{SBP}	164.0 ± 48.6	156.0 ± 50.9
LF_{DBP}	190.1 ± 22.6	178.5 ± 31.9

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure (mmHg); LF_{SBP}, low frequency power of systolic blood pressure; LF_{DBP}, low frequency power of diastolic blood pressure ($mmHg^2$). Values are means ± S.D.

Chapter 6

General Discussion and Future Directions

General discussion and future directions

Summary of major findings

Spinal cord injury (SCI) results, most notably, in partial or complete muscular paralysis and a loss of mobility. These functional impairments are the most obvious consequences of SCI, and in many cases, the greatest initial concern for the injured individual. Unfortunately, in the weeks and months that follow, many individuals come to realize that the full impact of SCI extends well beyond the already devastating loss of ambulation. Loss of sexual function and bladder control, frequent skin ulcerations and intractable pain become common obstacles for many individuals with SCI, while an increased risk of morbidity and mortality from many diseases become serious long term concerns. Accordingly, individuals with SCI are characterized by an increased risk of cardiovascular mortality and often suffer from cardiovascular dysfunction such as an increased propensity to orthostatic intolerance. The mechanisms underlying this increased risk and the potential to reverse it with exercise training have yet to be fully explored. The purpose of this thesis was to examine the effects of exercise training on the cardiovascular regulation of individuals with SCI, and to provide insight into how exercise may reduce the risk of cardiovascular disease and dysfunction in this population.

The reproducibility of heart rate variability and blood pressure variability measures in individuals with spinal cord injury

In the first study of the thesis it was hypothesized that measures of heart rate variability (HRV) and blood pressure variability (BPV) would be reproducible in individuals with SCI, regardless of the level of injury. The results showed that the

reproducibility of the LF:HF ratio, a HRV measure of sympathovagal balance and LF_{SBP}, a common index of neurovascular outflow were found to be very high and comparable to literature values of reproducibility for the able-bodied population. These findings are relevant for two major reasons. First, previous research has suggested that the sympathetic outflow to the cardiovascular system is completely ablated in individuals with SCI, and when evidence of sympathetic tone has been observed via HRV and BPV measures, it has been dismissed as the result of random sympathetic reflexes. However, the day-to-day reproducibility of HRV and BPV measures that were found in this study strongly suggest that sympathetic outflow to the cardiovascular system may persist in individuals with SCI, and further, that this autonomic regulation is physiologically relevant. Second, the findings of this study demonstrate that measures of HRV and BPV may be used as reliable indices of cardiovascular autonomic regulation in individuals with SCI. Further, because these measures have been shown to be predictors of cardiovascular risk, clinicians and researchers may now be encouraged to use measures of HRV and BPV to determine the effectiveness of various drug or exercise interventions on the cardiovascular health of individuals with SCI.

The effects of exercise training on heart rate variability in individuals with SCI

Previous research has suggested that the reduction of cardiac sympathetic tone that follows SCI results in a compensatory reduction in cardiac vagal tone and a concomitant maintenance of autonomic balance. Such a compensation would suggests that exercise-induced enhancements of vagal tone, which are indicative of a reduced cardiovascular risk, may be limited or prevented by the partial sympathetic

decentralization which commonly occurs after SCI. Thus, the purpose of the second study of this thesis was to determine if individuals with SCI could make positive adaptations to their cardiac autonomic control with exercise training as determined by measures of HRV. *It was hypothesized that the previously observed reduction in vagal tone was not a compensatory reduction, but rather a reflection of reduced activity levels, and that positive neurocardiac changes would be made with exercise training.* As hypothesized, the results of this study demonstrated that individuals with incomplete tetraplegia retain the ability to make positive changes in cardiac sympathovagal balance following 3 months of combined arm ergometry and resistance exercise training.

The effects of body-weight supported treadmill training on heart rate and blood pressure variability in individuals with SCI

Body-weight supported treadmill training (BWSTT) has shown promise as a means of enhancing gait recovery in individuals with incomplete SCI. To date, however, there are no published studies regarding the effects of BWSTT on the cardiovascular health and function of individuals with SCI, despite the fact that this type of exercise may hold particular promise as a means of improving such health issues and it may not carry the risks associated with functional electrically stimulated (FES) exercise. *It was hypothesized that 6 months of BWSTT would result in positive changes in measures of HRV and BPV in individuals with incomplete SCI.* The results of this study demonstrated that individuals with incomplete tetraplegia can make positive adaptations to the autonomic regulation of the cardiovascular system following 6 months of BWSTT as indicated by measures of HRV and BPV. In addition, these adaptations occurred without

an accompanying tendency to become less tolerant of orthostatic stress. BWSTT should therefore, be encouraged as a safe and effective means of improving cardiovascular health in individuals with incomplete tetraplegia.

The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI

Several studies have confirmed that individuals with complete SCI do not show improvements in ambulation following BWSTT, and therefore, are generally excluded from this therapy. Still, BWSTT may be ideal as a means to promote cardiovascular benefit in individuals with motor-complete SCI as it is an upright exercise that specifically targets the lower limbs and it may be performed for longer durations and without the risks associated with FES exercise. *It was hypothesized that individuals with motor-complete SCI would make positive changes in vascular dimension and function, as well as in measures of HRV and BPV after 4 months of BWSTT.* The results of this study showed that individuals with motor-complete SCI may experience favourable vascular changes (a significant decrease in femoral artery resistance and a strong trend for an increased femoral artery compliance) following 4 months of BWSTT. Further, although there were no significant exercise induced changes in neurocardiac or neurovascular control as indicated by measures of HRV and BPV, the results suggested that favourable changes in both these measures may occur in individuals who experience a substantial HR response to this type of training. These individuals tended to be more orthostatically intolerant and had greater muscle spasticity than the rest of the group. While it is difficult to draw major conclusions from such a small sample, these results suggest that a simple

pre-screening of individuals with motor-complete SCI over a few treadmill sessions, might predict who may or may not benefit from BWSTT with positive autonomic changes. Finally, BWSTT was found to worsen orthostatic intolerance in individuals with tetraplegia, but not in those with paraplegia.

Recommendations for cardiovascular exercise rehabilitation for individuals with spinal cord injury: The role of BWSTT

As previously mentioned, because of the many possible combinations of the level and severity of injury, individuals with SCI present an extremely varied array of abilities and disabilities in terms of both function and health. Similarly, the suitability of various exercise interventions cannot be made in a generalized fashion to the entire SCI population, but rather, different exercise strategies should be recommended based on the abilities and tolerances that may be associated with varying types of injury.

Individuals with less severe SCI (ASIA C and D injuries) may be particularly well suited for BWSTT as a means to promote cardiovascular improvement. First, in the present thesis, individuals with spared motor function (ASIA C injuries) made positive adaptations in measures of HRV and BPV after 6 months of BWSTT. Second, due to the spared sensory ability, these individuals may not be able to tolerate FES exercise. Although not measured in the present thesis, it would be predicted that favourable vascular adaptations would have accompanied the observed autonomic changes, especially in light of the subsequent results from those with more severe SCI (ASIA A and B injuries).

In the present thesis, BWSTT was associated with positive peripheral vascular adaptations in individuals with motor-complete SCI, evidenced by a significant 25% reduction in femoral artery resistance and a trend for an increased femoral artery compliance. There were however, no significant changes in femoral artery dimension or blood flow. In addition, those with high muscle spasticity and a susceptibility to orthostatic intolerance may experience positive adaptations in measures of HRV and BPV. Still, the benefits of BWSTT must be put in the proper perspective and compared to other existing modes of exercise for this population. When consulting the literature, FES exercise seems to confer the greatest cardiovascular adaptations for individuals with complete SCI. Specifically, Nash et al. (1997), found significant 33% increase in femoral artery cross-sectional area, accompanied by a significant 56% increase in resting femoral artery blood flow following 32 sessions of FES ambulation exercise (approximately 10 weeks). Likewise, Gerrits et al., (2001), found a significant 8% increase in femoral artery diameter and a significant 37% increase in femoral inflow volume following 6 weeks of FES cycling. Although femoral compliance was not measured in those studies, preliminary results from our lab suggest that FES exercise may also increase femoral compliance (de Groot et al., unpublished observations). Further, although changes in HRV have never been investigated following FES training, Jacobs et al. (1997) have shown evidence of central cardiovascular adaptation following FES ambulation exercise. Thus, individuals with motor-complete SCI who can tolerate and have access to FES exercise, especially FES ambulation, should pursue that option as a means of promoting cardiovascular adaptation. From a practical perspective, such individuals would most

likely be classified as ASIA A injuries, as they would lack sensation and not experience the pain sometimes associated with FES exercise. Nevertheless, those with motor-complete SCI who cannot tolerate (most likely ASIA B injuries), or do not have access to FES exercise, may look to BWSTT an effective means to promote peripheral vascular benefit. In general, those with motor-complete SCI who do not experience a substantial heart rate response to BWSTT (greater than 100 beats/min) should supplement this training with arm ergometry as a means of promoting positive adaptations in cardiac autonomic regulation.

Limitations and future directions

There are many difficulties and limitations when conducting exercise training studies in individuals with SCI. First, the recruitment of participants is extremely challenging as the SCI population is a relatively small one, and many individuals with SCI lack the transportation or the freedom of time that is required to make the initial commitment to exercise training studies. Further, once recruited and enrolled, many individuals with SCI lack the consistency of good health that is necessary for adequate exercise adherence. Common health issues that were encountered in the present thesis included frequent bladder infections, problems with temperature regulation and intractable pain, and as a result exercise adherence often suffered, or required a great deal of scheduling and rescheduling to accommodate the frequent absenteeism.

For those individuals with SCI who are willing and able to exercise consistently, BWSTT per se is a particularly challenging form of exercise to coordinate. First, 3 exercise assistants are required per session to help in the production of gait and the

maintenance of a safe exercise environment. As the exercise assistants used for the present thesis projects were primarily working on a volunteer basis and could not fully commit to the research, an enormous volume of volunteers was needed for the series of studies to run smoothly. In addition, each volunteer exercise assistant must be trained to deal with certain medical situations that may arise during BWSTT such as autonomic dysreflexia or syncope, and be made aware of the possibility of bone fracture and pressure sore formation. Such a high demand on resources is reflected in the characteristically small number of participants that are included in studies regarding BWSTT.

There are also limitations when attempting to study autonomic function in individuals with SCI. Specifically, because the ASIA impairment scale is strictly a reflection of sensory and motor ability, two individuals with apparently similar injuries based on level and ASIA classification may have substantially different autonomic function. This shortcoming of SCI classification may often result in a greater amount of variability between participants than would otherwise be expected. Accordingly, there is a general call for a classification system relating to autonomic function in the field of SCI research.

The present thesis helped to pose new questions and open new avenues for SCI research. It should be noted however, that because of the difficulties in participant recruitment and the resources needed for exercise training in SCI research, future studies would be well advised to adopt a multi-centered approach. This would not only benefit

the quality of future SCI research, but it would also encourage the initiation of new training facilities for individuals with SCI.

Perhaps the most interesting question posed by the present thesis is regarding the possible suitability of BWSTT as a means to promote cardiovascular benefit in individuals with lower motor neuron (LMN) injuries. As stated, although they were only single-case observations, the one individual with a LMN injury in the present study did experience improvements in femoral blood flow and compliance following 4 months of BWSTT. This may be a particularly promising finding as individuals with LMN injuries are not eligible for FES exercise training.

Another interesting future direction would be to investigate if the vascular benefits that are achieved with BWSTT actually confer a reduced risk of cardiovascular complications such as thrombosis formation and an increased ability for wound healing, pressure sore prevention and temperature regulation. We have anecdotal evidence that such may have been the case, but this needs to be investigated further with larger-scale studies.

Finally, it would be a great asset to cardiovascular research in the SCI population to construct an autonomic impairment scale. Such a scale would have a very wide range of application as the changes in autonomic function could be accurately quantified after various drug or exercise interventions, and importantly, after neural regeneration when this application becomes feasible for individuals with SCI.

References:

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Nash MS, Jacobs PJ, Montalvo BM, Klose JK, Guest RS, Needham-Shropshire BM. Evaluation of a training program for persons with SCI paraplegia using the parastep 1 ambulation system: Part 5. Lower extremity blood flow and hyperemic responses to occlusion are augmented by ambulation training. Arch Phys Med Rehabil. 1997; 78: 808-814.

Appendix A

American Spinal Injury Association (ASIA) Impairment scale

American Spinal Injury Association (ASIA) Impairment scale

ASIA A: No sensory or motor function is preserved in the sacral segments S4-S5

ASIA B: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5

ASIA C: Sensory and motor function is preserved below the neurological level (including S4-S5) and more than half of the key muscles below the neurological level have a muscle grade less than 3

ASIA D: Sensory and motor function is preserved below the neurological level (including S4-S5) and at least half of the key muscles below the neurological level have a muscle grade greater than or equal to 3

ASIA E: Normal sensory and motor function

Strength grading scale:

0 total paralysis

1 palpable or visible contraction

2 active movement with full ROM, gravity eliminated

3 active movement with full ROM, against gravity

4 active movement with full ROM, against moderate resistance

5 (normal) active movement with full ROM, against full resistance

NT Not testable

STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

MOTOR

	R	L	KEY MUSCLES
C2			
C3			
C4			
C5	☐	☐	Elbow flexors
C6	☐	☐	Wrist extensors
C7	☐	☐	Elbow extensors
C8	☐	☐	Finger flexors (distal phalanx of middle finger)
T1	☐	☐	Finger abductors (little finger)
T2			
T3			
T4			
T5			
T6			
T7			
T8			
T9			
T10			
T11			
T12			
L1			
L2	☐	☐	Hip flexors
L3	☐	☐	Knee extensors
L4	☐	☐	Ankle dorsiflexors
L5	☐	☐	Long toe extensors
S1	☐	☐	Ankle plantar flexors
S2			
S3			
S4-5			

0 = total paralysis
1 = palpable or visible contraction
2 = active movement, gravity eliminated
3 = active movement, against gravity
4 = active movement, against some resistance
5 = active movement, against full resistance
NT= not testable

☐ Voluntary anal contraction (Yes/No)

TOTALS ☐ + ☐ = ☐ **MOTOR SCORE**

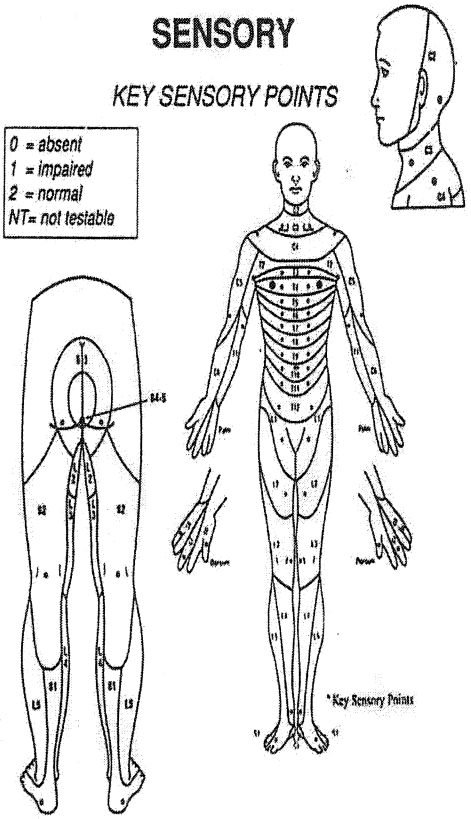
(MAXIMUM) (50) (50) (100)

SENSORY

	LIGHT TOUCH R	LIGHT TOUCH L	PIN PRICK R	PIN PRICK L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S4-5				

KEY SENSORY POINTS

0 = absent
1 = impaired
2 = normal
NT= not testable



☐ Any anal sensation (Yes/No)

TOTALS ☐ + ☐ = ☐ **PIN PRICK SCORE** (max: 112)

TOTALS ☐ + ☐ = ☐ **LIGHT TOUCH SCORE** (max: 112)

(MAXIMUM) (56) (56) (56) (56)

NEUROLOGICAL LEVELS

The most caudal segment with normal function

	R	L
SENSORY	☐	☐
MOTOR	☐	☐

COMPLETE OR INCOMPLETE? ☐

Incomplete = Any sensory or motor function in S4-S5

ASIA IMPAIRMENT SCALE ☐

ZONE OF PARTIAL PRESERVATION

Partially innervated segments

	R	L
SENSORY	☐	☐
MOTOR	☐	☐

Version 4
GHC 199

13–10

Appendix B

Picture of BWSTT apparatus