Cardiovascular and Cerebrovascular Consequences of Spinal Cord Injury

by

Jessica Ann Inskip

M.Sc., University of British Columbia, 2010
B.Sc., University of British Columbia, 2006

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Approval

Name: Jessica Ann Inskip
Degree: Doctor of Philosophy
Title: Cardiovascular and Cerebrovascular Consequences of Spinal Cord Injury

Examinining Committee:

Chair: Thomas Claydon
Associate Professor

Victoria Claydon
Senior Supervisor
Associate Professor

William Cupples
Supervisor
Professor

Brian Kwon
Supervisor
Professor
Department of Orthopaedics
Faculty of Medicine, University of British Columbia

William Sheel
Supervisor
Professor
School of Kinesiology
Faculty of Education, University of British Columbia

David Clarke
Internal Examiner
Assistant Professor

Jill Wecht
External Examiner
Associate Professor
Medicine and Rehabilitation Medicine
Mount Sinai School of Medicine

Date Defended/Approved: June 8, 2015
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Abstract

Spinal cord injury (SCI) has profound effects on motor, sensory, and autonomic function. The autonomic repercussions of SCI are widespread and demand life-long management and care. Cardiovascular problems are particularly common after high-level SCI that disrupts spinal sympathetic pathways to the heart and blood vessels.

In this thesis I investigated the effect of damage to autonomic pathways on cardiovascular control during routine activities of daily living. In Chapter 2, I showed that moderate changes in wheelchair seating positions could challenge or bolster blood pressure and cerebral blood flow in individuals with damage to autonomic pathways. This shows that positional changes can be used as physical manoeuvres to maintain blood pressure. Chapter 3 documented the progression of autonomic function over time in the acute post-injury period, demonstrating the wide range of trajectories of cardiovascular function after injury. This work also highlighted how motor, sensory and autonomic function can be affected differently by SCI; damage to motor and sensory pathways cannot always predict autonomic deficits. Next, in Chapter 4, I examined cerebrovascular control, and found that individuals with damage to autonomic pathways have a reduced cerebral blood flow response to low oxygen. While the aetiology of this difference is unclear, the results suggest that exposure to low oxygen, for example during sleep apnea, may be particularly detrimental in this population. Finally, in Chapter 5, I conducted a survey examining bowel care and cardiovascular function after SCI that identified a significant need for ongoing support to improve bowel management. It also revealed the major limitations that bowel care can have on social participation and employment. A knowledge gap was also identified regarding blood pressure control and cardiovascular symptoms triggered by bowel care.

This work reiterates the importance of autonomic assessment after SCI and the value of combining physiological recording with symptom assessments. Autonomic dysfunctions have significant ramifications for blood pressure control, cerebrovascular control, and quality of life after SCI. The integrity of the autonomic nervous system should be incorporated into research outcomes and stratification and be used to help guide clinical decision-making and self-management.

Keywords: Spinal cord injury; autonomic function; cardiovascular system; cerebral blood flow; orthostatic hypotension; autonomic dysreflexia
For my Marjories
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Chapter 1.

Introduction

The loss of autonomic functions -- not simply the inability to walk -- robs people living with paralysis of time. The ongoing management of body temperature, sexual function, bladder and bowel shave hours off our days; sometimes full experiences from our lives; and if ignored, the possibilities of far more permanent loss. …

Explaining that I cannot walk is not terribly difficult because you can see it with your own eyes. Explaining that my body cannot regulate temperature, sexual function, bladder or bowel, without some combination of supplements, medication, equipment, and strict timetables, that's more difficult to understand given the general public's current level of awareness.

A lot of folks don't want to discuss the graphic details of acts that happen in the bedroom, or the bathroom, or the act of perspiration seeping (or not seeping) through your skin. Yet, no one can deny the important roles these play in daily experiences and personal health. For most people, these actions are simply a part of daily life, but for many people living with spinal cord injuries, these activities never stray far from the forefront of their mind.

We never fully conquer secondary conditions. We manage them.

- Dan Griffin [1]

1.1. Spinal cord injury in Canada

Approximately 86,000 Canadians are currently living with the effects of traumatic or non-traumatic spinal cord injury (SCI) [2]. While the incidence of traumatic SCI in Canada is quite small, with approximately 1800 new cases annually [2], the financial cost is enormous [3]. The individual lifetime economic burden is estimated to range from
$1.5 to 3 million, depending on injury level and severity, creating a massive national annual cost of $2.7 billion for the care of those newly injured [3]. Beyond the economics, SCI can result in profound physical, social and personal costs for individuals [4, 5].

1.2. Secondary complications of SCI

SCI is a complex and heterogeneous condition with a wide range of functional sequelae. Generally speaking, the motor and sensory consequences of damage to the spinal cord are well appreciated, but the effects of damage to autonomic pathways, which also travel in the spinal cord, are rarely discussed. However the autonomic repercussions of SCI are widespread and can create some of the most frustrating barriers to community and job participation after injury. Bladder dysfunction, bowel dysfunction, sexual dysfunction, gastrointestinal dysfunction and cardiovascular dysfunction are all common after SCI [6, 7] – each demanding specific care and management and some causing substantial physical and psychological burden [8]. Improving both cardiovascular function and bowel function have been identified on several occasions as key priorities by individuals living with SCI [9, 10].

1.3. Overview of cardiovascular dysfunction after SCI

The widespread complications of cardiovascular dysfunctions in particular, negatively impact rehabilitation [11], quality of life [12], and are a common cause of morbidity and mortality after SCI [13, 14]. Cardiovascular disease appears to strike earlier in individuals with SCI, and life expectancy is decreased compared to the broader population [15]. Data from a recent Canadian Community Health Survey indicate that SCI is associated with significantly increased odds of heart disease and stroke compared to the general population [16]. Therefore, careful management of cardiovascular disease risk is increasingly becoming a priority in this population [17-19].

In terms of day-to-day cardiovascular function, deficits in short-term control of the cardiovascular system are also common after SCI. The particular manifestation depends strongly on injury level and completeness, as explored further below. Generally
speaking, SCI can disrupt central sympathetic control of cardiac function and peripheral vasomotor pathways resulting in reduced ability to adapt the cardiovascular system to particular situations. This manifests itself in a number of different ways, but two specific conditions – orthostatic hypotension (OH) and autonomic dysreflexia (AD) – are particularly common and will be described in more detail below.

1.4. Impact of SCI on autonomic control

The level and completeness of damage to autonomic pathways dictates the severity of cardiovascular dysfunction (Figure 1.1). Individuals with complete high-level injuries in the cervical spinal cord essentially lose all sympathetic control of the heart and blood vessels [20]. Therefore, resting seated blood pressure is low and typical cardiovascular responses to physiological perturbations are impaired, resulting in poor control of blood pressure and heart rate.

![Autonomic innervation of the heart and splanchnic vasculature](image)

**Figure 1.1. Autonomic innervation of the heart and splanchnic vasculature**

Note: Parasympathetic innervation to the heart (green) exits the central nervous system at the level of the brainstem and is rarely disrupted by spinal cord injury (SCI). Sympathetic outflow to the heart and splanchnic vasculature (yellow) exits the central nervous system in the thoracolumbar cord (T1-L2). Sympathetic innervation of the heart (T1-T4) and splanchnic vessels (T5-T10) can be disrupted by SCI. The splanchnic vasculature plays a key role in blood pressure control and SCI above T6 can have significant ramifications on blood pressure control. Illustration by Yona Gellert.
Injuries in the thoracolumbar region can also result in altered cardiovascular function [21-23]. The sympathetic control of the heart and the upper body vasculature exits the spinal cord between the first and fourth thoracic levels (T1-T4), while the spinal outflow to the splanchnic vasculature and the vessels of the lower limbs exits the spinal cord in the low thoracic and lumbar regions (T5-L2) [24]. Therefore, sympathetic control of the heart and blood vessels is essentially titrated by lesion level throughout the thoracolumbar cord. Generally speaking, those with injuries above T6 are most prone to cardiovascular complications due to the loss of descending control of the splanchnic vasculature bed, which is a critical region for both resistance and capacitance vessels that can quickly increase blood pressure and mobilise a significant volume of blood, respectively [25, 26].

1.4.1. The arterial baroreflex

The arterial baroreceptor reflex, or baroreflex, is a negative feedback system that buffers acute blood pressure changes for moment-to-moment control of arterial blood pressure. Changes in pressure are detected by baroreceptors and the efferent arm of this reflex results in changes in sympathetic activity to the heart and vasculature to modulate heart rate, cardiac contractility, and total peripheral resistance (Figure 1.2). Changes in total peripheral resistance in the splanchnic vasculature play a key role in this response [27, 28].

The splanchnic vasculature, including the blood vessels that supply and are located within the stomach, intestines, liver, pancreas and spleen, is a key effector of the arterial baroreflex. A significant proportion of total cardiac output is delivered to these organs and consequently, alterations in resistance in this region have prominent effects on overall blood pressure. The splanchnic vasculature is densely innervated by the sympathetic nervous system and activation of sympathetic outflow triggers vasoconstriction in splanchnic arterioles, a reduction in blood flow, and ultimately increased blood pressure [29]. The splanchnic veins also actively participate in changes in capacitance and redistribution of blood. In fact, a significant proportion (25%) of cardiac output feeds the splanchnic system, and a similar proportion of total blood volume (20%) is stored in the splanchnic veins [30]. Like arterial vasoconstriction, the
venous system is also very sensitive to sympathetic activation [31]. The effective circulating volume can be rapidly increased when the splanchnic veins are stimulated by sympathetic activation, reducing capacitance [30].

Baroreflex activation begins with changes in blood pressure, which are detected by stretch-sensitive mechanoreceptors (baroreceptors) in the aortic arch, coronary arteries, and carotid sinus [32]. The baroreflex response is generally proportional to the stimulus [33]; an increase in pressure triggers an increase in firing frequency in baroreceptors, whose terminals project into the medulla via the cranial nerves (IX and X). The primary components in the central circuitry are the nucleus tractus solitaries (NTS), where cranial nerves IX and X terminate bilaterally, the nucleus ambiguus and the nuclei of the rostral and caudal ventrolateral medulla (RVLM and CVLM) [reviewed in 34]. From the NTS, second-order neurons travel to the ipsilateral CVLM and RVLM, where signals are integrated and from where projections descend to vasomotor and cardiomotor sympathetic preganglionic neurons in the intermediolateral cell columns of the thoracolumbar cord [35, 36]. The axons of the preganglionic sympathetic neurons exit the central nervous system and synapse in sympathetic ganglia, where convergence and divergence results in a generalised sympathetic response [37]. Ultimately, sympathetic nerve activity is modulated resulting in changes in plasma noradrenaline and other co-transmitters such as adenosine 5'-triphosphate (ATP) [38, 39].

The sensitivity of the baroreflex can be quantified by comparing the magnitude of vasomotor and cardiac responses to alterations in blood pressure. Baroreflex sensitivity can differ within individuals throughout the day [40] and between days [41], between individuals [42], and in diseased or injured states [43, 44]. After SCI, control of parts of the effector arm of the baroreflex may be compromised depending on the level and severity of injury to spinal autonomic nerves. For example, while the vagal outflow to the heart, and therefore the cardiac response, is generally preserved because the parasymptathetic cardiac efferents do not travel in the spinal cord (Figure 1.1 and Figure 1.2), the sympathetic cardiac and vasomotor response below the lesion site may be disrupted by the injury. Therefore, baroreflex function can be impaired by SCI, such as reductions in baroreflex sensitivity [45-47]. The cardiac baroreflex delay is also increased by SCI that disrupts cardiac sympathetic pathways [21].
1.5. Cardiovascular function after SCI

Acutely after SCI, the primary cardiovascular concern is supporting patients through the period of neurogenic shock. The loss of sympathetic outflow to the peripheral vasculature results in profound hypotension secondary to the decrease in peripheral resistance and increased vascular capacitance [48-50]. Volume support is often administered to maintain sufficient blood pressure in this population (mean arterial pressure $\geq 85$ mmHg) [49].
In the days and weeks after SCI, neurogenic shock is resolved, but resting blood pressure can remain low due to the loss of descending supraspinal excitatory and inhibitory control from the brainstem [51]. This results in reduced total peripheral resistance and decreased venous return [52]. Resting hypotension can be further reduced by postural changes which can significantly limit early rehabilitation after SCI [11].

1.5.1. Orthostatic hypotension

The disruption of sympathetic control of the vasculature, and loss of appropriate vascular resistance and capacitance responses, makes individuals with SCI particularly susceptible to OH, a condition characterised by a marked decrease in blood pressure upon postural change (Figure 1.3) [53, 54]. OH is defined clinically as a decrease of ≥ 20 mmHg systolic, or ≥ 10 mmHg diastolic, within three minutes of orthostasis, with or without symptoms [55]. Recently this definition has been expanded to specify that the blood pressure decline should be sustained [56], and to include progressive and delayed falls in blood pressure after three minutes [57, 58]. OH has been documented in up to 74% of individuals with SCI [11], and is most common in those with lesions above the level of the neural outflow to the splanchnic vascular bed (which exits the spinal cord between T5-T9 [24]). It is common in the early post-injury period, but its prevalence and severity decreases over the first month after SCI [59].

In the SCI population, OH is triggered by routine events, such as moving from a supine to seated position (Figure 1.3) [60]. OH is problematic because it further lowers blood pressure, from already low resting values, and can decrease cerebral perfusion to critically low levels, reducing cognitive function [61] and triggering symptoms of fatigue, dizziness, and fainting [53, 54]. A reduction in cerebral blood flow seems to be a key component in symptomatic OH [62, 63]. Therefore, individuals with SCI may be further predisposed to experiencing symptoms of OH due to their impairments in cerebral autoregulatory control [64].
Figure 1.3. Orthostatic hypotension during movement from a supine to seated position

Note: Beat-to-beat blood pressure was recorded during passive seating of an individual with cervical (C4) motor and sensory complete SCI (AIS A). Supine hypotension is noted and the movement from supine to seated position triggered a prominent reduction blood pressure. Despite quite marked orthostatic hypotension this individual was asymptomatic.

1.5.2. Autonomic dysreflexia

Despite the loss of central control to distal blood vessels and the heart below the level of an autonomically-complete lesion, the end-organ innervation typically remains structurally intact. This leaves a substrate for reflex sympathetic activity below the level of SCI. A second common condition after high-level SCI is AD, which is a reflex activation of the sympathetic nerves triggered by sensory stimulation below the level of injury [54, 65, 66]. The triggered sympathetic activity below the lesion causes vasoconstriction and acute systemic hypertension. This typically initiates baroreflex-mediated bradycardia [67], as the intact vagal control of the heart attempts to compensate for the sudden surge in blood pressure. However, other cardiac abnormalities may also occur, including atrial fibrillation [68-70], premature atrial, junctional, and ventricular contractions [71-73]. Individuals with injuries that disrupt cardiac sympathetic neural control are vulnerable to high sympathetic and parasympathetic co-activation; cardiac sympathetic circuits below the lesion are activated as part of the dysreflexia, and baroreflex-mediated vagal response to hypertension. High cardiac sympathetic and parasympathetic activity – a so-called
“autonomic conflict” [74] - has been hypothesised to result in cardiac arrhythmias in able bodied controls [74, 75]. Extreme co-activation during episodes of AD may also be arrhythmogenic.

Baroreflex-mediated withdrawal of sympathetic activity above the level of injury induces vasodilation in regions that remain under supraspinal control, resulting in flushing and heat loss [48]. The acute hypertension characteristic of AD can also be accompanied by uncomfortable symptoms including profound headache, large changes in heart rate, sweating and chills [76]. Extreme cases of AD have been documented to cause stroke [77], cerebral vasospasm [78], cerebral haemorrhage [79], seizures [80], and sometimes death [81]. While most individuals are symptomatic during AD, others report no symptoms or discomfort despite pronounced increases in blood pressure [76, 82]. This is particularly worrisome because without symptoms, individuals are unlikely to act to remove the offending stimulus and terminate the dysreflexic episode.

AD can be triggered by any afferent stimulus – noxious or non-noxious – below the level of injury, but visceral stimuli originating from a distended bladder, an impacted bowel, or routine bladder and bowel care, are particularly potent stimuli [73, 83, 84]. Figure 1.4 shows the blood pressure of an individual with a cervical SCI during their routine bowel care management, using a combination of suppositories and digital stimulation. Prominent increases in systolic and diastolic blood pressure are noted.

AD also evolves with time after injury. While there have been documented cases of AD in the early days after injury [85-87], in most cases AD does not develop until about one to six months after injury [83]. This also suggests that there is some evolution of cardiovascular dysfunction in the acute post-injury period. Ultimately, to develop treatments and therapies targeted to improve cardiovascular function, we must first understand the typical progression of cardiovascular dysfunction after SCI.
1.6. Cardiac arrhythmias

Cardiac arrhythmias are another concern in the SCI population - as described above with respect to AD [12]. The heart normally operates with a balance between sympathetic and parasympathetic activation and significant perturbations such as very high sympathetic or parasympathetic cardiac activity, or both, are pro-arrhythmogenic [74, 88]. Therefore, in a population where sympathetic activity to the heart can be significantly reduced or abolished, or intermittently increased such as in reflex sympathetic activation during AD, it is predictable that the risk for and frequency of arrhythmia is enhanced in this population [89]. However, documenting and identifying individuals with SCI who may have, or be at risk for, arrhythmias is difficult due to the transient nature of arrhythmias, which makes them hard to capture in physiological tests.

In the absence of capturing specific arrhythmias as they occur, there are unique aspects of atrial and ventricular repolarisation that are known to be predictors of arrhythmias, that can be quantified more easily [90, 91]. The spatial dispersion of repolarisation in the ventricles gives the T wave its characteristic shape, and the duration
of the T-wave (T_{peak}-T_{end}) of the ECG describes the transmural dispersion of ventricular repolarisation. An increased T_{peak}-T_{end} indicates greater electrical heterogeneity in the ventricular wall, providing a substrate for ventricular arrhythmias [90, 91]. Our laboratory has recently shown that individuals with high-level autonomically-complete SCI show an increased T_{peak}-T_{end} variability [89]. This increase in the dispersion of repolarisation may contribute to the increased risk of arrhythmias in this population.

The QT variability index (QTVI) – a measure of the beat-to-beat fluctuations in QT interval - is another independent predictor of ventricular arrhythmia risk [92-95]. QTVI is an inverse score such that QTVI scores are typically a negative value and values closer to zero are considered abnormal [95, 96]. QTVI has been documented to increased after cervical, high, and low thoracic SCI compared to able-bodied controls [96]. Therefore, it is possible that the QTVI reflects an increase in cardiovascular disease risk, known to be elevated in SCI, rather than a loss of cardiac sympathetic control specifically – as individuals with low SCI have preserved cardiac sympathetic control [96]. However, results from our laboratory showed that QTVI was increased particularly in individuals with damage to autonomic pathways, compared to individuals with preserved autonomic function [89]. Conversely, research in individuals with essential hypertension shows that elevated sympathetic cardiac activation, measured by cardiac noradrenaline spill over, is associated with higher QTVI than in normotensive individuals [93]. It is likely that increased QTVI after SCI is partly related to altered balance of cardiac autonomic control after SCI. However, we do not know whether this increased variability begins immediately after SCI or develops with time after injury.

Several atrial arrhythmias also have their aetiology in altered autonomic tone [88]. The pathogenesis of atrial fibrillation has been linked to both sympathetic and parasympathetic dominance [88, 97]. SCI that disrupts sympathetic cardiac control would therefore likely predispose individuals to atrial fibrillation, due to a resting parasympathetic dominance, and episodic sympathetic hyperactivity during AD. Indeed, as described above, atrial fibrillation secondary to AD has been documented on multiple occasions [69, 70]. Apart from these discrete events, there are other indications of altered atrial function. In the absence of detecting atrial fibrillation directly, P-wave dispersion, measured as the range of p-wave durations from a surface 12-lead
electrocardiogram (ECG), has been identified as an independent predictor for atrial fibrillation [98, 99]. Abnormalities in conduction time, and long intra-arterial conduction times are known to predispose able-bodied individuals to atrial fibrillation [100, 101]. Generally speaking, prognostic ECG abnormalities have been documented to be similar in the SCI population compared to the able-bodied [102]. Indeed, damage to autonomic pathways by SCI increases p-wave dispersion - measured across leads on a 12-lead ECG [103], or over time in one lead [89]. This suggests individuals with SCI that impacts cardiac autonomic pathways are also at risk for atrial fibrillation. Indeed, atrial fibrillation is a documented cause of death in the SCI population [104]. Accordingly, pulmonary embolism, which has been associated with atrial fibrillation as both a cause and effect [105, 106], is a major cause or mortality after SCI [107, 108]

1.7. Cerebrovascular control after SCI

Many of the dangers associated with cardiovascular dysfunction ultimately relate to the control of blood flow in the brain. Both OH and AD challenge cerebral blood flow – and ultimately perfusion – risking either inadequate or excessive flow. The maintenance of adequate cerebral blood flow (CBF), and ultimately oxygen (O₂), to the brain is of paramount importance. As a result, the cerebral circulation demonstrates autoregulation, whereby CBF is maintained at a fairly constant level in the face of changes in cerebral perfusion. Local myogenic responses, local metabolic changes and neural control all play a role in autoregulatory responses; however, the relative contribution of these different effectors is not well understood.

While cerebral arteries are richly innervated by sympathetic neurons [109, 110], their functional contribution to alterations in CBF has been vigorously debated [111, 112]. Pharmacological gain-of-function and loss-of-function studies reveal that there is a measurable effect on cerebral autoregulation when normal sympathetic activity is disrupted or enhanced. This suggests that the sympathetic nervous system has a role in the normal control of the cerebral vasculature. Sympathetic blockade increases the gain between arterial pressure and CBF, suggesting impaired pressure autoregulation in the absence of normal sympathetic control [113]. Recent evidence using a specific α-1 adrenergic blocker suggests that cerebral reactivity to carbon dioxide (CO₂) is also partly
regulated by sympathetic activity [114]. Sympathetic blockade reduced the sensitivity of the cerebral vasculature to low levels of CO$_2$ – the normal cerebral vasoconstrictor response was impaired [114]. Conversely, sympathetic activation was also shown to reduce the sensitivity of the cerebral vasculature to CO$_2$ in the hypercapnic range [115]. These results suggest that there is sympathetic influence on the cerebral reactivity to CO$_2$.

Unlike the cerebral responsiveness to CO$_2$, the cerebral vasculature does not respond significantly to acute changes in O$_2$ in the physiological range [116]. However, CBF does increase dramatically once the partial pressure of O$_2$ in the blood (PaO$_2$) decreases to 60 mmHg or lower [116]. This vasodilation of the cerebral vasculature in response to hypoxia is driven by multiple mechanisms [117]. Denervation studies in rabbits shows the absence of functional sympathetic nerves increases the CBF response to hypoxia [118].

Presently, little is known about how cerebrovascular control is affected by SCI. We suspect that the impaired autonomic control in individuals with high-level autonomically-complete SCI may have repercussions on their cerebrovascular response to O$_2$ and CO$_2$. Given the evidence that suggests a role of sympathetic activity in reactivity to CO$_2$, it is essential to determine the autonomic control when testing individuals with SCI, to avoid combining groups with individuals with and without sympathetic neural control of the cerebral vasculature. The sympathetic control of the cerebral vasculature is susceptible to SCI because the descending tracts travel through the cervical and upper thoracic spinal cord (Figure 1.5). The sympathetic neurons that innervate the cerebral vasculature originate primarily in the superior cervical ganglion, which receives sympathetic outflow from the thoracic cord (T1-T5) [24, 119, 120]. Therefore, individuals with high-level autonomically-complete SCI at or above T1 have disrupted extrinsic sympathetic neural control of the cerebral vasculature. This presents a unique opportunity to investigate the role of the sympathetic nervous system in cerebrovascular control.
Figure 1.5. Origin of extrinsic sympathetic pathway from brainstem nuclei to cerebral vasculature

Note: The cerebral vasculature is densely innervated by sympathetic nerves, some of which originate in the superior cervical ganglion [119]. Descending control from the brainstem synapses with sympathetic preganglionic neurons in the upper thoracic cord (T1-T5), which terminate in the superior cervical ganglion [24, 119, 120]. Ganglionic neurons in the superior cervical ganglion ultimately innervate the cerebral vasculature, among other targets. This pathway is vulnerable to SCI due to its location in the cervical and high thoracic spinal cord.

Our laboratory has recently shown that individuals with high-level autonomically-complete SCI have impaired cerebrovascular autoregulation during orthostasis and impaired dynamic autoregulation [64]. Whether their responsiveness to CO$_2$ and O$_2$ is also related to their severity of autonomic injury remains to be determined. To date, there are no data on the cerebral responsiveness to O$_2$ after SCI, and existing studies investigating responsiveness to CO$_2$ show conflicting results [121]. An early study performed in individuals with cervical and thoracic SCI showed reduced cerebrovascular sensitivity to hypocapnia in those with tetraplegia [121-123]. Two subsequent studies have failed to replicate those results [122, 123]. However, none of these studies controlled for autonomic completeness of injury or concurrent changes in O$_2$, so the results in all cases may be confounded by these variables [124].
Many individuals with SCI also suffer from comorbidities that may affect their cerebrovascular control. Obstructive sleep apnea (OSA) is very common among individuals with complete tetraplegia (91%) and affects more than half of those with incomplete tetraplegia (56%) [125]. The acute periods of hypoxia throughout the night that characterize this disorder result in haemoglobin desaturation [126]. These short nocturnal hypoxic events seem to reduce the sensitivity of the cerebral vasculature to hypoxia in able-bodied controls [127-129].

1.8. Assessing autonomic function after SCI

As outlined above, SCI can have a range of effects on autonomic cardiovascular control depending on the level and severity of injury. Therefore, the assessment of autonomic function is critical in this population, in order to guide clinical treatment and for research purposes. The standard assessment of neurological function after SCI, the American Spinal Injury Association Impairment Scale (AIS) is used to determine the motor and sensory level and completeness of SCI [130]. However, there is often dissociation between AIS score and the autonomic level and completeness of injury – autonomic function is not reliably predicted by the degree of motor or sensory function [21, 64, 89, 131]. Therefore, specific assessment and quantification of the autonomic nervous system is necessary. In recognition of this need, recent guidelines have been created to document remaining autonomic function after SCI [6, 132, 133]. While these guidelines will encourage physicians to discuss these secondary consequences with their patients, they fail to quantify autonomic function, considering only binary statements such as presence or absence of hypotension, and relying heavily on participant self-awareness of and knowledge surrounding the autonomic consequences of SCI.

The diffuse anatomy and function of the autonomic nervous system makes it challenging to assess. Many types of autonomic assessments are time consuming and require specialist equipment and expertise to perform. However, there are some more simple approaches that have been successful in quantifying autonomic function. There is no gold standard among these approaches, and different tests may be more appropriate in certain clinical populations than others. This discussion is restricted to assessments of autonomic function feasible in the SCI population. It focuses primarily on quantification of
sympathetic function, which is strongly influenced by level of injury. There are three main approaches used in this testing: 1) functional challenges; 2) end-target measurement and direct recording; and 3) observation of natural variability.

1.8.1. Functional assessments of autonomic function

Sympathetic skin responses (SSR) are commonly used to assess sympathetic activity. In this test, electrical stimulation is used to activate sympathetic sudomotor activity, via pathways that include pre- and postganglionic sympathetic sudomotor fibers and supraspinal involvement [134]. Therefore, an absence of sudomotor activity indicates disruption of the spinal or peripheral sympathetic pathways [134]. While this test assesses cholinergic sympathetic function specifically, its results are presumed to extrapolate to adrenergic regulation as well. The technique is normally performed a number of times in each location on each side of the body. The result of each iteration are scored in a binary fashion – the response is either present or not. One of the challenges of this technique is the interpretation of results: conclusions about sympathetic integrity are somewhat unclear when only a fraction of SSR are present, or when SSR are present unilaterally, or when they are present in response to some stimuli and not others [131]. Finally, because the recording locations are on the hands and feet, conclusions about the level of autonomic injury from SSR are restricted to high (above arms and legs) or low (above legs only).

Skin vasomotor reflex assessment is another way to measure sympathetic function. Similar to SSR, skin vasomotor responses are triggered by brief electrical stimuli or other sympathetic activator stimuli, such as an inspiratory gasp [135, 136]. With intact responses, skin blood flow, recorded using an infrared pulse plethysmograph, is reduced secondary to vasoconstriction [136]. Skin responses below complete injuries that disrupt autonomic pathways are significantly reduced or disrupted completely [135]. Like SSR, however, the conclusions are not particularly precise, as the vasomotor activity is typically recorded only in the toe and finger. However, the vasomotor response seems to be more sensitive than SSRs in response to the same stimulus [136]. It remains to be determined whether this technique can be used in the trunk to define autonomic level of injury with even greater precision [135].
Another way to test the sympathetic nervous system is to measure the cardiovascular response to perturbations that should activate the sympathetic nervous system. The two most commonly used techniques in the SCI population are the Valsalva maneuver and orthostatic testing.

The Valsalva maneuver produces a series of stereotyped phases in blood pressure and heart rate responses to forceful attempted exhalation against a closed airway. Quantification of blood pressure and heart rate in these different phases can be used to measure sympathetic vasomotor and cardiac control. In the first phase of the Valsalva maneuver, as forceful attempted exhalation is initiated, blood pressure increases transiently due to the pressure on the heart, and increase in stroke volume, at the beginning of the expiratory force [137, 138]. However, the high positive intrathoracic pressure soon decreases venous return, cardiac output, and blood pressure (Phase IIa) [138]. This activates the baroreflex, triggering an increase in heart rate and blood pressure (Phase IIb) [139]. When the pressure is released, there is a brief reduction in cardiac output, as the aortic pressure is briefly reduced and HR increases reflexively (Phase III)[138]. Finally, there is an increase in cardiac filling due to the reduction in intrathoracic pressure, and a brief overshoot of blood pressure, due to residual sympathetic activation from phase II, before returning to baseline values. After SCI, the sympathetic contribution in both phase II and IV can be disrupted [140]. Blood pressure recovery in phase II, realised by sympathetic vasoconstriction, was slower and smaller in magnitude in individuals with tetraplegia and paraplegia than able-bodied controls. The blood pressure overshoot at the end of the Valsalva maneuver was abolished in individuals with tetraplegia, but not paraplegia [140, 141]. Furthermore, the heart rate response was slower and smaller in individuals with tetraplegia, suggesting an absence of sympathetic cardiac control in this group [140]. While this technique has been successfully used in some populations with SCI, we have found that some individuals – particularly those with tetraplegia who are unable to activate abdominal and intercostal muscles – can have trouble maintaining the desired pressure of the forced expiratory effort (unpublished observation).

Orthostatic stress testing is another functional assessment used to assess cardiac and vasomotor sympathetic function, including in those with SCI. The orthostatic
challenge is commonly performed using a tilt table to trigger passive orthostasis from a supine to a standing position (often at an angle of 60°, or a progressive increase in angle over time) [62, 142-147]. However, this can trigger profound hypotension in many individuals with SCI, so a milder challenge – a passive supine to seated position change – tends to be preferred in this population [53, 64]. This also better reflects the postural challenges associated with activities of daily living in individuals with SCI, which increases the clinical relevance of any abnormal responses.

Individuals with tetraplegia tend to show marked hypotension in response to tilting compared to individuals with low-level SCI and able-bodied controls [65, 143]. In particular, the autonomic completeness of injury is an important discriminator of which individuals will show pronounced hypotension, and which are able to maintain blood pressure during orthostasis [64]. Individuals with low-level paraplegia have a blunted sympathetic response to tilting [146], but are often able to maintain blood pressure in the face of orthostatic stress [64]. The heart rate response to orthostatic challenge is dominated by vagal withdrawal; both able-bodied controls and individuals with SCI increase their heart rate during tilt [64].

1.8.2. End-target measurement and direct recording of autonomic activity

The measurement of plasma noradrenaline is another commonly used technique to quantify sympathetic activity, as plasma noradrenaline is correlated to muscle sympathetic nerve activity [148]. This technique relies on the fact that some of the noradrenaline released from sympathetic post-ganglionic terminals spills over into plasma and can be detected using high-pressure liquid chromatography [149, 150]. Plasma noradrenaline can be assessed at rest, and again following a stimulus that is known to activate the sympathetic nervous system. In the intact autonomic system, this should increase the sympathetic activity and subsequently the noradrenaline spillover from nerve terminals. However, the noradrenaline clearance and reuptake are also important considerations [151]– as both increased release or decreased reuptake can have similar effects on the target effector [152]. The failure to increase noradrenaline is one indication of abnormal global sympathetic function [153].
Direct recording of sympathetic nerve activity is also possible and is another common way of assessing sympathetic function. Muscle sympathetic nerve activity (MSNA) records the extracellular electrical activity from sympathetic nerves, which travel in fascicles, using a tungsten microelectrode [154, 155]. The magnitude and frequency of sympathetic bursts can be quantified. Typically, baseline recordings are compared to recordings during a task that activates sympathetic activity, such as handgrip exercises [156]. MSNA testing requires significant expertise and specialised equipment to perform. Furthermore, there can sometimes be a functional disconnect between the MSNA and the ultimate neurotransmitter release and target effector activation, due to different levels of noradrenaline release and clearance [151].

Most of these assessments can only discriminate between high-level (cervical) and low-level (thoracic) injury. These tests can be informative, but they leave out important information about the autonomic control in the trunk region. The trunk region is particularly challenging to assess due to the diffuse nature of the sympathetic control in this region. This is unfortunate as the control of the splanchnic vasculature lies within this region.

1.8.3. Assessing natural cardiovascular variability

There is significant variability in a healthy cardiovascular system [157]. Multiple feedback and feed forward control systems interact to produce variability in both heart rate and blood pressure. This variability can be detected over short time periods – such as over each breath – and longer periods, such as diurnal oscillations [158-160]. The magnitude and frequencies of these oscillations can provide information about the function of the autonomic nervous system [160, 161]. There are three major frequency ranges of oscillations in heart rate and blood pressure that relate to specific physiological phenomena. The total power as well as changes in the relative contributions of these different domains and their central frequency of oscillation can reveal information about the autonomic nervous system [158].

High frequency (HF) oscillations (0.15 to 0.4 Hz) in both heart rate and blood pressure primarily reflect the effects of respiration. HF heart rate variability (HRV)
reflects changes in cardiac vagal activity associated with respiratory sinus arrhythmia [162, 163] and power in this frequency range is often used as a measure of cardiac parasympathetic function [164, 165]. HF blood pressure oscillations are also generated by respiration: changes in intrathoracic pressure associated with the mechanical effects of respiration modify the filling pressure in the heart and ultimately cardiac output [166, 167]. In addition, central respiratory-related signalling alters sympathetic nerve activity and as a result, peripheral resistance [38, 168, 169]. Both of these effects are independent of respiratory effects on HR [170], but respiratory sinus arrhythmia-induced changes in HR also influence HF blood pressure variability (BPV) in this range through the baroreflex [171].

Low frequency (LF) oscillations (from 0.04 to 0.15 Hz [172]) reflect rhythmic vasomotor changes with a period of approximately 6-10 seconds. These oscillations are caused by waves of sympathetic nerve activity [173-175], and the LF oscillations in blood pressure are termed Mayer waves [after 176]. There has been significant debate over whether these oscillations are centrally mediated or result from peripheral signalling, such as baroreflex responses to hemodynamic perturbations [177]. There is evidence to support influence from both central and peripheral sources [177, 178]. Regardless of the sources, the magnitude (power) of LF oscillations in systolic arterial pressure (SAP) is related to the level of sympathetic activity and can provide an index of sympathetic vasomotor modulation [179, 180] and ultimately of cardiovascular autonomic dysfunction [21, 173]. Oscillations of blood pressure at this frequency are not driven by heart rate changes because they persist even when the heart is paced [181]. However, oscillations in LF HRV seem to be primarily driven by LF BPV through the arterial baroreflex response resulting in changes in vagal tone [182-184]. Therefore, the LF HRV conveys information about both the sympathetic and parasympathetic systems [162, 185, 186].

The mechanisms generating very low frequency (VLF) oscillations (<0.03 Hz) are less well understood and have been attributed to many different physiological sources. VLF BPV likely represents numerous different influences on the vasculature, including the effects of catecholamines, the renin-angiotensin-aldosterone system [187, 188] and circadian temperature changes [189, 190]. Recent evidence suggests that VLF BPV is
primarily mediated by L-type calcium channels generating myogenic vascular responses
to changes in blood pressure [159]. VLF HRV is thought to be a combination of
baroreflex-mediated HR response to variability in blood pressure, unique effects of renin-
angiotensin [162, 187, 188], thermoregulation [191, 192], and endothelial factors [193].

Due to their close association with the autonomic nervous system, frequency
analyses permit quantitative evaluation of the balance and integrity of the autonomic
nervous system [21, 160, 164]. The balance of autonomic control of the heart, the
sympathetic control of the vasculature, and the sensitivity and delay of the cardiac
baroreflex can be quantified using the beat-to-beat fluctuations in heart rate and blood
pressure. However, some caution is warranted when using frequency analyses to
assess autonomic function. Generally speaking, conclusions about magnitude from
power spectral analysis can be problematic because both high and low unwavering
values appear as low variability; more evidence is needed in combination with frequency
analyses to make certain conclusions. By far the most common error, however, is
overstated confidence in the LF to HF HRV ratio (LF:HF). While the LF:HF HRV can give
an indication of the autonomic balance and relative sympathetic-parasympathetic
activity, it is important to remember that the LF HRV is complex and includes both
sympathetic and parasympathetic influences, so that the ratio is not simply sympathetic:
parasympathetic [162, 185, 186]. Therefore, while changes in LF:HF within subjects
might be informative [194, 195], the magnitude of the value on its own is likely not very
meaningful.

1.8.4. Cardiovascular variability and pathophysiology

Too much or too little cardiovascular variability can each be pathophysiological.
Low variability suggests a system that is static and not responsive to its environment,
and therefore ill equipped to deal with challenges. Low HRV is an early biomarker of
several pathophysiological states, including autonomic dysfunction in diabetes [196],
fetal distress [197]. Low HRV has also been associated with all-cause mortality in the
elderly [198, 199] and can be used to predict risk of cardiac events [200].
There is mounting evidence that very high cardiovascular variability can also be problematic. High variability suggests a system that is overreacting to its environment and unable to regulate efficiently. Very high blood pressure variability can physically stress the cardiovascular system, resulting in organ damage in the heart, kidneys and arteries [201-206]. Large variance in visit-to-visit systolic blood pressure is a strong predictor of stroke, independent of mean systolic blood pressure [207-209]. To date, no clear thresholds have been set as to how much variability is too much, and what target ranges should be [202]. However, both very little and too much variability in blood pressure and heart rate are associated with pathophysiological conditions.

1.8.5. **Cardiovascular variability after SCI**

Cardiovascular variability can be significantly altered by SCI. Overall HRV is reduced by high-level autonomically-complete SCI, but not lower level SCI [21, 210]. High-level autonomically-complete SCI reduces overall BPV and practically abolishes variability in the LF range (Figure 1.5) [21, 211]. Therefore, LF BPV can be used to determine severity of injury to sympathetic pathways [21]. LF HRV is also reduced by SCI [212], but due the vagal contribution to variability in this range, it is not as clear a measure for distinguishing injury severities.

Despite low resting cardiovascular variability, individuals with autonomically-complete injuries can also alternately experience periods of very high variability such as episodes of AD or OH, as described above. These events can be triggered by routine activities of daily living such as moving from a supine to seated position – triggering hypotension - or performing routine bladder or bowel care – triggering hypertension. Blood pressure changes triggered by these events can range from around 80 mmHg systolic [11, 64] to more than 200 mmHg [82, 213, 214]. The changes in autonomic outflow during these events, combined with the cardiac baroreflex response to blood pressure changes, also trigger significant abnormalities in heart rate. Ultimately these events can cause cardiovascular events and end-organ damage due to their sheer magnitude as well as the extreme variability that they cause from resting levels [82, 213, 214].
Figure 1.6. **Blood pressure variability after cervical SCI**

Note: A. Time series showing supine systolic arterial pressure (SAP) variability in an individual with a C5 motor and sensory complete (AIS A) and autonomically-complete SCI and an able bodied control. B. This same period expressed in the frequency domain. Grey shaded area indicates low frequency (LF) region.

In this thesis, I use spectral analyses of HRV and BPV as the primary means to determine autonomic function after injury. Our laboratory has shown that this simple and non-invasive technique discriminates between individuals with and without damage to autonomic pathways and is reproducible after SCI [21]. In Chapter 2, I also used plasma supine and seated noradrenaline levels to corroborate spectral analyses of autonomic function. The overall aim of my thesis is to investigate the secondary cardiovascular and cerebrovascular consequences of SCI, particularly as they relate to activities of daily living and experiences that individuals with SCI encounter routinely.
1.9. Thesis outline

This thesis investigates cardiovascular function after SCI from a varied perspective, and considers quantitative indicators of variability and how these change after injury, physiological stressors replicated in a laboratory setting, and the relationship between cardiovascular symptoms and activities of daily living.

My first study (Chapter 2) investigated functional blood pressure control in different wheelchair seating positions, and how this is affected by injury to autonomic pathways. I hypothesised that individuals with damage to autonomic pathways would show significant changes in blood pressure and cerebral blood flow in different wheelchair positions compared to those without autonomic injury.

My second study (Chapter 3) explored cardiovascular autonomic function in the acute post-injury period using measures of heart rate and blood pressure variability. I hypothesised that changes in spectral analyses over time would be able to identify individuals with increased risk of cardiovascular dysfunction and risk of arrhythmias.

My next study (Chapter 4) characterised the cerebrovascular responses to changes in CO₂ and O₂ in individuals with and without damage to autonomic pathways. I hypothesised that the vasculature would be less responsive to changes in these vasoactive stimuli.

My last study (Chapter 5) used a questionnaire to explore an understudied secondary autonomic complication of SCI – bowel care – and its relationship with cardiovascular symptoms and damage to autonomic pathways.

Finally, in Chapter 6, I discuss the overall clinical, self-management, and research implications of my research, including the limitations and interesting avenues for future study.
Chapter 2.

Dynamic wheelchair seating positions impact cardiovascular function after spinal cord injury

2.1. Abstract

Innovative wheelchairs allow individuals to change position for comfort and social situations. While these wheelchairs are beneficial in multiple ways, the effects of position changes on blood pressure might exacerbate hypotension and cerebral hypoperfusion, particularly in those with spinal cord injury (SCI). Conversely, cardiovascular benefits may be conferred by lowered seating. Here we established the effect of wheelchair position on orthostatic cardiovascular and cerebrovascular control.

Cardiovascular recordings were performed on 19 individuals with SCI and 10 controls; beat-to-beat blood pressure, heart rate and cerebral blood flow velocity (CBFv) were recorded. Participants with SCI were stratified by severity of autonomic injury. Participants were tested in neutral, lowered, and elevated wheelchair seated positions (Elevation™). Controls were also tested in a passive standing wheelchair (LEVO active-easy™).

Supine blood pressure and CBFv were reduced in individuals with autonomically-complete SCI, and declined further with neutral seating compared to those with autonomically-incomplete SCI. In the Elevation™ wheelchair, movement to elevated seating triggered pronounced falls in blood pressure and CBFv in those with autonomically-complete lesions, while the lowered seating position bolstered blood pressure. Total time spent below supine blood pressure was greatest in those with autonomically-complete SCI, suggesting a cumulative burden of orthostasis. Passive standing in the LEVO™ wheelchair triggered presynope in some controls, and was not further investigated in participants with SCI.
2.2. Introduction

Innovative new wheelchairs facilitate mobility and improve quality of life for wheelchair users. Many of these new devices permit dynamic “on-the-fly” modification of seating position and height in order to better navigate physical and social barriers. However, altered seating positions likely also influence the physiological stressors placed on the cardiovascular system.

Dynamic seating options range from a ‘dumped’ position, to a reclined supine position, to a near standing position. Seating positions can easily be adjusted in real time to suit particular activities, such as wheeling, reaching, or speaking with someone standing, to maximise function and promote independence [215]. There may also be physiological benefits to dynamic seating, including reduction of pain, improved comfort, and relieving pressure points to prevent skin damage [216-219].

Elevated seating permits functional benefits for activities of daily living, including improved reaching, and the ability to be at the same level in interpersonal interactions [220]. Weight-bearing standing positions also increase longitudinal loading of the legs, which may improve bone density [221-224]. In some cases, more vertical positions might also condition the cardiovascular responses to standing by improving baroreflex function [225].

A lowered, or dumped, wheelchair position, where the back of the seat is lower than the knees, also has benefits for particular tasks. This position provides improved seating stability, balance, reaching, and ergonomic wheeling efficiency [215, 226]. From a cardiovascular perspective, a lowered wheelchair position, and the resulting compression of the abdominal area, could benefit venous return from the key vascular resistance and capacitance regions in the splanchnic circulation to the heart – similar to the effect of using an abdominal binder [144, 145, 227]. This might improve blood pressure and cardiac output, with improved exercise performance [228].

Upright seating positions likely challenge blood pressure regulation due to increases in orthostatic stress, which cause large fluid shifts to the lower body and abdomen. This distends the veins in the lower body, and increases capillary filtration of
plasma, reducing venous return to the heart. This would normally be mitigated by baroreflex responses that increase heart rate and contractility, and increase sympathetic vasoconstriction. If these reflexes are impaired then this compensation may be insufficient to maintain blood pressure [229]. A drop in blood pressure ≥20 mmHg systolic and/or ≥10 mmHg diastolic constitutes orthostatic hypotension (OH) [55, 56], and can lead to reduced cerebral blood flow, with associated symptoms of fatigue, and impending loss of consciousness (presyncope) [230-233].

Impaired blood pressure regulation is a concern for individuals with high-level (above T5) SCI when sympathetic pathways to the heart and vasculature are damaged [34]. This leads to low resting blood pressure (hypotension) in addition to short periods of OH triggered by positional changes – such as moving from a lying to seated position [21, 234, 235]. This resting and positional hypotension likely reduces cerebral blood flow, contributing to the chronic fatigue experienced by many individuals with SCI [236-238]. Elevation of a dynamic wheelchair from a seated to upright position might further exacerbate OH. Conversely, lowered seating positions might ameliorate OH.

Here we tested the effect of wheelchair position on cardiovascular and cerebrovascular function. We aimed to determine the effects of elevated and lowered wheelchair seating positions compared to standard seating on blood pressure, heart rate and cerebral blood flow in two different wheelchairs that permit dynamic seating modification. Responses were compared between individuals with cardiovascular autonomic dysfunction after SCI, those with SCI but without autonomic dysfunction, and able-bodied controls. We hypothesised that: (i) elevated seating positions would further exacerbate the orthostatic impairment in individuals with damage to cardiovascular autonomic pathways (defined here as autonomically-complete SCI), but not in controls or those with autonomically-incomplete injuries; (ii) lowered seating positions would ameliorate this effect.

2.3. Methods

This study conformed to the principles outlined in the Declaration of Helsinki [239], and received ethical approval from the Simon Fraser University Office of Research
Ethics, and the Vancouver Coastal Health Research Institute. All participants provided written informed consent.

2.3.1. Participants

All participants were aged ≥18 years old, apparently healthy and free of hypertension, diabetes mellitus and other overt cardiovascular disease. Nineteen individuals with SCI (8 women) who were regular wheelchair-users for at least one year participated. All participants with SCI and ten controls (4 women) were studied in elevated, lowered, and standard seating positions (Figure 2.1A, Elevation™ wheelchair, PDG Mobility Technologies, Vancouver, BC) [215].

On a separate testing day, twelve able-bodied controls (6 women) were also tested in supine, standard seating and supported standing positions (LEVO active-easy™, LEVO AG, Wohlen, Switzerland).

Neurological classification of level and severity of SCI was determined from the American Spinal Injury Association Impairment Scale (AIS) [130]. Participants with SCI were subdivided into two groups (autonomically-incomplete SCI and autonomically-complete SCI) based on the presence or absence of cardiovascular autonomic dysfunction. We considered an individual to have an autonomically-complete lesion if they had: a) a lesion above T5; and b) low supine plasma noradrenaline spillover (<0.5 nmol/L); and c) low systolic blood pressure variability in the low frequency range (~0.1 Hz, power <2 mmHg²), as is standard in our laboratory [21, 64, 89].

2.3.2. Equipment

Beat-to-beat blood pressure and lead II electrocardiogram (ECG) were recorded continuously (Finometer Pro, Finapres Medical Systems BV, Amsterdam, Netherlands). Stroke volume (SV) and cardiac output (CO) were calculated using the Modelflow technique [240]. Middle cerebral artery (MCA) blood flow velocity was measured bilaterally using transcranial Doppler ultrasound with 2 MHz probes through the temporal windows (Doppler Box, Compumedics DWL, Singen, Germany) and attached to a headband to maintain constant angles of insonation throughout testing. Partial pressures
of expired oxygen and carbon dioxide (\(P_{ET}CO_2\)) were recorded on a breath-by-breath basis (O\(_2\)Cap, Oxigraf Inc, Mountain View, CA). All recordings were sampled at 1 KHz (Powerlab 16/30, AD Instruments, Colorado Springs, CO), acquired using LabChart (AD Instruments), and stored for offline analysis.

### 2.3.3. Experimental protocol

Participants were asked to abstain from caffeine or alcohol, and to avoid strenuous exercise, for 12 hours prior to testing. Testing was carried out in a quiet room at 20°C. Participants were instrumented while lying supine, and all parameters were recorded for 15 minutes. Participants then transferred to the Elevation™ wheelchair in the neutral seated position (horizontal seat, 90° shin-to-seat angle) for 15 minutes. In a crossover design, individuals were randomly assigned to move to the maximally elevated (seat raised 20° above level), or lowered position (seat lowered 10° below level), and then returned to the neutral seated position, followed by the opposite position, with each block lasting 15 minutes (Figure 2.1A).

In the LEVO active-easy™ wheelchair, able-bodied control participants were tested in the supine, seated (horizontal seat), and supported standing position (full leg extension reclined just off the vertical to 85° [241]), each for 15 minutes. Individuals with SCI did not undergo this protocol because we were concerned about their ability to tolerate the more severe orthostatic stress associated with supported standing; several able-bodied controls experienced symptomatic OH in the standing position, necessitating early termination of testing.

End points for testing were determined \textit{a priori}, and included any of: systolic arterial blood pressure below 80 mmHg; symptoms of presyncope, such as dizziness; or participant request.

### 2.3.4. Data analyses

We applied a low-pass filter (<50 Hz) to remove electrical noise from the ECG signal and a median filter (~51 samples, or 0.05 s) to remove artefacts from the MCA
signal. Beat-to-beat heart rate (HR), systolic (SAP), diastolic (DAP), arterial pressure, as well as MCA systolic (MCA_{sys}), diastolic (MCA_{dia}), and mean (MCA_{mean}) cerebral blood flow velocities, and breath-by-breath \text{P}_{ET}\text{CO}_2 were determined using cyclic peak detection measurement algorithms in LabChart. Mean arterial pressure (MAP) was calculated from the raw blood pressure signal ($1/3$ SAP $+ 2/3$ DAP) and cerebrovascular conductance was also calculated ($MCA_{mean}$/MAP). For each individual, the most reliable and consistent signal from either the left or right MCA was used for analysis.

A five-beat moving average was applied across all variables. Average values were calculated over the last five minutes of each condition (supine, seated, lowered, seated repeat, and elevated). Values from the two neutral seated conditions were averaged as they were not significantly different from each other.

Averaged data can hide the true magnitude and temporal information of the orthostatic response. The timing and size of the blood pressure nadir in response to orthostatic stress varies between individuals and together this information can provide insight into the severity of sympathetic dysfunction [57]. Therefore, we also investigated the absolute magnitude and timing of the nadir SAP in each wheelchair position. Nadir values were calculated from five-beat moving averages and the time at nadir was determined.

The \textit{duration} of hypotension following postural change and ability to recover blood pressure during orthostasis have been identified as key measures of severity of OH [57, 242]. We quantified the overall orthostatic burden of each position as the cumulative magnitude and duration spent below resting supine SAP levels. The cumulative area under the curve (AUC) was calculated as the sum of the difference between baseline SAP and SAP at each beat [242].

For data collected in control subjects during the supported standing protocol in the LEVO active-easy™ wheelchair, averages are presented for the final 30 seconds of each minute of testing in each phase.
2.3.5. Statistical analyses

Data processing was conducted using R version 3.0.1 and data were analysed using JMP Version 10.0 and SigmaPlot Version 12. Descriptive statistics were calculated per group for the baseline variables. Comparisons between the two SCI sub-groups of SCI-specific measures such as duration of injury, were conducted using t-tests. Distribution of level and severity of injury between groups was compared using Fisher’s exact test. One-way ANOVAs were used for comparison of demographic information and baseline variables, with Tukey’s post-hoc test to examine between group differences. Cardiovascular responses to different wheelchair positions were compared using a two-way ANOVA with repeated measures on one factor (position). Where main effects were present, post-hoc comparisons were conducted. Statistically significance differences were assumed where $\alpha<0.05$.

2.4. Results

2.4.1. Participant characteristics

Participant demographics as well as supine cardiovascular and cerebrovascular parameters are shown in Table 2.1. We did not detect any differences in sex distribution, age, height, or weight between groups. For comparisons between the two SCI groups, we did not detect differences in time since injury, but there were more participants with cervical SCI ($p=0.002$), and tended to be more participants with motor and sensory complete lesions (AIS A) ($p=0.057$), in the autonomically-incomplete SCI group.

The autonomically-complete SCI group had significantly lower SAP, DAP, MCA$_{dia}$ and MCA$_{mean}$ compared to the autonomically-incomplete group (all $p<0.05$). The autonomically-incomplete SCI group had higher DAP ($p=0.015$) and MAP ($p=0.035$) compared to the control group. We did not detect any differences between groups in the remaining cardiovascular and cerebrovascular parameters in the supine position.
Table 2.1. Participant demographics and supine cardiovascular parameters

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>10</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.9 (2.6)</td>
<td>42.6 (3.1)</td>
<td>37.0 (3.1)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>6:4</td>
<td>6:6</td>
<td>5:2</td>
</tr>
<tr>
<td>Time since injury (years)</td>
<td>18.9 (4.1)</td>
<td>16.6 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Lesion level</td>
<td></td>
<td>Cervical</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thoracic</td>
<td>11</td>
</tr>
<tr>
<td>AIS grade</td>
<td></td>
<td>A</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B/C/D</td>
<td>4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (2)</td>
<td>170 (2)</td>
<td>176 (5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 (3)</td>
<td>67 (3)</td>
<td>68 (5)</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>120 (3)</td>
<td>128 (3)</td>
<td>113 (6)*</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>64 (2)*</td>
<td>73.4 (2)</td>
<td>65 (2)*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83 (2)*</td>
<td>91 (2)</td>
<td>81 (3)*</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;sys&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>91 (7)</td>
<td>99 (5)</td>
<td>87 (6)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;dia&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>45 (4)</td>
<td>47.5 (2)</td>
<td>39 (2)*</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;mean&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>63 (6)</td>
<td>67 (3)</td>
<td>56 (3)*</td>
</tr>
<tr>
<td>CVC (cm.s&lt;sup&gt;-1&lt;/sup&gt;.mmHg&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.81 (0.07)</td>
<td>0.74 (0.05)</td>
<td>0.70 (0.06)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65.1 (2.6)</td>
<td>67.0 (2.6)</td>
<td>63.8 (5.2)</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>96.1 (4.0)</td>
<td>90.9 (4.3)</td>
<td>88.4 (4.8)</td>
</tr>
<tr>
<td>CO (L.min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>6.2 (0.3)</td>
<td>6.0 (0.3)</td>
<td>5.8 (0.5)</td>
</tr>
</tbody>
</table>

Note: Data are presented as group means with SEM shown in brackets. SCI groups were divided according to autonomic completeness of injury. Cardiovascular variables were recorded in the supine position for 15 minutes. Asterisk (*) indicates significant difference from autonically-incomplete SCI (p<0.05); † indicates significantly different from able-bodied control group (p<0.05).

Abbreviations: SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; MCA<sub>sys</sub>, systolic middle cerebral artery blood flow; MCA<sub>dia</sub>, diastolic middle cerebral artery blood flow; MCA<sub>mean</sub>, mean middle cerebral artery blood flow; CVC, cerebrovascular conductance; HR, heart rate; SV, stroke volume; CO, cardiac output.

2.4.2. Cardiovascular responses to different wheelchair positions

Cardiovascular parameters in different wheelchair positions are reported in Table 2.2. Movement from a supine to seated position had different effects on SAP depending on autonomic completeness of injury (p=0.0014), as we have previously reported [53, 64] (Figure 2.1B). SAP increased in controls (p=0.0006), and in autonically-incomplete SCI (p=0.024), and did not change in the autonically-complete SCI group. Movement from the seated to elevated position did not further affect SAP in autonically-incomplete SCI and control groups. In the elevated position, mean SAP
was lower in the autonomically-complete SCI group compared to resting supine levels (p=0.037). Conversely, the lowered position bolstered SAP compared to standard seating in the autonomically-complete SCI group (p=0.029). Movement to the lowered position did not change SAP in autonomically-incomplete SCI and control groups. Compared to the other two groups, SAP was lower in the autonomically-complete SCI group during standard and elevated, but not lowered, seating positions (Figure 2.1).

Similarly to SAP, DAP (Figure 2.1D) and MAP increased from supine to seated, elevated and lowered levels in control and autonomically-incomplete SCI groups (all p<0.05, see Figure 2.1D). There were no significant differences in DAP or MAP between positions in the autonomically-complete SCI group.

HR increased from supine values during seated, elevated and lowered positions in both the control and the autonomically-incomplete SCI group (all p<0.05). There were no significant changes in HR in the autonomically-complete SCI group.

SV decreased in all groups from supine to all seated positions (Table 2.2). In the autonomically-complete group only, movement from the seated to elevated position further reduced SV (p<0.05). In the control group, the reduction in SV was compensated by HR increases, so CO was unchanged. However, both SCI groups showed a decrease in CO in the elevated position compared to supine; in the autonomically-complete group CO was significantly lower than in controls (Table 2.2).
Figure 2.1. Blood pressure and cerebral blood flow responses to different wheelchair seating positions
Note: A. Experimental protocol outline of crossover design: individuals were randomly assigned to move from the standard seating position to the maximally elevated or lowered position, and then returned to the standard seating position, followed by the opposite position (each block lasting 15 minutes). B-E. Grouped mean data (± SEM) are presented in the supine, seated, elevated, and lowered wheelchair seating positions. Data were averaged over the last five minutes of each 15-minute trial. B. Systolic arterial pressure (SAP); C. systolic blood flow in the middle cerebral artery (MCA_{sys}); D. diastolic arterial pressure (DAP); and E. diastolic blood flow in the middle cerebral artery (MCA_{dia}) are presented. Vertical adjoining lines denote significant differences between indicated groups; asterisk (*) indicates significant difference from supine position; double dagger (‡) indicates significant difference from seated position.

2.4.3. Cerebrovascular responses to different wheelchair positions

Group average cerebrovascular parameters in different wheelchair positions are also reported in Table 2.2. In all seating positions, MCA_{sys} was reduced compared to supine in those with autonomically-complete SCI (p=0.02), but not in those with autonomically-incomplete SCI. In controls, MCA_{sys} was reduced relative to supine only in the elevated position (Figure 2.1C). In all seated positions, MCA_{sys} was significantly lower in the autonomically-complete SCI group compared to the autonomically-incomplete group (p<0.05).

Diastolic cerebral blood flow velocity (MCA_{dia}) was particularly affected by orthostatic challenge in the autonomically-complete SCI group, similar to our previous report [64] (Figure 2.1E). MCA_{dia} was significantly lower in the autonomically-complete SCI group compared to both groups in the seated, elevated, and lowered positions (all p<0.05). Movement from the seated to the elevated position did not further decrease MCA_{dia} in the autonomically-complete SCI group, but it did decrease MCA_{dia} in the control group compared to supine (p<0.05). Similar group results and changes with position were seen in MCA_{mean}. Significant changes in P_{ET}CO_{2} were not detected and do not explain these results. There was a significant effect of position (p<0.001) on cerebrovascular conductance; all groups showed reduced conductance in all seated positions compared to supine (all p<0.05).
### Table 2.2. Mean cardiovascular variables in different wheelchair positions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw % supine</td>
<td>Raw % supine</td>
<td>Raw % supine</td>
</tr>
<tr>
<td><strong>SEATED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>131 (4)*</td>
<td>138 (4)*</td>
<td>112 (5)*</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>71 (3)*</td>
<td>81 (3)*</td>
<td>68 (3)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>91 (3)*</td>
<td>100 (3)*</td>
<td>83 (4)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;sys&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>91 (4)</td>
<td>96 (3)</td>
<td>96 (5)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;dia&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>44 (2)</td>
<td>95 (5)</td>
<td>43 (2)*</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;mean&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>61 (3)*</td>
<td>94 (5)</td>
<td>62 (3)*</td>
</tr>
<tr>
<td>CVC (cm.s&lt;sup&gt;-1&lt;/sup&gt;.mmHg&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.67 (0.03)*</td>
<td>0.63 (0.04)*</td>
<td>0.55 (0.05)*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71.1 (3.0)*</td>
<td>73.8 (2.3)*</td>
<td>70.7 (6.7)</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>85.2 (3.5)*</td>
<td>74.8 (4.2)*</td>
<td>74.9 (3.7)</td>
</tr>
<tr>
<td>CO (L.min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>6.1 (0.3)</td>
<td>5.6 (0.3)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td><strong>ELEVATED</strong></td>
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<td></td>
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</tr>
<tr>
<td>SAP (mmHg)</td>
<td>131 (4)*</td>
<td>142 (3)*</td>
<td>107 (5)*</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>72 (3)*</td>
<td>85 (3)*</td>
<td>67 (3)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92 (4)*</td>
<td>104 (3)*</td>
<td>80 (4)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;sys&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>88 (4)</td>
<td>93 (3)*</td>
<td>94 (5)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;dia&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>42 (2)*</td>
<td>92 (5)</td>
<td>43 (2)*</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;mean&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>58 (3)*</td>
<td>91 (4)*</td>
<td>61 (3)*</td>
</tr>
<tr>
<td>CVC (cm.s&lt;sup&gt;-1&lt;/sup&gt;.mmHg&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.64 (0.03)*</td>
<td>0.61 (0.04)*</td>
<td>0.56 (0.06)*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>74.7 (3.8)*</td>
<td>76.6 (3.2)*</td>
<td>79.4 (6.5)*</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>80.2 (4.1)*</td>
<td>69.3 (3.6)*</td>
<td>62.3 (4.5)*</td>
</tr>
<tr>
<td>CO (L.min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>5.9 (0.3)</td>
<td>5.3 (0.3)*</td>
<td>4.5 (0.3)*</td>
</tr>
<tr>
<td><strong>LOWERED</strong></td>
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<td></td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>136 (5)*</td>
<td>140 (5)*</td>
<td>119 (6)</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>75 (4)*</td>
<td>84 (4)*</td>
<td>72 (5)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>94 (4)*</td>
<td>103 (4)*</td>
<td>88 (5)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;sys&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>87 (3)</td>
<td>95 (5)</td>
<td>94 (5)</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;dia&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>43 (2)</td>
<td>95 (6)</td>
<td>42 (2)*</td>
</tr>
<tr>
<td>MCA&lt;sub&gt;mean&lt;/sub&gt; (cm.s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>59 (3)*</td>
<td>94 (6)</td>
<td>61 (3)*</td>
</tr>
<tr>
<td>CVC (cm.s&lt;sup&gt;-1&lt;/sup&gt;.mmHg&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.63 (0.04)*</td>
<td>0.61 (0.04)*</td>
<td>0.52 (0.05)*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71.3 (3.3)*</td>
<td>75.9 (3.8)*</td>
<td>71.7 (5.1)</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>85.4 (3.5)*</td>
<td>69.3 (4.9)*</td>
<td>76.5 (3.9)*</td>
</tr>
<tr>
<td>CO (L.min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>6.0 (0.2)</td>
<td>5.2 (0.4)*</td>
<td>5.0 (0.2)</td>
</tr>
</tbody>
</table>
2.4.4. Temporal information and magnitude of the cardiovascular responses to different wheelchair positions

The nadir SAP in each wheelchair position is shown in Figure 2.2A. In the seated and elevated positions, nadir SAP was significantly lower in the autonomically-complete SCI group compared to both autonomically-incomplete (p<0.05) and control groups (p<0.05). Within the autonomically-complete SCI group, minimum SAP was significantly lower in the elevated position compared to seated (p<0.05). In all positions, there was no statistical difference in the timing of the SAP nadir between groups over the 15-minute period (all p>0.05).

The $MCA_{dia}$ was calculated for each position at each subjects’ SAP nadir to determine the minimum blood flow to the brain at this time (Figure 2.2B). $MCA_{dia}$ was lower in the autonomically-complete SCI group compared to both groups in all wheelchair positions (all p<0.05). Considering only the pairwise change from seated to elevated, $MCA_{dia}$ was significantly lower when elevated only in the autonomically-complete SCI group (p=0.039, Figure 2.2B).
Figure 2.2. Nadir systolic arterial pressure and cerebral blood flow in seated, elevated and lowered wheelchair positions

Note: A. Nadir systolic arterial pressure (SAP) and time at nadir in each wheelchair position. B. Diastolic middle cerebral artery blood flow ($\text{MCA}_{\text{dia}}$) at nadir SAP. Asterisk (*) indicates significant difference from both autonomically-incomplete SCI and control groups; double dagger (‡) indicates significant difference from seated position.
Figure 2.3. Cumulative orthostatic burden in seated and elevated wheelchair positions.
Note: A. Cumulative orthostatic burden was calculated as the cumulative area under the curve (AUC) for the duration of each wheelchair position: the difference between baseline systolic arterial pressure (SAP) and SAP multiplied by the duration of each beat. B. Example traces from a representative individual in each group. Dotted horizontal line indicates supine SAP for that individual and shaded area indicates regions below supine SAP. Asterisk (*) indicates significant difference from both autonomically-incomplete SCI and control groups; double dagger (‡) indicates significant difference from seated position.

2.4.5. Cumulative orthostatic burden

The overall burden of OH in each position is shown in Figure 2.3. There was no significant difference in AUC between groups in the seated position (p>0.05). However, the AUC of individuals with autonomically-complete SCI was increased in the elevated position, compared to both seated and lowered positions, and was significantly different from autonomically-incomplete SCI and control groups (all p<0.05). There were no significant differences in orthostatic burden between the seated, elevated, and lowered positions in either the control or autonomically-incomplete SCI groups. Figure 2.3B shows an example of the OH burden in each condition from one representative individual in each group.

2.4.6. Cardiovascular responses in the LEVO active-easy™ wheelchair

Figure 2.4A shows the group mean cardiovascular responses of controls to different positions in the LEVO active-easy™ wheelchair. The grouped averages do not show pronounced changes in blood pressure; however, several able-bodied controls were symptomatic during the passive standing portion of testing. Two individuals were not able to complete the test and were returned early to a supine position (one asked to stop the test due to symptoms and the other met our end-point blood pressure criteria for stopping testing: SAP < 80 mmHg).

Figure 2.4B shows an individual trace for one control participant who showed a pronounced orthostatic response to the standing wheelchair position. This trace demonstrates the magnitude of response possible in a passive orthostatic stress – even in a healthy able-bodied control. Given these pronounced responses in some of our
control participants, we opted not to test individuals with SCI in the supported standing position.

2.5. Discussion

Wheelchair technologies continue to improve to meet the needs of individuals living with disability. Our results show that some caution is warranted before encouraging all individuals to adopt and use new wheelchairs without prior education and planning. Individuals with high-level SCI tend to have low resting blood pressure, particularly when seated. In this population, moderate changes in body position can result in periods of low blood pressure and cerebral blood flow that can potentially trigger symptoms of presyncope or even syncope [21, 64]; lowered seating positions may somewhat mitigate these effects. Although we considered wheelchair users with SCI, our results may have implications for other non-SCI wheelchair users with autonomic impairment such as individuals with multiple sclerosis, diabetic neuropathy, and autonomic failure syndromes.

We showed that cardiovascular homeostasis in individuals with autonomically-complete SCI is perturbed by positional changes. Similar to our previous work [21, 64], averaged data showed lower seated blood pressure in this group compared to individuals with autonomically-incomplete SCI and controls. Movement to an elevated wheelchair position further challenged blood pressure, triggering pronounced falls in SAP and cerebral perfusion, with nadir values significantly lower than in the seated or lowered positions. There may be some concern about the cumulative burden of hypotension – and potentially cerebral hypoperfusion – over long periods in the elevated position. Hypotension in individuals with SCI has been associated with deficits in memory and attention processing speed [243, 244], and in the able-bodied orthostatic hypotension is associated with a 36% increase in overall mortality risk [245].

We found that lowered seating improved SAP and SV compared to elevated seating in those with autonomically-complete SCI (Figures 2.1 and 2.2; Table 2.2) and could, therefore, be used as a counter-maneuver for individuals to bolster blood pressure. In fact, a lowered position – often lower than 10° - tends to be the preferred
seating position for individuals with high-level SCI because it improves trunk stability [215, 246]. These results highlight the importance of changing positions often to limit overall time spent with low resting blood pressure. Dynamic wheelchairs facilitate frequent position changes that can help with blood pressure control and hopefully limit orthostatic symptoms and fatigue.

While there was an improvement in SAP in the lowered position, this was not the case for MCA_{sys} (Figure 2.1). This failure to improve cerebral perfusion despite improvements in blood pressure could be an indicator of impaired autoregulation, as we have previously reported in this population [64].

The benefit of the lowered seating position may be more apparent during dynamic exercise. We focused on static positioning and did not test cardiovascular function while wheeling. Body movement and dynamics during wheeling may accentuate the differences in cardiovascular parameters between positions. For example, when wheeling, the lowered position provides improved ergonomics compared to the seated or elevated position, and individuals often lean forward to move the center of gravity forward [247]. This would further compress the abdomen and increase venous return to the heart [248]. Therefore, the functional cardiovascular benefits of the lowered position might be enhanced during exercise.

While not the main focus of this study, our results reiterate the dissociation between AIS score, which classifies motor and sensory injury impairment, and the autonomic completeness of injury [21, 64, 89]. It is not always possible to predict autonomic injury from the status of motor and sensory pathways.

Given the disruption of sympathetic nerve pathways in those with autonomically-complete injuries, we might have expected greater impairments in cardiovascular control during orthostatic stress in this group; however, physiological adaptations, such as changes in the renin-aldosterone-angiotensin system [249] and antidiuretic hormone release [250], may help them to cope with orthostatic stress over time. The extent of spasticity may also play an important role in these adaptations – muscle contractions associated with lower extremity spasticity can activate the skeletal muscle pump and improve venous return [251, 252]. Therefore, those with increased spasticity might better
tolerate orthostatic stress. Conversely, muscle atrophy and flaccid paralysis might minimise lower limb blood flow and limit venous pooling and subsequent capillary filtration [253]. Indeed, reduced arterial diameter and blood flow in the distal limbs has been noted in those with SCI [254], and might actually mitigate orthostatic intolerance. We did not evaluate the contribution of lower limb spasticity to orthostatic cardiovascular control, but its role as an explanatory variable would be of interest in future studies.

We chose not to test individuals with SCI in the supported standing position, because we were concerned about the significant orthostatic stress posed. Even the elevated seating position triggered a profound orthostatic response in individuals with high-level autonomically-complete SCI. Several of our able-bodied participants found the supported standing position triggered symptoms of OH, and two required early termination of testing with this position. Furthermore, with wheelchair testing it can be difficult to quickly return the individual to a supine, or head down, position to ensure prompt recovery of hemodynamic control and the termination of symptoms. Finally, the standing wheelchair used in the present study does not permit lowered seating, which we were interested in as a potential recovery position to bolster blood pressure. Therefore, this phase of testing was only conducted in able-bodied controls. Nevertheless, these data highlight the particular risk of OH during passive supported standing for some individuals - even those with intact autonomic reflexes. Presumably the risk would be even greater in those with cardiovascular autonomic deficit.

Here we considered only the acute impact of dynamic seating and associated orthostatic stress on cardiovascular control. However, there may be a training effect of repeated exposure to orthostatic stress [255]. This could explain, in part, the modest reduction in incidence and severity of OH with time after injury [59]. Whether this reflects a true reduction in the orthostatic burden through improved cardiovascular reflex control, increased tolerance to the symptoms of OH, or optimised treatment and management of OH is unclear. If orthostatic training is possible in individuals with SCI exposed to repeated orthostatic stresses, the potential concerns associated with dynamic seating might be mitigated over time, and could be considered a form of conditioning to improve cardiovascular responses [225].
Figure 2.4. Cardiovascular responses in able-bodied controls to seated and supported standing wheelchair positions

Note: A. Grouped mean data (± SEM) are presented in the supine, seated (90°) and standing positions, showing systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR) and mean blood flow in the middle cerebral artery (MCA mean). Data were averaged every 30 seconds. B. An example trace from one control participant in the supine, seated, and standing positions, showing SAP, DAP and MCA mean. Dotted horizontal lines indicate supine SAP and MCA mean respectively for that individual and shaded area indicates regions below supine SAP or MCA mean.
We employed well-used techniques to assess cardiovascular function. However, assessment of cerebral blood flow from indirect measurements of velocity using Doppler ultrasound relies on the assumption that the insonated vessel diameter remains constant [256]. Although we did not measure MCA diameter, it is thought to remain fairly constant [256] – except with large changes in \( P_{ET\text{CO}_2} \) [257, 258], which did not occur in our study. The absolute values of MCA blood flow velocity can also be affected by angle of insonation and probe positioning. Therefore, we report both absolute values and percentage changes in MCA (Table 2.2), with qualitatively similar results.

One limitation of this study is the smaller number of participants with cervical SCI – who comprise about half of all individuals living with SCI [259]. Given that individuals with high injury levels are most likely to experience abnormal blood pressure regulation, the current results may underestimate the severity of cardiovascular compromise. It is possible that this reflects self-selection of these individuals, because of known orthostatic intolerance or difficulty completing the transfers inherent in this study. In practice, it is likely that many individuals with high-level SCI would not elect to use wheelchairs with dynamic seating due to trunk instability; for those who do, cardiovascular complications should be taken into consideration.

Several new powered mobility alternatives have recently been developed for individuals with high-level SCI that likely pose similar challenges to cardiovascular control. These power wheelchairs permit a wide range of position flexibility, spanning from supine to standing [260, 261], enabling even individuals with very high-level SCI to access the benefits of standing. However, it may also make them vulnerable to severe orthostatic decreases in blood pressure. The effects of these wheelchairs on blood pressure and cerebral blood flow in individuals with high-level SCI – who are both the target user group and at the highest risk for cardiovascular dysfunction - are unknown. Furthermore, exoskeletons have recently been approved by the United States Food and Drug Administration [262] and will soon be viable alternatives for individuals with mobility impairments [263]. Devices that incorporate lower limb locomotion may bolster orthostatic blood pressures through lower limb skeletal muscle pumping activity [13]. It will be critical that cardiovascular studies are carried out with these new devices to
ensure appropriate configurations that mitigate the orthostatic cardiovascular deficit and consider the cardiovascular control of the user.

2.6. Conclusions

Integrity of the autonomic nervous system is an important variable that affects cardiovascular responses to orthostatic stress and should be considered when individuals are selecting and configuring wheelchairs with dynamic seating options. These results have implications for individuals with SCI and also non-SCI wheelchair users with autonomic impairment such as individuals with multiple sclerosis, diabetic neuropathy, and autonomic failure syndromes. We hope this research will encourage clients, physicians and seating specialists to consider cardiovascular stressors when they are selecting possible wheelchairs. Discussion and education around identification of early symptoms of OH and presyncope should be included when individuals are making wheelchair decisions. The ability to make rapid position changes (e.g. to a lowered position) to recover blood pressure if individuals begin to feel symptoms of presyncope is an important consideration for all wheelchair users – especially for those with autonomic impairment. With modest education and key contingency procedures in place, all wheelchair users should be able to access the myriad benefits of dynamic position changes to their health, independence, self-efficacy and quality of life.
Chapter 3.

Cardiovascular autonomic function in the acute post-injury period

3.1. Abstract

Cardiovascular control in the acute period after spinal cord injury (SCI) has not been well characterized. However, cardiovascular dysfunctions are common in this period. Here we aimed to evaluate cardiovascular autonomic function over the first year after SCI using spectral analyses of heart rate and blood pressure variability and other markers of cardiovascular dysfunction.

Twenty-nine participants were tested at four time points post-injury: within two weeks of injury; between two and four weeks post-injury; at three months post-injury; and between six to 12 months post-injury. Supine beat-to-beat blood pressure and heart rate were recorded at each visit, and participants completed a questionnaire examining cardiovascular symptoms: orthostatic hypotension, autonomic dysreflexia, arrhythmia and fatigue. Arrhythmia risk was also assessed using electrocardiogram (ECG) markers of ventricular and atrial arrhythmia risk. Frequency domain analyses of heart rate and blood pressure variability were also performed. Low frequency variability of systolic arterial pressure (LF SAP) was used as a key outcome measure and measure of sympathetic autonomic function.

In the first two weeks post-injury, most participants showed reduced LF SAP. By one month post-injury, two discrete groups emerged, an autonomically-complete group with sustained low LF SAP and an autonomically-incomplete group with higher LF SAP. These groups remained distinct over time post-injury. Those with autonomically-complete lesions experienced a number of cardiovascular impairments, including increased risk of ventricular arrhythmias that developed over time.

Ultimately to develop treatments to improve cardiovascular function after SCI we must first understand the typical progression of changes in autonomic control. Assessment of autonomic function is likely most informative at about one month after injury and LF SAP may provide a simple measure to assess autonomic function non-invasively.
3.2. Introduction

Traumatic injuries to the spinal cord frequently cause damage to autonomic nervous system pathways as well as to motor and sensory pathways. Accordingly, control of the cardiovascular system is often disrupted by spinal cord injury (SCI), resulting in impaired ability to control heart rate and blood pressure. Acutely after injuries that result in the loss of sympathetic outflow to the peripheral vasculature, the cardiovascular system often goes into a period of shock, known as neurogenic shock [48, 49]. During this time, individuals experience profound hypotension secondary to the decrease in peripheral resistance and loss of vascular capacitance [50]. Volume support is often administered to maintain sufficient blood pressure in this population (mean arterial pressure greater than 85 mmHg) [49].

In the chronic post-injury period, individuals with damage to autonomic cardiovascular pathways experience deficits in short-term control of the cardiovascular system. The particular manifestation depends strongly on injury level and completeness of injury. High-level SCI in the cervical and high-thoracic region can disrupt central control of cardiac function and peripheral vasomotor pathways resulting in reduced ability to adapt the cardiovascular system to imposed cardiovascular stressors. The low level of sympathetic nervous system activity and associated loss of vasoconstriction results in orthostatic hypotension (OH), a decrease in systolic blood pressure of 20 mmHg or more, or a reduction in diastolic blood pressure of 10 mmHg or more, upon changing from a supine to upright posture [55, 56]. Conversely, the loss of descending control of spinal sympathetic reflexes can result in periods of autonomic dysreflexia (AD), a sudden bout of hypertension triggered by a noxious or nonnoxious afferent stimulus below the level of SCI [48, 83, 264].

Both OH and AD evolve with time after SCI [59]. A retrospective chart review showed that the prevalence and severity of OH decreases over the first month after SCI [59]. While there have been documented cases of AD in the early days after injury [85-87], in most cases it does not develop until about one to six months after injury [83]. This suggests that there is some evolution of cardiovascular dysfunction in the acute post-injury period. Ultimately, to develop treatments and therapies to improve cardiovascular
function, we must understand the typical progression of cardiovascular autonomic function after SCI.

Spontaneous changes in somatic neurological function have been shown to occur in the early post-injury period. A high proportion of patients demonstrate spontaneous changes in sensory and motor function of at least one spinal level in the first year after SCI (improving in some individuals and worsening in others) [265, 266]. These spontaneous functional changes are likely mediated by spontaneous plasticity in neural circuitry. It is expected that the autonomic neural circuitry in the spinal cord also experiences spontaneous changes, which would alter cardiovascular control during this period. However, the acute changes in cardiovascular autonomic control and cardiovascular complications following SCI over time remain poorly documented.

Cardiovascular autonomic impairments are not captured by the typical method for determining the level and severity of SCI [130]. While cardiovascular consequences of injury are beginning to be documented with new standards to document autonomic function after SCI [6, 132], they remain poorly quantified, especially in the acute post-injury period. However, variability is one hallmark of a healthy cardiovascular system, and the assessment of heart rate variability (HRV) and blood pressure variability (BPV) is one method to quantify cardiovascular autonomic function. We, and others, have used HRV and BPV in the SCI population to document remaining autonomic function [21, 164, 211, 267]. BPV, particularly systolic arterial pressure (SAP) variability, in the low frequency domain (LF, ~0.1 Hz) corroborates other traditional clinical markers of sympathetic function and can be used to non-invasively identify individuals with damage to cardiovascular sympathetic pathways [21]. We recently demonstrated that LF SAP is also an effective measure of damage to cardiovascular autonomic pathways in animal models of SCI [210].

Electrocardiogram (ECG) abnormalities can also be used to quantify cardiac health and dysfunction non-invasively. Both atrial and ventricular ECG abnormalities have been documented in chronic SCI [89, 96, 103]. In the ventricles, the transmural dispersion of repolarisation reflects the different rates of repolarisation in the different cell types of the ventricular wall [268, 269]. In the ECG, this is represented by the
duration from the peak of the T-wave to the end of the T-wave ($T_{\text{peak}}-T_{\text{end}}$). An increased $T_{\text{peak}}-T_{\text{end}}$ presents substrate for ventricular arrhythmias and can be used as a measure of ventricular arrhythmia risk [268-270]. In some patients, it has been shown to be a better predictor of arrhythmia than the more traditional Q-T interval [271, 272]. The QT variability index (QTVI) is another independent predictor of ventricular arrhythmia risk that is associated with sympathetic activity [92, 93]. Finally, the risk of atrial arrhythmia can be assessed by analysing P-wave duration, which reflects the propagation of sinus impulses in the atria, with longer durations associated with increased risk for atrial arrhythmias [98, 99].

The duration of hospital stay following SCI is decreasing [273] so that some patients may be discharged while the cardiovascular system is still responding to injury, and possibly before the onset of symptoms and development of AD [274]. Being able to determine whether individuals – especially those with incomplete injuries – are likely to develop AD or cardiac arrhythmias would be an important addition to the patients’ care plan and discharge summaries. Furthermore, it is important to document the typical changes in cardiovascular function in the acute-post injury period before we intervene in any way, for example with therapeutic interventions to improve cardiovascular function. Until we understand the natural time course of these changes it will be impossible to distinguish any changes attributable to the impact of interventions, medications, or therapies. Here we present data from a longitudinal study on cardiovascular autonomic function in the first year after SCI. This research will help us build a complete picture of the evolution of cardiovascular autonomic control and the development of cardiovascular dysfunction after SCI.

3.3. Methods

3.3.1. Ethics

This study conformed to the principles outlined in the Declaration of Helsinki [239] and ethical approval was granted from the Simon Fraser University Office of Research Ethics and the Vancouver Coastal Health Research Institute.
3.3.2. Participants

Study participants were individuals who recently sustained a traumatic SCI. All participants were over 18 years old. Individuals were approached in the Acute Spine Unit at Vancouver General Hospital and invited to participate in this study by our research nurse. All participants gave written informed consent at the time of testing.

3.3.3. Experimental protocol

In this longitudinal study, participants were tested at four time points post-injury: Visit 1, within two weeks of injury; Visit 2, between two and four weeks post-injury; Visit 3, at three months post-injury; and Visit 4 at six to 12 months post-injury. At each visit, participants were fitted with a standard three-lead ECG (lead II) and non-invasive beat-to-beat finger blood pressure monitor (Finometer Model 2 (MIDI), Finapres Medical Systems (FMS), Amsterdam, Netherlands). Blood pressure and ECG were recorded for 15 minutes (sampling rate 200 Hz) and stored for off-line analysis.

Participants also completed a questionnaire about their cardiovascular symptoms including OH, AD, arrhythmia and fatigue, using a questionnaire tailored for people with SCI (see Appendix A.1. Cardiovascular symptoms after spinal cord injury questionnaire) [64]. The fatigue questions are an abbreviated form of the Fatigue Severity Scale [275], which was developed for use in individuals with multiple sclerosis, but has been validated for use in individuals with SCI [276, 277]. In these questions, respondents mark how they are feeling along a visual analogue scale and the distance from the anchor point (not fatigued) is measured, and divided by the total length of the scale. An average of all questions is calculated. Medical charts were also reviewed to identify injury information, signs and symptoms of cardiovascular dysfunctions, and medications with significant cardiovascular effects.

3.3.4. Data analyses

The primary outcome measure was the LF SAP variability obtained by spectral analysis of beat-to-beat systolic arterial pressure, which was used to determine the severity of injury to cardiovascular autonomic pathways. Parametric spectral analyses
were performed on the time series of successive beats extracted for R-R interval (RRI) and systolic arterial pressure (SAP) [21]. Rare ectopic beats or pressure artefacts were excised and adjacent beats were linearly interpolated. We fitted autoregressive monovariate models to the RRI and SAP time series [21]. Frequency peaks in the high frequency (HF, 0.15-0.3 Hz), LF (0.04-0.15 Hz) and very LF (VLF, <0.03 Hz) ranges were identified. The absolute power (variance), percentage power, and central frequencies of each frequency domain were calculated by computation of the residuals [278]. Because of the predominance of the VLF power, normalised units (n.u.) were also calculated to represent the relative values of each power component (LF and HF) in relation to the total power, not including the VLF (LF n.u. = (LF power/(total variance - VLF power))*100) [21, 158, 160, 172, 279].

We evaluated the incidence of ECG characteristics associated with increased risk of cardiac arrhythmias. This included examination of the ECG recordings from each time point to identify cardiac arrhythmias and other heartbeat abnormalities. ECG parameters were determined every beat using customised software (LabView 2009, National Instruments) as described previously [89]. At each beat, we measured the RRI, $T_{peak}$-$T_{end}$ interval, QT interval, rate-corrected QT interval (QTc) [280], and the P-wave duration. The variability of these indicators over the duration of testing was also calculated: $T_{peak}$-$T_{end}$ variability, P-wave duration variability, and the QTVI. The QTVI was calculated as follows: $QTVI = \log_{10} \left[ (QT_v/QT_m)^2/(RR_v/RR_m)^2 \right]$, where QTv is the QT variability, QTm is the mean QT interval, RRv is the variability of the RRI, and RRm is the mean RRI [89, 281, 282]. QTVI is an inverse score such that QTVI scores are typically negative and values closer to zero are considered abnormal [95, 96].

Cardiovascular symptoms were also quantified as additional outcome measures. A score was calculated for the symptoms of AD and OH individually, and a cumulative cardiovascular symptom score combined both symptoms scores. An average fatigue score was calculated from the three questions using the visual analogue scale, from the Fatigue Severity Scale [275].
3.3.5. Statistical analyses

Data processing and analysis was performed using R (Version 3.0.2), RStudio (Version 0.98.507), and SigmaPlot Version 12 (Systat Software Inc., San Jose, CA). Comparisons of proportions between groups were made using Fisher’s exact test. Two-way repeated measures ANOVA were used to compare groups. Where main effects were present, post-hoc comparisons were conducted. Statistically significant differences were assumed where $\alpha<0.05$.

3.4. Results

3.4.1. Participant demographics

Twenty-nine individuals with acute traumatic SCI were tested on at least one occasion. Demographic information from visit 1 is shown in Table 3.1. Participants included individuals with a wide range of injury levels and AIS grades. The mean age of participants was 54.4 years (range: 21-86 years).
Table 3.1. Participant demographics

<table>
<thead>
<tr>
<th>Lesion level</th>
<th>AIS grade</th>
<th>Sex</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C4</td>
<td>M</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>C4</td>
<td>M</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>C4</td>
<td>F</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>C4</td>
<td>M</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>C4</td>
<td>F</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>C4</td>
<td>F</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>C5</td>
<td>M</td>
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<td>C5</td>
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<tr>
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<td>T6</td>
<td>M</td>
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<td>T7</td>
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<td>22</td>
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<td>T9</td>
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</tr>
<tr>
<td>29</td>
<td>L1</td>
<td>M</td>
<td>55</td>
</tr>
</tbody>
</table>

3.4.2. Power spectral analyses of BPV

Many individuals showed low LF SAP at visit 1 compared to reference data [21]. At the second visit, there was a more broad range of LF SAP variability, and this time point was used to stratify individuals into groups of autonomically-complete or autonomically-incomplete injuries, in combination with injury level information: individuals with LF SAP greater than or equal to 3.75 mmHg² (the lowest LF SAP of an individual with low thoracic SCI) or injuries at or below T6 were considered to have autonomically-incomplete SCI (Figure 3.1). Individuals grouped into the autonomically-complete group
at visit 2 also had significantly lower LF SAP compared to the autonomically-incomplete groups at subsequent time points post-injury (Figure 3.1). There was no significant effect of time for either group.

![Graph showing LF SAP variability over time post-injury](image)

**Figure 3.1. Low frequency SAP variability over time post-injury**

Note: Low frequency (LF) systolic arterial pressure (SAP) variability at each visit post-injury. Individuals were stratified into autonomically-complete and autonomically-incomplete groups based on their level of injury and LF SAP at visit 2. Asterisk (*) indicates significantly lower than incomplete group (p<0.05).

Group demographic information based on autonomic-completeness of injury is shown in Table 3.2. When separated in this manner, there were no significant differences between groups in terms of age, sex distribution, or injury characteristics (all p>0.05).
Table 3.2. Autonomically-complete and -incomplete group demographics

<table>
<thead>
<tr>
<th></th>
<th>Autonomically-complete SCI</th>
<th>Autonomically-incomplete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Age</td>
<td>55.3 (2.8)</td>
<td>53.8 (4.2)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>8:4</td>
<td>15:2</td>
</tr>
<tr>
<td>Injury levels</td>
<td>C4-T6</td>
<td>C4-L1</td>
</tr>
<tr>
<td>AIS</td>
<td>A-D</td>
<td>A-D</td>
</tr>
</tbody>
</table>

Overall SAP BPV is shown in Table 3.3. As described above, there was no association between LF SAP and autonomic-completeness at visit 1. Groups were stratified at visit 2, where LF SAP measurements (raw, percentage and n.u.) were significantly lower in the autonomically-complete group compared to the autonomically-incomplete group (all p<0.05). LF SAP remained reduced in the autonomically-complete group at both visit 3 and 4. In addition to differences in LF SAP between groups, those with autonomically-complete SCI showed reduced total SAP variability at visit 2 and 3 (both p<0.05). VLF SAP was also reduced in the autonomically-complete group at visit 3 (p<0.05). While similar trends were seen to hold at visit 4, statistical power was reduced due to the attrition of some participants at this time point. Individuals with autonomically-complete SCI showed significantly increased HF SAP percentage power at visit 1 compared to the autonomically-incomplete group (p<0.05), suggesting an increased variability in intrathoracic pressure associated with breathing. There was a significant rightward shift in central frequency of the LF SAP in the autonomically-complete group at visit 4 compared to the autonomically-incomplete group (p<0.05). There were no other significant differences between groups.
Table 3.3.  Systolic arterial blood pressure variability over time post-injury

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (&lt; 2 weeks)</th>
<th>Visit 2 (2-4 weeks)</th>
<th>Visit 3 (3 months)</th>
<th>Visit 4 (6-12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomically-complete SCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Mean SAP (mmHg)</td>
<td>110.4 (8.6)</td>
<td>104.6 (8.4)†</td>
<td>114.4 (10.8)</td>
<td>134.1 (13.3)</td>
</tr>
<tr>
<td>LF (Hz)</td>
<td>0.109 (0.009)</td>
<td>0.108 (0.013)</td>
<td>0.081 (0.016)</td>
<td>0.116 (0.012)</td>
</tr>
<tr>
<td>LF power (mmHg²)</td>
<td>1.56 (0.70)</td>
<td>1.47 (0.31)*</td>
<td>2.22 (0.88)*</td>
<td>8.30 (2.92)</td>
</tr>
<tr>
<td>(%)</td>
<td>6.0 (2.3)</td>
<td>7.03 (2.69)*</td>
<td>9.33 (2.16)</td>
<td>14.83 (5.37)</td>
</tr>
<tr>
<td>(n.u.)</td>
<td>34.9 (8.0)</td>
<td>42.24 (5.65)*</td>
<td>47.18 (7.72)</td>
<td>63.26 (11.38)</td>
</tr>
<tr>
<td>HF (Hz)</td>
<td>0.292 (0.02)</td>
<td>0.274 (0.02)</td>
<td>0.264 (0.01)</td>
<td>0.264 (0.02)</td>
</tr>
<tr>
<td>HF power (mmHg²)</td>
<td>1.45 (0.51)</td>
<td>1.06 (0.35)</td>
<td>1.05 (0.27)</td>
<td>1.55 (0.17)</td>
</tr>
<tr>
<td>(%)</td>
<td>7.59 (3.24)*</td>
<td>3.60 (1.00)</td>
<td>4.93 (1.35)</td>
<td>3.14 (0.51)</td>
</tr>
<tr>
<td>(n.u.)</td>
<td>34.7 (8.2)</td>
<td>29.09 (5.43)</td>
<td>25.74 (3.68)</td>
<td>21.53 (6.42)</td>
</tr>
<tr>
<td>Total variance (mmHg²)</td>
<td>43.18 (21.09)</td>
<td>31.70 (7.34)*</td>
<td>24.35 (4.72)*</td>
<td>54.82 (12.06)</td>
</tr>
<tr>
<td>VLF power (mmHg²)</td>
<td>39.07 (20.40)</td>
<td>28.24 (7.07)</td>
<td>20.06 (4.08)*</td>
<td>43.61 (11.08)</td>
</tr>
</tbody>
</table>

| **Autonomically-incomplete SCI** |                     |                      |                    |                       |
| n              | 14                  | 10                   | 4                  | 7                     |
| Mean SAP (mmHg) | 108.7 (5.8)         | 122.2 (8.3)          | 138.3 (9.0)        | 129.2 (3.9)           |
| LF (Hz)        | 0.095 (0.010)       | 0.094 (0.013)        | 0.132 (0.015)*     | 0.085 (0.008)         |
| LF power (mmHg²) | 6.93 (4.03)       | 11.99 (4.3)          | 1.94 (0.33)*       | 9.14 (2.6)            |
| (%)            | 10.3 (3.3)          | 18.12 (4.43)         | 6.62 (2.59)*       | 14.43 (3.61)          |
| (n.u.)         | 50.5 (6.2)          | 58.90 (6.39)         | 43.16 (8.00)       | 59.81 (10.76)         |
| HF (Hz)        | 0.280 (0.01)        | 0.286 (0.02)         | 0.237 (0.02)       | 0.278 (0.02)          |
| HF power (mmHg²) | 1.62 (0.63)       | 2.48 (0.70)          | 1.63 (0.59)        | 3.05 (1.87)           |
| (%)            | 3.02 (0.67)         | 5.13 (1.21)          | 4.45 (1.11)        | 5.11 (2.15)           |
| (n.u.)         | 23.9 (4.0)          | 19.85 (4.44)         | 30.12 (3.85)       | 22.75 (7.13)          |
| Total variance (mmHg²) | 46.52 (9.69) | 52.70 (8.32)         | 38.15 (10.60)      | 53.92 (9.45)          |
| VLF power (mmHg²) | 36.40 (5.98)       | 35.03 (5.09)         | 35.21 (9.76)       | 39.81 (6.10)          |

Note: Asterisk (*) indicates significantly lower (p<0.05) and dagger (†) indicates trend towards lower (p<0.1) than autonomically-incomplete group at same visit.

Figure 3.2 shows several individual SAP BPV traces demonstrating some of the variability between individuals with different SCI and over time post-injury. Neither the AIS grade nor the level of injury was able to predict the SAP BPV. Figure 3.2A shows a tracing from three individuals: one individual with high cervical incomplete SCI who had pronounced SAP variability; another individual also with a high cervical incomplete SCI who had very low SAP variability; and a third individual with low thoracic complete SCI with high SAP variability. Figure 3.2B shows a series of four traces from an individual with low thoracic compete SCI. In this case, this individual shows decreased SAP variability following the first visit. Figure 3.2C shows a series of four traces from an individual with autonomically-complete SCI that do not change considerably over time.
Figure 3.2.  Example systolic blood pressure variability traces

Note:  A. SAP variability in three different individuals demonstrating the dissociation between motor and sensory injury (AIS score) and blood pressure variability. B. Representative traces from an individual with a low-level (T10) AIS A autonomically-incomplete SCI who demonstrates reduced BPV at subsequent visits post-injury (discussed further in text). C. Representative traces from an individual with high-level (C4) AIS D autonomically-complete SCI who demonstrates reduced LF BPV that does not change over time.
3.4.3. Power spectral analyses of HRV

Overall HRV is shown in Table 3.4. There were few significant differences between groups. At the first visit, the autonomically-complete group had greater HF power than the incomplete group. At the third visit, there was a significantly lower central frequency of the LF RRI in the autonomically-complete group (p<0.05). At the last visit, there was a significantly lower central frequency of the HF RRI in the autonomically-complete group (p<0.05). There were no other significant differences between groups.

Table 3.4. Heart rate variability over time post-injury

<table>
<thead>
<tr>
<th>Visit</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2-4 weeks)</td>
<td>(3 months)</td>
<td>(6-12 months)</td>
</tr>
<tr>
<td></td>
<td>n=6</td>
<td>n=7</td>
<td>n=8</td>
</tr>
<tr>
<td>Mean RRI (ms)</td>
<td>873.4 (94.4)</td>
<td>881.4 (44.9)</td>
<td>888.7 (28.3)</td>
</tr>
<tr>
<td>LF (Hz)</td>
<td>0.097 (0.013)</td>
<td>0.091 (0.016)</td>
<td><strong>0.077 (0.011)</strong></td>
</tr>
<tr>
<td>LF power (ms²)</td>
<td>117.7 (113.5)</td>
<td>187.5 (145.6)</td>
<td>169.0 (60.7)</td>
</tr>
<tr>
<td>(%)</td>
<td>10.0 (2.3)</td>
<td>8.49 (2.63)</td>
<td>12.8 (3.6)</td>
</tr>
<tr>
<td>(n.u.)</td>
<td>45.4 (6.7)</td>
<td>34.3 (8.9)</td>
<td>43.27 (7.90)</td>
</tr>
<tr>
<td>HF (Hz)</td>
<td>0.298 (0.030)</td>
<td>0.273 (0.015)</td>
<td>0.256 (0.011)</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>273.1 (244.2)†</td>
<td>74.0 (43.6)</td>
<td>83.1 (24.9)</td>
</tr>
<tr>
<td>(%)</td>
<td>14.2 (4.1)</td>
<td>7.80 (4.7)</td>
<td>7.59 (3.6)</td>
</tr>
<tr>
<td>(n.u.)</td>
<td>24.8 (1.0)</td>
<td>22.7 (1.0)</td>
<td>24.9 (0.1)</td>
</tr>
<tr>
<td>LF-to-HF ratio</td>
<td>2.45 (0.86)</td>
<td>2.48 (1.15)</td>
<td>2.48 (0.71)</td>
</tr>
<tr>
<td>Total variance (ms²)</td>
<td>1498.0 (799.9)</td>
<td>1407.0 (679.6)</td>
<td>1322.5 (394.7)</td>
</tr>
<tr>
<td>VLF power (ms²)</td>
<td>939.3 (373.8)</td>
<td>1031.6 (437.9)</td>
<td>994.5 (326.6)</td>
</tr>
</tbody>
</table>

Autonomically-incomplete SCI

|       | n=14 | n=9 | n=5 | n=6 |
| Mean RRI (ms) | 811.6 (50.7) | 827.7 (37.2) | 786.1 (78.6) | 817.6 (61.9) |
| LF (Hz) | 0.087 (0.006) | 0.094 (0.009) | 0.122 (0.009) | 0.095 (0.010) |
| LF power (ms²) | 332.6 (164.2) | 558.8 (292.6) | 579.8 (393.7) | 776.1 (296.5) |
| (%) | 14.2 (4.1) | 15.77 (4.85) | 21.5 (8.3) | 20.8 (4.7) |
| (n.u.) | 49.9 (6.5) | 49.0 (10.4) | 52.29 (13.40) | 56.10 (10.53) |
| HF (Hz) | 0.279 (0.010) | 0.281 (0.015) | 0.280 (0.024) | 0.267 (0.014) |
| HF power (ms²) | 55.1 (12.5) | 174.6 (62.2) | 94.6 (62.5) | 156.7 (52.7) |
| (%) | 4.15 (0.57) | 8.31 (2.84) | 5.05 (1.47) | 6.79 (1.64) |
| (n.u.) | 17.41 (2.22) | 19.97 (4.21) | 18.88 (4.64) | 23.66 (9.97) |
| LF-to-HF ratio | 4.08 (1.03) | 3.01 (0.74) | 4.71 (2.35) | 4.09 (1.18) |
| Total variance (ms²) | 1491.2 (337.6) | 2290.3 (572.6) | 1681.3 (934.6) | 2936.2 (1004.2) |
| VLF power (ms²) | 1022.3 (220.7) | 935.5 (456.9) | 1331.2 (348.8) | 1757.3 (632.5) |

Note: Asterisk (*) indicates significantly lower than autonomically-complete group (p<0.05). Dagger (†) indicated trend towards lower than autonomically-complete group (p<0.01).
3.4.4. Blood pressure variability and cardiac arrhythmia risk

The relationship between LF SAP and ECG-based parameters, including predictors of atrial and ventricular arrhythmias are shown in Table 3.5 at each time point post-injury. There was no significant effect of time post-injury. The QTc was significantly greater in individuals in the autonomically-complete group compared to autonomically-incomplete group at visit 4 (p<0.05). The QTVI (values closer to zero indicate increased impairment [281]) was also significantly greater in individuals in the autonomically-complete group compared to autonomically-incomplete group at visit 4 (p<0.05). There was a trend towards increased P-wave variability in the autonomically-complete SCI group.

Table 3.5. ECG-based parameters in autonomically-complete and –incomplete SCI over time post-injury

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (&lt;2 weeks)</th>
<th>Visit 2 (2-4 weeks)</th>
<th>Visit 3 (3 months)</th>
<th>Visit 4 (6-12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomically-complete SCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;peak&lt;/sub&gt;-T&lt;sub&gt;end&lt;/sub&gt; (ms)</td>
<td>59.2 (3.2)</td>
<td>60.1 (2.1)</td>
<td>62.7 (3.6)</td>
<td>67.7 (5.0)</td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;peak&lt;/sub&gt;-T&lt;sub&gt;end&lt;/sub&gt; variability (ms&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>77.6 (42.3)</td>
<td>67.0 (10.8)</td>
<td>106.6 (37.8)</td>
<td>91.8 (28.8)</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>408.4 (2.3)</td>
<td>385.0 (11.0)</td>
<td>391.1 (9.8)</td>
<td>413.6 (8.8)*</td>
</tr>
<tr>
<td>QTVI</td>
<td>-1.50 (0.29)</td>
<td>-1.96 (0.39)</td>
<td>-1.65 (0.42)†</td>
<td>-1.63 (0.39)*</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>111.7 (6.9)</td>
<td>97.0 (6.6)</td>
<td>121.2 (4.2)*</td>
<td>127.9 (6.0)</td>
</tr>
<tr>
<td>P-wave variability (ms&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>239.1 (124.7)</td>
<td>296.1 (113.5)</td>
<td>454.6 (151.5)</td>
<td>383.7 (169.7)</td>
</tr>
<tr>
<td><strong>Autonomically-incomplete SCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;peak&lt;/sub&gt;-T&lt;sub&gt;end&lt;/sub&gt; (ms)</td>
<td>63.6 (2.3)</td>
<td>64.5 (4.5)</td>
<td>63.2 (1.6)</td>
<td>63.0 (1.5)</td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;peak&lt;/sub&gt;-T&lt;sub&gt;end&lt;/sub&gt; variability (ms&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>115.3 (37.2)</td>
<td>73.4 (23.6)</td>
<td>76.13 (3.9)</td>
<td>115.4 (34.6)</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>405.6 (7.0)</td>
<td>411.5 (12.6)</td>
<td>376.9 (3.8)</td>
<td>382.8 (12.1)</td>
</tr>
<tr>
<td>QTVI</td>
<td>-1.90 (0.37)</td>
<td>-2.49 (0.23)</td>
<td>-2.88 (0.04)</td>
<td>-2.73 (0.42)</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>113.2 (4.4)</td>
<td>113.2 (7.3)</td>
<td>100.3 (3.6)</td>
<td>114.9 (10.2)</td>
</tr>
<tr>
<td>P-wave variability (ms&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>395.2 (81.1)</td>
<td>156.8 (44.5)</td>
<td>267.7 (26.4)</td>
<td>239.3 (28.6)</td>
</tr>
</tbody>
</table>

Note: Asterisk (*) indicates significantly larger than autonomically-incomplete group (p<0.05). Dagger (†) indicated trend towards larger than autonomically-incomplete group (p<0.1).

As we have shown previously [89], the two markers risk of ventricular arrhythmia, QTVI and T<sub>peak</sub>-T<sub>end</sub> variability, were significantly positively correlated with each other (p<0.0001, r=0.655). However, there were no significant linear correlations between LF SAP and the main predictors of arrhythmia.
3.4.5. Cardiovascular symptoms

Cardiovascular symptoms, assessed using our questionnaire are outlined in Table 3.6. There was a trend towards increased fatigue in the autonomically-complete SCI group at the first two visits. There were no significant changes over time.

<table>
<thead>
<tr>
<th>Table 3.6. Cardiovascular symptoms and autonomic completeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (&lt;2 weeks)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Autonomically-complete SCI</td>
</tr>
<tr>
<td>OH symptoms</td>
</tr>
<tr>
<td>AD symptoms</td>
</tr>
<tr>
<td>CV symptoms</td>
</tr>
<tr>
<td>Fatigue score</td>
</tr>
<tr>
<td>Autonomically-incomplete SCI</td>
</tr>
<tr>
<td>OH symptoms</td>
</tr>
<tr>
<td>AD symptoms</td>
</tr>
<tr>
<td>CV symptoms</td>
</tr>
<tr>
<td>Fatigue score</td>
</tr>
</tbody>
</table>

Note: Cardiovascular symptoms were assessed using a questionnaire (Appendix A.1.). The orthostatic hypotension (OH) symptoms and autonomic dysreflexia (AD) symptoms were calculated separately. An overall cardiovascular symptoms score was calculated as the sum of OH and AD symptoms. The average fatigue score was calculated. Dagger (†) indicates trend towards increased score compared to autonomically-incomplete group (p<0.1).

There was a significant positive linear correlation between symptoms of OH and AD (Figure 3.3A). There was also a significant positive correlation between symptoms of OH and fatigue (Figure 3.3B). There was a weak negative correlation between LF SAP and overall cardiovascular symptom score in autonomically-complete group (slope=-1.85, r=0.24, p=0.14) and in the autonomically-incomplete group (slope=-0.4, r=0.23, p=0.17).
Figure 3.3. **Cardiovascular symptoms and fatigue**

Note:  
A. Symptoms of orthostatic hypotension (OH) and symptoms of autonomic dysreflexia (AD) assessed using a symptoms questionnaire were positively correlated among participants with autonomically-complete and autonomically-incomplete SCI. B. Symptoms of OH were also positively correlated with fatigue score among participants with autonomically-complete and autonomically-incomplete SCI.

### 3.5. Discussion

It is important for us to know the typical progression of autonomic function in the early post-injury period in order to identify individuals at risk of cardiovascular dysfunction, interpret the effects of future interventions on cardiovascular autonomic function [283], and ultimately direct future cardiovascular care and rehabilitation. This research demonstrates the broad variability in trajectories of cardiovascular autonomic function after SCI. These heterogeneous trajectories will make the assessment of future therapeutic targets on cardiovascular function after SCI particularly complex. However, even in these heterogeneous populations, LF SAP appears to be a useful tool to discriminate between individuals with autonomically-complete and autonomically-incomplete injuries, even in the early post-injury period.
3.5.1. Variation in autonomic spectral analysis profile over time after injury

Our results demonstrate a pronounced variation in autonomic function over time after injury as assessed by spectral analysis. We were surprised to see a prominent decrease in LF SAP in almost all participants in the early time point after injury. At this time, some participants were likely in neurogenic shock, while others had significant volume depletion, recent surgeries, or extended bed rest and associated deconditioning [284, 285]. This suggests that the use of spectral analysis is not advised in the very early post-injury period, as there is a floor effect. Furthermore, at this point the variability in this range is likely associated with the more global cardiovascular effects of injury rather than the specific autonomic damage to descending autonomic pathways. Therefore, it is not possible to distinguish between autonomically-complete and -incomplete lesions at this time. However, our results show that the dissociation between individuals with autonomically-complete and autonomically-incomplete injuries, established at the period 2-4 weeks post-injury, is maintained in the months that follow.

LF SAP can be represented in several different ways, and there are benefits and challenges associated with each. In our experience, the absolute power of LF SAP and total SAP power have been the most robust predictors of severity of injury to cardiovascular pathways – as assessed by sympathetic skin responses [21]. In our previous work, we found that a threshold raw LF SAP of 1 mmHg\(^2\) discriminated between individuals with and without autonomic injury [64]. When applied to the current results, this cut-off seemed too conservative; therefore, we used the lowest LF SAP of an individual with low thoracic SCI as the cut-off (3.75 mmHg\(^2\)). However, in order to promote the use of this measure as an outcome measure after SCI, it would be helpful to have standard cut-off measures, which could be defined for different positions (supine, seated). Combining all pre-existing data using LF SAP might help clarify and increase our confidence in determining clear cut-off values that are more broadly applicable across populations. To date, the power in individual studies has not been very high.

The day-to-day reproducibility of HRV and BPV using autoregressive modeling has been quantified and, in the SCI population, measures of HRV and BPV were found to be reproducible indices of autonomic cardiovascular regulation [286]. When
considering particular frequency bands, the reproducibility was good in LF RRI, LF SAP and HF SAP frequency ranges, while HF RRI reproducibility was poor [286]. These analyses were conducted on the absolute power of HRV and BPV. Importantly, these experiments were all done in the chronic post-injury period. It is likely that the variability would be higher in the acute post-injury period, and it is possible that this increased variability has implications for reproducibility. However, even in this variable period, we found that we could discriminate between distinct groups of individuals that had discrete LF SAP variability.

In at least one subject, BPV and LF SAP decreased significantly over time (Figure 3.2B). This was perplexing because the individual had a low thoracic injury, so we would not normally predict cardiovascular autonomic deficit as a consequence of the spinal lesion. However, it is possible that medications and medical interventions contributed to these changes; this individual started taking metoprolol (a β-blocker) to manage tachycardia, and also had a failure of their spine hardware that could have included damage to the T6 region. This highlights one of the limitations of using spectral parameters to assess cardiovascular autonomic function. More generally, however, this speaks to the complexities of studying and quantifying autonomic function, which can be strongly affected by medications and the overall physiological state. Despite this individual case not making use of the technique in the way that we originally intended – to document cardiovascular autonomic function changes secondary to SCI – it supports the use of this technique to identify and monitor autonomic deficits more generally, which in this case likely relate to β-blockade. Therefore, LF SAP certainly is a clear indicator of risk that may be helpful for clinical use beyond stratifying patients based on their autonomic function.

3.5.2. Relationship between spectral parameters and risk factors for arrhythmia

Our lab has previously found a negative correlation between LF SAP and risk of atrial and ventricular arrhythmias, as assessed by P-wave variability and T_{peak}-T_{end} variability [89]. This previous study also found an increased risk of ventricular arrhythmias in individuals with autonomically-complete SCI as assessed by QTVI [89]. In
support of these results, here we also found QTVI was increased in those with autonomically-complete SCI, but only at the last time point post injury (6-12 months). This fits with our previous research conducted in the chronic period after SCI (average duration of injury around 10 years) [89] and suggests that the increased risk is not an inherent property of loss of autonomic control, but one that takes time to develop. The QTVI was correlated with $T_{\text{peak}}-T_{\text{end}}$ variability, but there was no statistically significant difference between groups in $T_{\text{peak}}-T_{\text{end}}$ variability. While both are measures of ventricular arrhythmia risk, it is possible that the risk of ventricular arrhythmia – as assessed by $T_{\text{peak}}-T_{\text{end}}$ – takes time to develop and is associated with other risk factors that evolve over time post-injury. For example, repeated exposure to AD might be an additional factor that could increase the risk of arrhythmia to the levels that our lab has previously documented in chronic SCI, more than one year post-injury [89]. Further increases in $T_{\text{peak}}-T_{\text{end}}$ and QTVI have also been documented during AD [89].

Finally, while there was a trend towards increased p-wave variability in the autonomically-complete group, there were no statistical differences between groups. This measure seems particularly variable between individuals in the autonomically-complete group. We did find that the faithful detection of the start and end of the p-wave was more challenging in the current recordings compared to our previous analyses [89], likely due to a reduced sampling rate in the ECG system used the current study (200 Hz compared to 1000 Hz previously [89]). However, we would not expect that this would affect one group more than another.

### 3.5.3. Cardiovascular symptoms

Cardiovascular symptoms were assessed using our questionnaire. While there was a trend towards increased fatigue in the autonomically-complete SCI group, especially in the early time post-injury, there were no statistical differences between groups. There were also no significant changes in symptoms reported over time; the OH symptoms did not ameliorate over time post-injury in individuals with autonomically-complete SCI. Previous studies have shown that the prevalence of OH decreases in the first month after injury [59]. However, OH does not resolve and continues to be prevalent
particularly among individuals with autonomically-complete injuries, and remains a lifelong management challenge [21, 60, 64, 147, 244].

The lack of significant differences in symptoms between groups and over time was somewhat surprising. While our questionnaire has not been validated, it asks questions about common hallmark symptoms associated with OH and AD, and we have used it in previous studies to assess cardiovascular symptoms [64]. However, it’s sensitivity to discriminate between individuals experiencing frank OH or AD has not been tested specifically. There are some identified symptoms, such as spasticity and general unwellness, that may be common among individuals with SCI more generally, and less specific to these two conditions. Therefore, the inclusion of these kinds of more generalised symptoms could dilute the contrast between groups. Furthermore, the survey quantifies the frequency of symptoms and not their severity, which captures one aspect, but perhaps it could be strengthened by a combination of severity and frequency measures. Finally, the frequency data was quantified linearly (scored as Daily = 4, Weekly = 3, Monthly = 2, Rarely = 1, and Never = 0). There is also some debate about whether assigning successive integers to the scale categories is appropriate and if it reflects the differences between categories (i.e. should Daily be twice as much as Weekly). Therefore, the fact that the symptoms scores here were not significantly different between groups should not be overly emphasised, and a revision of our questionnaire is perhaps warranted.

There was a positive correlation between symptoms of OH and AD (Figure 3.3A). This fits with the phenotype that most individuals with SCI who suffer from one of these cardiovascular conditions also experience the other [48]. There was also a significant positive correlation between symptoms of OH and fatigue (Figure 3.3B). While this by no means implies causation, this relationship fits with the hypothesis that OH, low resting blood pressure, and low cerebral blood flow, may contribute to fatigue in this population [60, 276, 287]. Fatigue after SCI is an area of research that is underexplored, yet it should be given considerably greater attention as it is one of the most common secondary health conditions in individuals living with SCI [288], and significantly negatively impacts quality of life and restricts activities of daily living [236, 277].
3.5.4. **Clinical relevance of these results**

The average age of our sample (54.4 years) fits well with the documented distribution of SCI in Canada and the age profile of the Canadian population [2]. Therefore, we believe that the heterogeneity and variability in injuries and cardiovascular function are representative of the reality of SCI in our aging population. The documentation of cardiovascular function in the aging SCI population, with complex co-morbidities and existing cardiovascular dysfunctions will be increasingly critical to identify individuals at risk of cardiovascular events and provide appropriate care.

In terms of use in the clinical setting, beat-to-beat blood pressure recording is not currently performed, and the cost of the research equipment we used here would likely be prohibitive in most clinical settings. However, beat-to-beat heart rate data are routinely gathered on patients in the hospital, and could conceivably be incorporated into routine workflow. Furthermore, there is an increase of wearable devices such as portable blood pressure monitors and heart rate monitors that might increase available data. Therefore, a measurement like the LF RRI might be feasible, with a small amount of processing. The LF RRI is an imperfect but reasonable measure of efferent cardiovascular control including the sympathetic control that is vulnerable to SCI. However, in the current cohort of 29 patients with SCI, we did not find that the LF RRI is statistically related to the autonomic-completeness of injury as assessed by LF SAP. The variability in the LF RRI domain is too great between individuals and over time, to be reliable in this population. In addition LF RRI has mixed input from both sympathetic and parasympathetic neural control through the baroreflex, which may also increase variability compared to LF SAP [289]. Therefore, while LF RRI is a somewhat imperfect measure, is worth continuing to explore this as a possibly useful parameter as the opportunities for data collection increase (and with them increases in statistical power).

3.5.5. **Relationship between autonomic and AIS severity of injury**

The current results corroborate our previous work showing the dissociation between motor and sensory and autonomic severity of injury [21, 64, 89]. Several participants with similar injury levels and AIS severities presented with very different degrees of autonomic control as assessed by BPV (Figure 3.3A). This reinforces the
necessity of including autonomic function testing in our clinical evaluation of individuals with SCI [132]. In particular, it speaks to the need in include *quantitative* assessments to document autonomic function as part of routine practice.

### 3.5.6. Study strengths and limitations

This study is an important first foray into using frequency domain analyses in the early post-injury period. We know comparably little about the acute post-injury period compared to the effects and condition of chronic SCI. The acute post-injury period is an extremely fragile time when medical needs greatly outweigh research interests. Indeed, in this study, some individuals were too ill in the very early time point to participate in research, and so we started at the second time point post-injury. This reality limits how invasive our research equipment and methodology protocols can be. Therefore, in this study we do not have additional autonomic assessments against which to compare our blood pressure and heart rate variability conclusions. However, in previous studies in chronic SCI, we have shown that this technique can reliably discriminate between individuals with autonomically-complete and autonomically-incomplete lesions [21, 64, 89].

One challenge of investigating physiological parameters during this dynamic period, as the nervous system and body responds to injury, is that there are many variables that are different between individuals. Individual differences in age, size, fitness, treatment and medications all have the potential to affect cardiovascular autonomic control. These differences compound the problem of heterogeneity already present in the broad variation in level and completeness of injury in this population. However, we tried our best to document the interventions that were administered to our participants to at least document the differences between subjects. Furthermore, the heterogeneity of this population is a reality that will only continue to increase as the population ages and the incidence of SCI in older adults increases [2]. Therefore, it is necessary that we begin to evaluate cardiovascular parameters in spite of their variability between individuals.
Unfortunately, for many different reasons, not all subjects participated in all testing sessions. This is partly due to the reality of individuals who come to a tertiary care centre for treatment from all over the province – and the world – and then return to their communities for longer-term rehabilitation. Therefore, not all subjects were tested at all time points. This reduced the power of our ability to detect differences between groups – particularly in the last time point after injury. We hope that ongoing recruitment will help to strengthen our conclusions.

The presence of even a few ectopic beats, or other arrhythmias, during recording can significantly alter the HRV analysis, falsely increasing the total calculated power and variance [290, 291]. The effects of these arrhythmias likely also influence BPV, as ectopic beats and other aberrant or non-conducting beats alter the size and waveform of the concomitant pressure wave. At least one recording was excluded here due to the presence of an arrhythmia, atrial fibrillation, during recording. Ultimately, this makes the use of this technique more challenging. The use of algorithms to identify ectopic beats and linearly interpolate between these beats can manage a small number of ectopic beats [290]. However, there may be problems making appropriate physiological conclusions from frequency analyses when there are large numbers of non-normal beats [290]. Finally, there is a challenge of identifying the risk of arrhythmia if the individual is experiencing an arrhythmia during recording. In the context of our results, the above could create a systematic bias in individuals with severe autonomic nervous system dysfunction that increased variability due to the presence of ectopic beats or other arrhythmias. Despite this potential bias, we observed reduced LF SAP variability.

3.5.7. Future directions

In terms of future studies, it would be ideal to include a mild stressor to activate the sympathetic nervous system. Because LF SAP is increased by manoeuvres that induce sympathetic activation, this would allow us to more reliably discriminate between individuals with and without damage to sympathetic pathways. In the present study, where individuals were tested in the supine position, there is minimal sympathetic activation – so the differences between neurologically intact sympathetic regulation of LF oscillations in blood pressure may be less pronounced. Co-ordination with
physiotherapists and occupational therapists, who help these patients routinely with mobilisation – even in this early period – could facilitate this aspect. A passive sit-up manoeuvre is one that we, and others, have employed in the chronic setting [64, 292].

A relevant question for follow up relates to a subpopulation of several individuals who demonstrated autonomically-complete injuries in spite of having incomplete SCI (AIS D) and being ambulatory by the final testing at 6-12 months post-injury. This is not the traditional population that we associate with cardiovascular autonomic impairment after SCI. Therefore, it would be interesting to perform follow-up tests on these particular individuals and determine whether they go on to develop frank AD and OH. If so, this could be one area where variability analyses could be particularly useful – for identifying those with cardiovascular deficits who might not otherwise be recognised.

Another pertinent question for further exploration is whether there are different degrees of autonomic-completeness that are functionally relevant. We tend to define those that lose central control of the splanchnic vasculature as autonomically-complete [21, 64, 89], as we have done here, but what about the loss of sympathetic cardiac control – especially as it relates to risk of arrhythmia? With a greater number of participants, it would be interesting to investigate whether there are any differences in risk of arrhythmias in individuals with and without preserved sympathetic cardiac control. The activation of both parasympathetic and sympathetic cardiac nerves is thought to be particularly pro-arrhythmogenic [72, 74]. Dual activation is most likely in individuals without descending sympathetic control of the heart and the vasculature – as the sympathetic hyper-reactivity characteristic of AD would be more likely to include reflex stimulation of the heart as well as the vasculature. This investigation would involve three groups: individuals with disrupted sympathetic cardiac and vasomotor control (cervical); individuals with disrupted sympathetic splanchnic control but preserved sympathetic cardiac control (T4-T6) and individuals with autonomically-incomplete SCI, for comparison. The challenge would be powering the mid-thoracic SCI group sufficiently, as it includes such a precise range of neurological injury levels. This study would also exclude individuals with injuries in the high thoracic range in the middle of the cardiac sympathetic outflow to the heart, as this unique subset of individuals can complicate the conclusions as they have partial – and likely altered – sympathetic cardiac control.
Chapter 4.

Cerebrovascular control in autonomically-complete spinal cord injury

4.1. Abstract

Cerebral blood flow is tightly regulated to maintain cerebral perfusion and sufficient O$_2$ supply. Carbon dioxide and oxygen are two potent vasoactive substances with roles in modulating cerebral blood flow. The contribution of the extrinsic sympathetic innervation of cerebral vasculature in the response to these vasoactive substances – and particularly CO$_2$ – remains equivocal. However, there is some evidence of impaired cerebrovascular control after SCI, where control of sympathetic pathways that innervate the cerebral circulation may be lost.

Here we studied cerebrovascular responses to independent changes in CO$_2$ and O$_2$ in individuals with autonomically-complete SCI, autonomically-incomplete SCI, and neurologically-intact controls.

Individuals with autonomically-complete SCI did not show a significant increase in cerebral blood flow in response to hypoxia, unlike in able-bodied controls and individuals with autonomically-incomplete SCI. No group differences were observed in cerebrovascular sensitivity to CO$_2$ in normoxic, hypoxic or hyperoxic conditions. Similar results were obtained when the hypocapnic and hypercapnic regions were considered separately, and when cerebral blood flow changes were expressed as conductance. All groups showed a trend towards a lower CO$_2$ operating point in a hypoxic environment compared to normoxia or hyperoxia.

Individuals with high-level autonomically-complete SCI showed reduced cerebrovascular response to hypoxia. The aetiology of this difference requires further investigation but could be related to repeated nocturnal hypoxic episodes that are common in this population.
4.2. Introduction

Spinal cord injury (SCI) can disrupt neural pathways that control normal cardiovascular function, resulting in a host of secondary complications related to blood pressure and heart rate control. The inability to mount appropriate blood pressure responses to changes in body position can result in chronic hypotension, fatigue, and reduced cognitive performance [21, 64, 243, 293, 294]. On the other hand, episodes of hypertension, or autonomic dysreflexia - an acute sympathetic vasoconstrictor reflex triggered by a sensory stimulus below the level of injury - are also common after high-level SCI that damages cardiovascular pathways [48].

The dangers of these cardiovascular complications relate particularly to their effects on the cerebral vasculature. Cerebral blood flow must be maintained in order to supply sufficient oxygen to the cerebral tissue without increasing flow so much that the structural integrity of the blood vessels is at risk. Blood pressure abnormalities secondary to SCI challenge this balance, resulting in fatigue, poor orthostatic tolerance, and syncope [64, 147, 295] as well as ischemic stroke, cerebral haemorrhage and even death [77, 78, 214, 296].

Cerebral blood flow is regulated by a number of mechanisms. Metabolic, neurogenic, and myogenic cues modulate cerebrovascular resistance to maintain cerebral perfusion, and ultimately oxygen (O$_2$) delivery, even in the face of changing blood pressure. Cerebral blood flow is particularly sensitive to changes in arterial carbon dioxide (CO$_2$), and it is also sensitive to low O$_2$ levels. Cerebral blood vessels are also richly innervated by extrinsic sympathetic nerves originating in the paravertebral ganglia; however, their role in the control of the cerebral vasculature remains equivocal [112, 114, 297-303]. Recent evidence implicates the sympathetic nervous system in modulating the sensitivity of the cerebral vasculature to CO$_2$: increased sympathetic activity influences cerebral responsiveness to changes in arterial CO$_2$ [115, 304].

Individuals with high-level SCI and damage to autonomic pathways may have disrupted extrinsic sympathetic neural control of the cerebral vasculature. Whether this directly influences cerebrovascular control remains to be determined. There are several other indications that the control of cerebral blood flow is impaired after high-level SCI.
Cerebral autoregulation, the ability to maintain cerebral blood flow in the presence of changes in blood pressure is challenged by high-level SCI [64, 305]. In addition, individuals with SCI are at increased odds of stroke [16], and impaired (reduced) cerebrovascular reactivity to CO$_2$ is independently associated with increased risk of stroke [306, 307]. Our lab has previously shown that end-tidal CO$_2$ ($P_{ET}CO_2$) decreases more in individuals with autonomically-complete SCI, when moving from supine to seated position, than in individuals with autonomically-incomplete SCI, or able-bodied controls [64]. However, the changes in cerebral blood flow were not different between groups, suggesting reduced cerebrovascular sensitivity to hypocapnia [64].

The effect of autonomically-complete SCI on cerebrovascular reactivity to CO$_2$ and O$_2$ remains unclear [308]. One previous study has investigated cerebrovascular reactivity to CO$_2$ in individuals with tetraplegia, and showed no frank differences in reactivity [123]. However, autonomic completeness of injury was not confirmed in these participants [123], and individuals with complete motor and sensory injuries (AIS A) can have preserved autonomic function [21, 64]. Therefore, we believe that it is critical to compare groups with autonomically-complete SCI to autonomically-incomplete SCI and to controls.

SCI might also alter sensitivity of the cerebral vasculature to O$_2$. Sleep studies suggest that a significant majority of individuals with tetraplegia experience obstructive sleep apnea [125], which, in able-bodied population, is associated with reduced sensitivity of the cerebral vasculature to hypoxia [127-129]. While intermittent hypoxia has received recent attention as a potential therapeutic intervention to improve function after SCI [309, 310], and the respiratory response to brief periods of hypoxia has been quantified [311] the cerebral effects of hypoxia after SCI have not been studied to our knowledge. Furthermore, the respiratory responses to hypoxia have only been quantified in mixed groups of SCI [311]. Therefore an investigation of cerebral blood flow during hypoxia is warranted, especially as it relates to autonomic completeness of injury.

One of the challenges of investigating cerebrovascular responses to changes in inspired gasses is their concurrent respiratory effect. For example, conditions of hypoxia induce increased ventilation, which decrease CO$_2$ levels, increasing cerebral
vasoconstriction [312]. Therefore, to consider the effects individual gases, it is essential to be able to independently control both O$_2$ and CO$_2$ levels. End-tidal forcing is one method to do this, in which expired end-tidal gas partial pressures are compared with target pressures on a breath-by-breath basis, and gases are mixed accordingly to modify the subsequent breath [313].

Here we studied cerebrovascular responses to CO$_2$ and O$_2$ in individuals with autonomically-complete SCI, autonomically-incomplete SCI, and neurologically-intact controls. Cardiovascular and cerebrovascular parameters were measured as subjects were exposed to a range of CO$_2$ levels through a combination of hyperventilation and end-tidal forcing, at three different oxygen levels. We hypothesised that individuals with autonomically-complete SCI would have: i) reduced cerebrovascular reactivity to CO$_2$; and ii) reduced cerebrovascular sensitivity to O$_2$, compared to able-bodied controls and individuals with autonomically-incomplete SCI.

4.3. Methods

This study received ethical approval from the Simon Fraser University Office of Research Ethics and was performed in accordance with the Declaration of Helsinki [239].

4.3.1. Participants

Studies were performed on 27 individuals: eight with high-level autonomically-complete SCI, seven with autonomically-incomplete SCI (including both high thoracic and cervical levels) and twelve neurologically-intact controls (we were unable to find the MCA using cerebral ultrasound in a thirteenth participant, and they were removed from further study). Injuries were considered to be autonomically-complete if the lesion level was above T6; supine plasma noradrenaline (<0.56 nM); and low frequency (LF) systolic blood pressure variability (<1 mmHg$^2$). The magnitude of LF oscillations (~0.1Hz) in systolic arterial pressure is related to sympathetic activity and high-level autonomically-complete SCI reduces both resting blood pressure and its variability - especially in the LF domain [21].
Participants were asked to abstain from drinking caffeine or alcohol, and to avoid strenuous exercise, for 12 hours prior to testing. Those who had undertaken long haul air travel or ascent to altitudes in excess of 2500m in the past month were excluded from participation.

4.3.2. Equipment

The experimental equipment and end-tidal forcing set-up is outlined in Figure 4.1. Beat-to-beat blood pressure and lead II electrocardiogram (ECG) were recorded throughout the experiment (Finometer Pro, Finapres Medical Systems BV, Amsterdam, Netherlands) and O₂ saturation (SaO₂) was measured using pulse oximetry (Nonin 7500, Nonin Medical, Plymouth, MN, USA). Middle cerebral artery blood flow velocity (MCAv) was measured using transcranial Doppler ultrasound (2 MHz, Doppler Box, Compumedics DWL, Singen, Germany) with the probe positioned overlying the left or right temporal window and secured to a headband to ensure a constant angle of insonation.

Subjects were fitted with an oro-nasal facemask (V2 Mask, Hans Rudolph, Shawnee, KS) connected to a two-way flow sensor (Vmax, SensorMedics, Yorba Linda, CA) and a two-way non-rebreathing valve (NRB 2700, Hans Rudolph). Breath-by-breath partial pressures of end-tidal oxygen (P_ETo₂) and end-tidal carbon dioxide (P_ETCO₂), as well as inspiratory and expiratory flow rates, were measured continuously.

The end-tidal forcing system was designed to mix inspiratory gases on a breath-by-breath basis in order to control or clamp the end-tidal gases (as in [313]). The gas control system consisted of non-sparking solenoid valves that regulated the release of compressed gases (medical-grade compressed air, O₂, nitrogen, and CO₂) through a humidifier and into a reservoir bag attached to the non-rebreathing valve. A real-time computer control system (Simulink Real-Time Workshop, The Mathworks Inc., Natick, MA, USA) compared measured end-tidal gas partial pressures with target pressures, chose inspired air proportions to minimize the differences based on feedback control laws, and computed the timing of solenoid valve opening to provide the desired mixture and volume of gas to the subject at each breath. The volume of air delivered at
each breath was matched to the previous breath to maintain a sufficient reserve volume in the reservoir bag of ~ 1.5 L. As an additional safety feature, the system included an emergency stop button that would deliver room air to the bag, and could be easily pressed by participants if they were feeling uncomfortable.

End point criteria for trials, particularly relevant during hypoxic and hyperventilation trials, were SAP less than 80 mmHg or oxygen saturation less than 80%, or by participant request. One dedicated experimenter closely monitored these parameters throughout testing. In no case was early termination of testing required.

All recordings were sampled at 1 KHz using an analog-to-digital converter (PowerLab 16/30, AD Instruments, Colorado Springs, CO, USA), acquired using LabChart (AD Instruments), and stored for offline analysis.

Figure 4.1. Experimental equipment and end-tidal forcing set-up
Note: A gas controller compared target and measured end-tidal oxygen (P_{ET}O_2) and end-tidal carbon dioxide (P_{ET}CO_2) and determined the gases to be administered in the next inspiration. These gases were released by electronic valves into the ventilatory bag, attached to a facemask, flow sensor and two-way non-rebreathing valve. Middle cerebral artery blood flow velocity (MCAv) was measured using transcranial Doppler ultrasound. Electrocardiogram (ECG) and beat-to-beat blood pressure were measured using the Finometer. Pulse oximetry was used to monitor O_2 saturation (SaO_2). An emergency button was part of the system that would stop the controlled air and deliver room air, if necessary.
4.3.3. Experimental protocol

Subjects were tested in a supine position on a hospital bed. Baseline data were recorded while subjects were instrumented (except for the two-way valve and ventilatory bag) and breathing freely on room air for five minutes to allow acclimatisation to the experimental set up and any increase in inspiratory resistance associated with the use of the facemask. Steady-state values during the last two minutes of this acclimatisation phase were taken as the baseline measure. Once baseline $P_{ET}CO_2$ and $P_{ET}O_2$ values were obtained, the two-way valve and ventilatory bag were attached. Isocapnic $P_{ET}CO_2$ was set at the subject’s resting $P_{ET}CO_2$ plus 2 mmHg, facilitating control of CO$_2$ levels, which can be added to the system but not removed below resting levels, due to its metabolic production.

Cerebrovascular responsiveness to O$_2$ was assessed by changing the inspired O$_2$ during isocapnia and observing the changes in MCAv. The inspired gas levels were modified to create hypoxic ($P_{ET}O_2 = 50$ mmHg), normoxic ($P_{ET}O_2 = 100$ mmHg) and hyperoxic ($P_{ET}O_2 = 150$ mmHg) conditions, while isocapnic (Figure 4.2). The order of the three conditions was randomised. Each condition was maintained for ten minutes and normoxic isocapnic resting end-tidal values were restored for one minute between conditions, when moving from hypoxia to hyperoxia, or the reverse.
Figure 4.2. **Cerebrovascular responsiveness to O\textsubscript{2} protocol**

Note: Protocol included controlling both end-tidal oxygen (P\textsubscript{ET}O\textsubscript{2}, top) and end-tidal carbon dioxide (P\textsubscript{ET}CO\textsubscript{2}). Dotted line indicates period when individual baseline parameters were recorded for each participant in the absence of manipulation of inspired gases. All participants started with a five-minute period of normoxia to obtain resting clamped values. The order of the three subsequent oxygen trials was randomised for each participant. Isocapnia was maintained at individuals’ baseline P\textsubscript{ET}CO\textsubscript{2} plus 2 mmHg throughout the different oxygen trials.

Cerebrovascular reactivity to CO\textsubscript{2} was assessed during normoxia, hypoxia, and hyperoxia (Figure 4.3). End-tidal forcing was initiated with P\textsubscript{ET}CO\textsubscript{2} clamped at the normocapnic level and P\textsubscript{ET}O\textsubscript{2} clamped at normoxia. To begin each trial, the appropriate P\textsubscript{ET}O\textsubscript{2} level was also established and clamped at the desired level for 2 minutes to allow for stabilisation. Subjects were then instructed to voluntarily hyperventilate to a target P\textsubscript{ET}CO\textsubscript{2} between 15-20 mmHg. The total hyperventilation phase typically lasted between 12-15 breaths. After hyperventilation, subjects naturally returned to isocapnia at which point we initiated P\textsubscript{ET}CO\textsubscript{2} forcing, elevating it in 2 mmHg increments to a target hypercapnia of 45-50 mmHg.

The Berlin Questionnaire for sleep apnea was administered after testing to identify individuals who might be at risk of sleep apnea [314]. This questionnaire stratifies respondents into “High risk” or “Low risk” for sleep apnea.
4.3.4. Data analyses

A low-pass filter (<50Hz) was used to remove electrical noise from the ECG. A median filter (0.055s running median, 55 samples) was used to remove artefacts from the MCAv and flow signals. Beat-to-beat heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), SaO₂, and MCAv values were recorded continuously. Mean arterial pressure (MAP) was calculated from the raw blood pressure signal \( \frac{1}{3} \text{SAP} + \frac{2}{3} \text{DAP} \). MCA_{mean} was calculated as the integral of the MCA blood flow signal. End-tidal values were calculated on a breath-by-breath basis from the CO₂ recording (peak CO₂, \( P_{\text{ETCO}_2} \)) and the O₂ recording (minimum O₂, \( P_{\text{ETO}_2} \)). Beat-to-beat cardiovascular data were averaged over each breath and all data were reported breath-by-breath. Ventilation rate (L/min), tidal volume (L) and respiratory frequency (breaths/min) were calculated from the flow measurements.

Cerebrovascular responsiveness to O₂: Steady state values for HR, SAP, DAP, MAP, MCAv and end-tidal gases were averaged over the last five minutes of each oxygen condition. Percentage change in MCA_{mean} from normoxic conditions, and cerebrovascular conductance \( \text{MCA}_{\text{mean}}/\text{MAP} \), were also calculated.
Cerebrovascular responsiveness to CO$_2$: CO$_2$ reactivity was calculated separately for hypoxia, normoxia and hyperoxia. For each condition, MCA$_{\text{mean}}$ was plotted against P$_{\text{ET}}$CO$_2$ and fitted with a sigmoid curve (Levenberg-Marquardt algorithm minimising the sum of squares). The gain (cerebrovascular reactivity, maximum first derivative of sigmoid), operating-point (P$_{\text{ET}}$CO$_2$ at the inflection point), onset and threshold (indicated by second derivatives of sigmoid), and MCA$_{\text{mean}}$ range were compared between groups and across oxygen conditions [315].

![Graph showing MCA$_{\text{mean}}$ against P$_{\text{ET}}$CO$_2$](image)

**Figure 4.4. Calculation of cerebrovascular reactivity to CO$_2$**

Note: Individual breath-by-breath raw data (filled circles) of end-tidal CO$_2$ (P$_{\text{ET}}$CO$_2$) against mean middle cerebral artery velocity (MCA$_{\text{mean}}$) were fitted with a sigmoid curve (solid line) [315]. The first derivative (dashed line) was used to determine the peak slope of the curve (cerebrovascular reactivity) shown on right y-axis.

4.3.5. Statistical analyses

All statistical analyses were performed using SigmaPlot Version 12 (Systat Software Inc., San Jose, CA). Baseline values were compared with one-way ANOVA. Cerebral blood flow parameters in different O$_2$ conditions, and cerebrovascular reactivity to CO$_2$ and operating point were compared with two-way repeated-measures ANOVA (RM-ANOVA), using pairwise Holm-Sidak post-hoc comparisons. All data are presented as mean ± standard error of the mean (SEM), with significance assumed when p<0.05.
4.4. Results

4.4.1. Participant demographics

Participant demographics are shown in Table 4.1. There were no significant differences between groups in the age of participants. There was no difference in the time since injury between the two groups with SCI.

4.4.2. Supine cardiovascular and cerebrovascular parameters

There were no statistical differences between supine cardiovascular and cerebrovascular parameters between groups (all $p>0.05$). There was a trend towards lower SAP in autonomically-complete SCI group compared to autonomically-incomplete ($p=0.056$).

4.4.3. Cardiorespiratory responses to $O_2$

The cardiorespiratory parameters in different oxygen conditions under isocapnic conditions were similar between groups (Table 4.2). Hypoxia resulted in increased tidal volume in all groups compared to normoxic and hyperoxic conditions. Minute ventilation was increased in control and autonomically-incomplete groups, with the autonomically-complete group showing a similar trend ($p<0.01$). Heart rate was increased in control and autonomically-incomplete groups both ($p<0.05$), but not in autonomically-complete group. Systolic arterial pressure tended to be lower in autonomically-complete group compared to autonomically-incomplete group.
Table 4.1. Demographic information and supine cardiorespiratory and cerebrovascular parameters

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>12</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.3 (3.4)</td>
<td>38.6 (3.8)</td>
<td>37.6 (4.2)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>10:2</td>
<td>3:4</td>
<td>7:1</td>
</tr>
<tr>
<td>Time since injury (years)</td>
<td>-</td>
<td>16.4 (4.2)</td>
<td>16.8 (3.5)</td>
</tr>
<tr>
<td>Lesion level</td>
<td>Cervical</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>Thoracic</td>
<td>-</td>
<td>6</td>
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<tr>
<td>AIS grade</td>
<td>A</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>B/C/D</td>
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<td>3</td>
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<tr>
<td>Berlin score</td>
<td>Low risk</td>
<td>5</td>
<td>4</td>
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<tr>
<td></td>
<td>High risk</td>
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<td>0</td>
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<tr>
<td>SAP (mmHg)</td>
<td>125 (3)</td>
<td>131 (4)</td>
<td>118 (6)*</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>71 (2)</td>
<td>72 (3)</td>
<td>68 (2)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>90 (2)</td>
<td>91 (3)</td>
<td>85 (3)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>63.2 (4)</td>
<td>67.3 (6.3)</td>
<td>72.4 (6.0)</td>
</tr>
<tr>
<td>MCA_{sys} (cm.s^{-1})</td>
<td>105.4 (5.1)</td>
<td>97.4 (6.4)</td>
<td>91.6 (9.7)</td>
</tr>
<tr>
<td>MCA_{dia} (cm.s^{-1})</td>
<td>48.9 (3.1)</td>
<td>43.8 (2.8)</td>
<td>40.3 (4.9)</td>
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<tr>
<td>MCA_{mean} (cm.s^{-1})</td>
<td>74.1 (5.2)</td>
<td>65.4 (5.8)</td>
<td>60.7 (7.2)</td>
</tr>
<tr>
<td>CVC (cm.s^{-1}.mmHg^{-1})</td>
<td>0.84 (0.06)</td>
<td>0.72 (0.06)</td>
<td>0.71 (0.07)</td>
</tr>
<tr>
<td>P_{ET}CO_{2} (mmHg)</td>
<td>38.4 (0.7)</td>
<td>39.0 (1.9)</td>
<td>36.9 (0.7)</td>
</tr>
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<td>P_{ET}O_{2} (mmHg)</td>
<td>98.9 (2.5)</td>
<td>96.6 (0.9)</td>
<td>97.0 (1.3)</td>
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<tr>
<td>O_{2} saturation (%)</td>
<td>97.0 (0.6)</td>
<td>96.4 (0.5)</td>
<td>95.4 (0.7)</td>
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<td>Tidal volume (L)</td>
<td>0.63 (0.04)</td>
<td>0.56 (0.06)</td>
<td>0.67 (0.11)</td>
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<td>Respiratory frequency (bpm)</td>
<td>15.7 (0.6)</td>
<td>13.1 (0.7)</td>
<td>14.2 (1.1)</td>
</tr>
<tr>
<td>Minute ventilation (L/min)</td>
<td>9.9 (0.7)</td>
<td>7.5 (0.9)</td>
<td>8.9 (0.9)</td>
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</tbody>
</table>

Note: Baseline cardiovascular and cerebrovascular variables in able-bodied controls, autonomically-incomplete spinal cord injury (SCI) and autonomically-complete SCI. Asterisk (*) indicates trend towards difference from autonomically-incomplete group (p=0.056). Dagger (†) indicates significant difference in injury levels compared to autonomically-incomplete group. Values are expressed as group means with standard error of the mean in brackets (SEM). Abbreviations: DAP, diastolic arterial pressure; MAP, mean arterial pressure; MCA_{sys}, systolic middle cerebral artery blood flow; MCA_{dia}, diastolic middle cerebral artery blood flow; MCA_{mean}, mean middle cerebral artery blood flow; CVC, cerebrovascular conductance; P_{ET}CO_{2}, end-tidal carbon dioxide; P_{ET}O_{2}, end-tidal oxygen; SAP, systolic arterial pressure.
## Table 4.2. Cardiorespiratory parameters in different oxygen conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAP (mmHg)</strong></td>
<td>130 (3)</td>
<td>138 (5)</td>
<td>119 (4)*</td>
</tr>
<tr>
<td><strong>DAP (mmHg)</strong></td>
<td>72 (2)</td>
<td>75 (3)</td>
<td>68 (2)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>92 (2)</td>
<td>96 (4)</td>
<td>85 (2)*</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td><strong>71.9 (3.4) N,H</strong></td>
<td><strong>73.6 (5.7) N,H</strong></td>
<td>72.9 (4.4)</td>
</tr>
<tr>
<td><strong>PETCO₂ (mmHg)</strong></td>
<td>41.5 (0.7)</td>
<td>42.4 (1.6)</td>
<td>39.5 (1.4)</td>
</tr>
<tr>
<td><strong>PETO₂ (mmHg)</strong></td>
<td>47.3 (1.7)</td>
<td>49.4 (0.9)</td>
<td>48.4 (1.5)</td>
</tr>
<tr>
<td><strong>O₂ saturation (%)</strong></td>
<td>84.7 (0.8)</td>
<td>85.3 (0.9)</td>
<td>85.5 (0.6)</td>
</tr>
<tr>
<td><strong>Tidal volume (L)</strong></td>
<td>1.12 (0.10 N,H)</td>
<td>0.99 (0.12 N,H)</td>
<td>0.91 (0.12 N,H)</td>
</tr>
<tr>
<td><strong>Respiratory frequency (bpm)</strong></td>
<td>17.7 (1.2)</td>
<td><strong>16.3 (1.1) N</strong></td>
<td>14.5 (1.1)</td>
</tr>
<tr>
<td><strong>Minute ventilation (L/min)</strong></td>
<td><strong>19.1 (2.1) N,H</strong></td>
<td><strong>16.6 (3.1) N,H</strong></td>
<td>12.2 (1.1)</td>
</tr>
<tr>
<td><strong>SAP (mmHg)</strong></td>
<td>128 (3)</td>
<td>138 (5)</td>
<td>121 (6)†</td>
</tr>
<tr>
<td><strong>DAP (mmHg)</strong></td>
<td>72 (2)</td>
<td>75 (2)</td>
<td>70 (3)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>91 (2)</td>
<td>96 (3)</td>
<td>87 (4)†</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>62.5 (4.5)</td>
<td>65.7 (6.0)</td>
<td>67.4 (5.5)</td>
</tr>
<tr>
<td><strong>PETCO₂ (mmHg)</strong></td>
<td>40.9 (0.8)</td>
<td>41.8 (1.5)</td>
<td>37.8 (1.3)</td>
</tr>
<tr>
<td><strong>PETO₂ (mmHg)</strong></td>
<td>100.5 (0.5)</td>
<td>100.3 (0.5)</td>
<td>101.5 (0.8)</td>
</tr>
<tr>
<td><strong>O₂ saturation (%)</strong></td>
<td>97.0 (0.3)</td>
<td>97.8 (0.5)</td>
<td>96.4 (0.7)</td>
</tr>
<tr>
<td><strong>Tidal volume (L)</strong></td>
<td>0.83 (0.06)</td>
<td>0.72 (0.06)</td>
<td>0.65 (0.12)</td>
</tr>
<tr>
<td><strong>Respiratory frequency (bpm)</strong></td>
<td>16.7 (0.8)</td>
<td>13.6 (1.0)</td>
<td>14.3 (1.0)</td>
</tr>
<tr>
<td><strong>Minute ventilation (L/min)</strong></td>
<td>13.3 (1.1)**</td>
<td>9.5 (0.8)</td>
<td>8.6 (1.1)</td>
</tr>
<tr>
<td><strong>SAP (mmHg)</strong></td>
<td>130 (4)</td>
<td>141 (5)</td>
<td>123 (6)†</td>
</tr>
<tr>
<td><strong>DAP (mmHg)</strong></td>
<td>74 (2)</td>
<td>76 (2)</td>
<td>69 (2)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>92 (2)</td>
<td>98 (3)</td>
<td>87 (3)*</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>60.8 (3.9)</td>
<td>61.8 (5.3)</td>
<td>66.9 (5.3)</td>
</tr>
<tr>
<td><strong>PETCO₂ (mmHg)</strong></td>
<td>41.1 (0.6)</td>
<td>41.8 (1.6)</td>
<td>39.3 (1.1)</td>
</tr>
<tr>
<td><strong>PETO₂ (mmHg)</strong></td>
<td>150.8 (0.8)</td>
<td>151.3 (0.8)</td>
<td>149.6 (0.8)</td>
</tr>
<tr>
<td><strong>O₂ saturation (%)</strong></td>
<td>98.1 (0.2)</td>
<td>99.0 (0.3)</td>
<td>97.9 (0.5)</td>
</tr>
<tr>
<td><strong>Tidal volume (L)</strong></td>
<td>0.84 (0.07)</td>
<td>0.72 (0.07)</td>
<td>0.66 (0.10)</td>
</tr>
<tr>
<td><strong>Respiratory frequency (bpm)</strong></td>
<td>16.1 (1.0)</td>
<td>14.5 (1.1)</td>
<td>14.1 (1.0)</td>
</tr>
<tr>
<td><strong>Minute ventilation (L/min)</strong></td>
<td>13.3 (1.1)</td>
<td>9.9 (0.8)</td>
<td>8.7 (1.1)</td>
</tr>
</tbody>
</table>

**Note:** Cardiorespiratory variables in able-bodied controls, autonomically-incomplete spinal cord injury (SCI) and autonomically-complete SCI. Isocapnia (baseline +2 mmHg PETCO₂) was maintained throughout each oxygen condition. Data were averaged over the last five minutes of each trial and are presented as group means (SEM). Asterisk (*) indicates significant difference from autonomically-incomplete group (p<0.05). N indicates significant differences from normoxia (p<0.05). H indicates significant differences from normoxia (p<0.05). Dagger (†) indicates trend towards difference from autonomically-incomplete group (p<0.01). Abbreviations: DAP, diastolic arterial pressure; MAP, mean arterial pressure; PETCO₂, end-tidal carbon dioxide; PETO₂, end-tidal oxygen; SAP, systolic arterial pressure.
4.4.4. Cerebrovascular responsiveness to $O_2$

Cerebrovascular responses to hypoxia were significantly different between groups (Figure 4.5). Control and autonomically-incomplete groups had significantly elevated cerebral blood flow ($\text{MCA}_{\text{sys}}, \text{MCA}_{\text{mean}}, \text{and } \text{MCA}_{\text{dia}}$) in hypoxic conditions compared to normoxic and hyperoxic conditions (all $p<0.05$). There were no differences in cerebral blood flow between oxygen conditions in those with autonomically-complete SCI (all $p>0.05$). The same results were obtained when the $\text{MCA}_{\text{mean}}$ was expressed as absolute or percentage changes from normoxia, or as cerebrovascular conductance (Table 4.3). There were no differences in $P_{ET}CO_2$ between groups or between conditions (Table 4.2; all $p>0.05$).

Table 4.3. Mean middle cerebral artery blood flow velocity in response to different oxygen conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOXIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{MCA}_{\text{mean}}$ (cm.s$^{-1}$)</td>
<td>78.6 (4.7)*</td>
<td>74.8 (5.2)*</td>
<td>64.6 (5.7)</td>
</tr>
<tr>
<td>$\Delta$normoxia  (cm.s$^{-1}$)</td>
<td>+5.9 (1.5)*</td>
<td>+6.0 (1.6)*</td>
<td>+0.9 (1.6)</td>
</tr>
<tr>
<td>$\Delta$normoxia  (%)</td>
<td>+7.7 (1.8)*</td>
<td>+9.3 (2.6)*</td>
<td>+1.3 (2.2)</td>
</tr>
<tr>
<td>CVC  (cm.s$^{-1}$.mmHg$^{-1}$)</td>
<td>0.87 (0.06)*</td>
<td>0.78 (0.06)*</td>
<td>0.76 (0.06)</td>
</tr>
<tr>
<td>NORMOXIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{MCA}_{\text{mean}}$ (cm.s$^{-1}$)</td>
<td>73.2 (4.0)</td>
<td>68.8 (5.2)</td>
<td>63.8 (5.1)</td>
</tr>
<tr>
<td>CVC  (cm.s$^{-1}$.mmHg$^{-1}$)</td>
<td>0.81 (0.05)</td>
<td>0.72 (0.05)</td>
<td>0.73 (0.05)</td>
</tr>
<tr>
<td>HYPEROXIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{MCA}_{\text{mean}}$ (cm.s$^{-1}$)</td>
<td>71.9 (4.9)</td>
<td>68.0 (4.8)</td>
<td>65.4 (6.0)</td>
</tr>
<tr>
<td>$\Delta$normoxia  (cm.s$^{-1}$)</td>
<td>-0.1 (1.6)</td>
<td>-0.8 (0.7)</td>
<td>+1.7 (2.6)</td>
</tr>
<tr>
<td>$\Delta$normoxia  (%)</td>
<td>-0.6 (1.9)</td>
<td>-0.9 (1.2)</td>
<td>+2.6 (4.1)</td>
</tr>
<tr>
<td>CVC  (cm.s$^{-1}$.mmHg$^{-1}$)</td>
<td>0.78 (0.05)</td>
<td>0.70 (0.04)</td>
<td>0.75 (0.05)</td>
</tr>
</tbody>
</table>

Note: Mean middle cerebral artery ($\text{MCA}_{\text{mean}}$) cerebral blood flow velocity in hypoxic, normoxic, and hyperoxic conditions. $\text{MCA}_{\text{mean}}$ expressed as means, absolute and percentage change from normoxic conditions. Cerebrovascular conductance ($\text{MCA}_{\text{mean}}/\text{MAP}$) is also shown. Values are expressed as group means with standard error of the mean in brackets (SEM). Asterisk (*) indicates significant within-group differences from normoxia and hyperoxia ($p<0.05$).
Figure 4.5. Cerebral blood flow velocity changes in response to different oxygen conditions

Note: Systolic ($MCA_{sys}$, A), mean ($MCA_{mean}$, B) and diastolic ($MCA_{dia}$, C) middle cerebral artery blood flow velocity in different oxygen conditions. Double asterisks (**) indicate significant within-group difference from normoxia and hyperoxia conditions (both $p<0.05$). Abbreviations: SCI, spinal cord injury.
4.4.5. Cerebrovascular reactivity to CO₂

Cerebrovascular reactivity to CO₂, the maximal gain calculated from the relationship between MCA_{mean} and P_{ETCO₂}, was not different between groups or between conditions (Figure 4.6A, Table 4.4). When the hypocapnic region (below operating point but still in the linear range) was considered separately, there was no difference in cerebrovascular reactivity to CO₂ between groups or between conditions (Table 4.4). Similarly, there was also no difference in cerebrovascular reactivity in the hypercapnic region (above operating point but still in the linear range) between groups or between conditions.

However, there was a significant difference in operating point between conditions (Figure 4.6B). Post-hoc comparisons revealed significant differences in operating point in the autonomically-incomplete group between hypoxic and both normoxic (p<0.001) and hyperoxic (p=0.001) conditions. A similar trend of a leftward shift in operating point in hypoxia was observed in both the autonomically-complete SCI (p=0.06 vs. normoxia) and control groups (p=0.08 vs. hyperoxia). Similar results were seen when the cerebrovascular reactivity to CO₂ was calculated as the CVCi (Figure 4.7).

Table 4.4. Cerebrovascular reactivity to CO₂ in different oxygen conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomically-incomplete SCI</th>
<th>Autonomically-complete SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm.s⁻¹.mmHg⁻¹</td>
<td>%</td>
<td>cm.s⁻¹.mmHg⁻¹</td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full range</td>
<td>3.41 (0.35)</td>
<td>4.65 (0.40)</td>
<td>2.80 (0.31)</td>
</tr>
<tr>
<td>Hypocapnic</td>
<td>2.67 (0.73)</td>
<td>4.49 (0.62)</td>
<td>2.46 (0.79)</td>
</tr>
<tr>
<td>Hypercapnic</td>
<td>2.55 (0.46)</td>
<td>1.09 (0.68)</td>
<td>2.78 (0.62)</td>
</tr>
<tr>
<td>Hypocapnic</td>
<td>3.67 (0.61)</td>
<td>4.18 (0.42)</td>
<td>3.08 (0.50)</td>
</tr>
<tr>
<td>Hypercapnic</td>
<td>1.82 (0.46)</td>
<td>1.09 (0.68)</td>
<td>2.78 (0.62)</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full range</td>
<td>3.41 (0.34)</td>
<td>5.19 (0.47)</td>
<td>2.88 (0.44)</td>
</tr>
<tr>
<td>Hypocapnic</td>
<td>2.90 (0.57)</td>
<td>2.97 (0.65)</td>
<td>3.10 (0.69)</td>
</tr>
<tr>
<td>Hypercapnic</td>
<td>3.22 (0.88)</td>
<td>1.64 (0.55)</td>
<td>2.33 (0.31)</td>
</tr>
</tbody>
</table>

Note: Cerebrovascular reactivity to CO₂ in hypoxic, normoxic, and hyperoxic conditions, expressed as the full range, in the hypocapnic region, below the operating point, and in hypercapnic region, above the operating point. Values are expressed as group means with standard error of the mean in brackets (SEM). Abbreviations: SCI, spinal cord injury.
Figure 4.6.  Cerebrovascular reactivity to CO\textsubscript{2} and operating point in different oxygen conditions

Note:  A. Cerebrovascular reactivity to CO\textsubscript{2} in different oxygen conditions. B. Operating point for CO\textsubscript{2} reactivity in each oxygen condition. Double asterisks (**) indicate significant within-group difference from normoxia and hyperoxia conditions (both p<0.05). Asterisk (*) indicates trend towards difference from normoxia condition (p=0.06). Double dagger (‡) indicates trend towards difference from hyperoxia condition (p=0.08). Abbreviations: SCI, spinal cord injury.
Figure 4.7. Cerebrovascular conductance in response to CO$_2$
Note: A. Cerebrovascular reactivity to CO$_2$ expressed as cerebrovascular conductance index (CVCi = MCA$_{mean}$/MAP). B. Operating point for CO$_2$ reactivity in each oxygen condition. Asterisk (*) indicates significant within-group difference from hyperoxia conditions (p<0.05). Abbreviations: SCI, spinal cord injury.

4.5. Discussion

Individuals with high-level SCI and damage to autonomic pathways are susceptible to orthostatic intolerance and have been documented to have impaired cerebrovascular control [64, 123]. For example, our laboratory has shown that cerebral autoregulation during orthostatic challenge is compromised in individuals with autonomically-complete SCI [64]. Here we show that this group also has reduced sensitivity to hypoxia, failing to increase cerebral blood flow during hypoxia in the same
way that individuals without autonomic injury and able-bodied controls do. However, we were unable to detect any differences in cerebral sensitivity to CO$_2$ between those with and without damage to autonomic pathways and able-bodied controls.

The changes in cerebral blood flow between oxygen conditions were not due to differences in $P_{ET}CO_2$ between groups. It is likely that other secondary changes associated with high-level SCI contribute to these differences. In particular, it is estimated that the majority (91%) of individuals with tetraplegia have obstructive sleep apnea [125]. Repeated exposure to intermittent hypoxia has been shown to reduce the sensitivity of the cerebral vasculature to hypoxia [127, 129]. Therefore, it is very likely that this could contribute to the reduced sensitivity in the autonomically-complete SCI group, which had a significantly higher proportion of individuals with cervical level SCI compared to the autonomically-incomplete group. In addition, it is possible that individuals with autonomically-complete SCI are accustomed to low perfusion due to their constitutive hypotension and reduction in cerebral blood flow when seated (Chapter 3 and [64]). Unlike the cerebral vasoconstriction that we suspect mediates the reduced cerebral blood flow in response to hypocapnia, and that may include a role for the extrinsic sympathetic innervation, it is unlikely that the sympathetic nervous system is implicated in the cerebral vasodilation and overall increase in cerebral blood flow in hypoxia.

There was no difference in cerebrovascular reactivity to CO$_2$ between groups. This suggests that the disruption of extrinsic sympathetic neural control of the cerebral vasculature in individuals with autonomically-complete SCI does not significantly alter the sensitivity to CO$_2$ in conditions of normoxia, hypoxia or hyperoxia. Furthermore, no differences in cerebrovascular reactivity to CO$_2$ were observed when hypocapnic regions and hypercapnic sensitivity were considered separately. In hypoxic conditions, there was a trend towards a leftward shift in operating point in all groups, despite the usual decrease in $P_{ET}CO_2$ during hypoxia being prevented with end-tidal forcing.

The cerebral circulation is sensitive to numerous vasoactive stimuli, and one of the complexities of studying cerebrovascular reactivity to CO$_2$ is attempting to vary only one of these stimuli while observing the resulting change in blood flow. Cerebral
autoregulation buffers changes in blood pressure by altering blood flow to ultimately maintain adequate cerebral perfusion. Therefore, when varying stimuli such as CO₂, it is important to consider both the blood pressure effects (vasodilation through the chemoreflex response) and the direct effects in the cerebral vasculature. This makes blood pressure recording critical during cerebrovascular reactivity to CO₂ testing so that concurrent blood pressure changes can be taken into account [315-317]. One way to mitigate this effect is to calculate the conductance index (MCA_{mean}/MAP) to account for any changes in MAP that may have occurred in response to changes in P_{ET}CO₂ [315-317]. Although no pronounced blood pressure changes were noted during hyperventilation, we calculated the conductance index, and found that the same relationships between groups and conditions were seen when raw cerebral blood flow or conductance were used.

Despite CO₂ being a known vasoactive stimulus, we did not observe significant blood pressure changes in response to changes in CO₂. This fits with recent research showing that below a given CO₂ threshold (around 52 mmHg P_{ET}CO₂, in hyperoxic conditions; 45 mmHg P_{ET}CO₂ in hypoxia) MAP does not change considerably, while beyond this threshold, once vasodilation has reached its limit, MAP increases linearly with CO₂ [124]. Given that our range of P_{ET}CO₂ fell mostly below this threshold, it is not surprising that we did not observe significant effects of P_{ET}CO₂ on MAP.

There are a number of different techniques of assessing cerebrovascular reactivity to CO₂ [318]. The unique ability of ETF to control and correct end-tidal gases on a breath-by-breath basis makes it an attractive research tool; however, it is unlikely to be practical in a more clinical setting due to the equipment and expertise necessary to run the control systems. Several parameters, such as the participant’s tidal volume, must be used to tailor the equipment for each test. For the purposes of the current experiment, however, ETF was ideal in order to closely control both O₂ and CO₂ on a breath-by-breath basis.
4.5.1. Study limitations

We did not detect differences between groups in the risk for sleep apnea (as assessed by the Berlin Score) [314, 319]. This is an imperfect surrogate measure of sleep apnea in the SCI population and may underestimate prevalence in this population [320]. However, our participants – both those with SCI and those without also – represent a fairly young and athletic population which may reduce the prevalence compared to reported values [125, 321]. Ideally we would have gathered sleep study information from our participants to detect whether they have sleep disorders, including sleep apnea, which might expose them to multiple low oxygen and desaturation events throughout the night. Repeated exposure to such stimuli might alter participants’ response to the hypoxic condition tested here. Full-scale laboratory sleep studies are resource-intensive and more complex in this population; however, recent advances in portable blood oxygen saturation monitors that link with smartphones could make this kind of question simpler to answer in the future [322]. In the mean time, it is recommended that researchers in this area gather history data on sleep quality, and use existing questionnaires as a surrogate measures of OSA in this population [320].

Cerebral ultrasound is used to measure velocity as a surrogate measure of blood flow. This relationship is quite robust as long as the diameter does not change significantly. In the physiological range, and especially in the linear region of the sigmoid relationship, this assumption appears to be supported in the MCA [256]; however, there is new MRI evidence that the diameter of the MCA may vary near the limits of our \( P_{ET}CO_2 \) range (23 mmHg and 47 mmHg) [257, 258]. This technique is also dependent on the angle of insonation of the vessel of interest, where changes in cosine of steeper insonation angles have a greater impact than changes in the cosine of shallower angles. The anatomy of the MCA – with blood flow direction towards the transtemporal window – makes it fairly straightforward to insonate at a narrow angle so that small differences in angles within or between subjects would have little effect on velocity. Nevertheless, to account for any potential errors when comparing raw values, cerebral blood flow velocities are increasingly being represented as both absolute values and as change, or percentage change in response to a certain stimulus. Here we saw similar trends...
between all measurement types, corroborating the results seen in the absolute velocity (Figure 4.5 and 4.6).

Measurement of expired $P_{ET}CO_2$ has been used as an estimate of arterial $CO_2$ in many situations. However, the difference between $P_{ET}CO_2$ and $P_{a}CO_2$ can be altered by physiological manipulations, such as orthostasis [323] and exercise [324]. Natural physiological variability in tidal volume, dead space and in alveolar emptying patterns can also increase or decrease the $P_{a}CO_2$-$P_{ET}CO_2$ gradient [325, 326]. Furthermore, pathophysiological conditions that alter the ventilation-perfusion match, such as chronic obstructive pulmonary disease and respiratory failure, can alter the gradient depending on the mismatch [324, 327]. In this study, all subjects were tested in the supine position, which should minimise the effect of orthostasis, and improve the ventilation-perfusion match. In addition, we were not able to detect a difference in tidal volume between groups. Therefore, we argue that there was not a group effect on the arterial to end-tidal $CO_2$ tension difference that influenced our results.

All participants were tested in the supine position, for both safety and convenience. Therefore, our experiments do not capture the more common physiological milieu that our participants experience throughout most of their waking hours. It would have been interesting to also test participants in the seated position to get a more thorough picture of their normal experiences. On the other hand, while more representative of routine function, it is possible that the combination of orthostatic intolerance and changes in gas concentrations would make it difficult to dissociate their individual effects on cerebral blood flow, as discussed above. Furthermore, considering that the hypoxic and hypocapnic episodes accompanying OSA would occur while supine, it seems most appropriate to test the cerebral blood flow changes in this position.

Finally, it is important to acknowledge the directionality of $P_{ET}CO_2$ changes used in this study. There is evidence of hysteresis in the cerebral response to changes in $P_{ET}CO_2$, such that the sensitivity to an increasing $P_{ET}CO_2$ protocol is somewhat higher than a decremental protocol [328]. While we do not expect that the direction of the
stimulus would influence one group more than any other, our results might be slightly different than experiments using a decremental protocol.

4.6. Conclusions

In summary, individuals with high-level autonomically-complete SCI did not increase their cerebral blood flow in response to hypoxia, as was observed in able-bodied controls and individuals with autonomically-incomplete SCI. The failure to modify cerebral blood flow might further predispose these individuals to hypoperfusion and syncope and may have implications given the high prevalence of OSA in this population.

In contrast, no group differences were observed in cerebrovascular sensitivity to CO$_2$ in either normoxic, hypoxic or hyperoxic conditions. This suggests that extrinsic sympathetic neural control of the cerebral vasculature does not directly influence its sensitivity to CO$_2$. All groups showed a trend towards a lower CO$_2$ operating point in a hypoxic environment compared to normoxia or hyperoxia.

Future studies in this population should consider including the potential relationship between OSA and decreased reactivity to hypoxia.
Chapter 5.

Bowel management and cardiovascular dysfunction after spinal cord injury

5.1. Abstract

Constipation and incontinence are common problems for individuals with spinal cord injury (SCI) and improving bowel function has been identified as a key target to enhance their quality of life. Bowel care is a potent trigger for autonomic dysreflexia (AD) - sudden and extreme hypertension provoked by a sensory stimulus below the injury. Here we sought to gather more information about bowel management practices among individuals with SCI and determine the prevalence of cardiovascular symptoms during routine bowel care.

A survey combining the International Bowel Function Basic and Extended Data Sets and our Cardiovascular Symptoms Questionnaire was completed by participants recruited from local rehabilitation centres, online SCI discussion forums, our institution website (www.icord.org), and social media. The study sample (n=101) included participants with a range of SCI levels (C4-sacral) and severities (AIS A-D).

More than half of participants (56%) reported being unsatisfied with their current bowel care routine. The majority of respondents (84%) reported at least one symptom of AD during their routine bowel care, including 29% who described experiencing palpitations. Overall, 39% felt AD interfered with their activities of daily living.

A considerable proportion of individuals with SCI are experiencing symptoms of AD during their routine bowel care, including sensations of palpitations. We believe it is a significant priority to investigate strategies to effectively manage bowel care and minimise AD and associated cardiovascular risk in people with SCI.
5.2. Introduction

Constipation and incontinence are common problems for individuals with SCI and improving bowel function has been identified as a key target to enhance quality of life by individuals with tetraplegia and paraplegia [9, 329]. Routine bowel management may be time consuming [1], and bowel accidents, urgency, constipation, haemorrhoids and abdominal distension can all disrupt quality of life for individuals living with SCI [329-332]. Taken together, changes in bowel motility, sphincter control and impaired hand function combine to make bowel management a key cause of morbidity after SCI [329-332]. However, there is remarkably little research or robust evidence on effective bowel management strategies after SCI.

There are many different bowel management approaches and individuals often take time to determine what works best for their lifestyle. Successful bowel management is often multifactorial, with important roles for dietary approaches, fluid consumption, routine bowel practice, fibre supplementation, and the use of suppositories, digital rectal stimulation and abdominal massage [329-332]. Appropriate timing, use of assistive devices and positioning are also key components of a successful bowel routine [331, 333]. Even with a successful program in place, individual approaches can evolve over time with aging, changes in diet, and physical activity.

Bowel care problems are significantly affected by the level of injury and the resulting disruption of normal central nervous system control [329-331]. The coordination of gastrointestinal motility and function relies on the balance and interaction between the somatic, sympathetic and parasympathetic nervous systems. Therefore, a major factor that complicates bowel care for individuals with SCI is the impact of injury to descending spinal autonomic (sympathetic) pathways on gastrointestinal function [48, 53, 334]. The disruption of sympathetic pathways primarily affects the motor coordination of the gastrointestinal system, reducing colonic motility and increasing overall gastrointestinal transit time [335]. Low-lesions do not impact the sympathetic nervous system but can disrupt the coordination of evacuation.
If the lesion does not interrupt the sacral circuitry (above S2-4) then the sacral reflexes remain intact and reflexive defecation can occur when the rectum fills (also known as upper motor neuron bowel syndrome [329]). However, the bowel tends to be hyperreflexic, and without voluntary control of the external anal sphincter, it is overly active resulting in stool retention. Reflex activation can be stimulated to assist with evacuation in individuals with upper motor neuron bowel syndrome. On the other hand, if the sacral circuitry is damaged then the bowel is said to be areflexic, and the rectal musculature is flaccid (also known as lower motor neuron bowel syndrome [329]). Depending on the activation of the external anal sphincter, this can alternately result in constipation and incontinence.

Disruption of sympathetic pathways also leads to numerous cardiovascular abnormalities, depending on the level of injury. Of particular concern is the phenomenon of autonomic dysreflexia (AD), in which sudden and extreme reflex hypertension is elicited by afferent stimuli originating from below the lesion level. These episodes can be life-threatening, and may result in vascular dysfunction [336], seizures [80, 83, 296], cardiac arrest [337], cerebral vascular haemorrhage [79, 213, 214, 296, 338], and even death [83, 213, 296, 338].

AD typically occurs with lesions above the level of sympathetic outflow to the splanchnic vascular bed (T5-T9) [83, 274, 339]. The splanchnic vasculature is an important resistance and capacitance bed that can mobilise large volumes of blood quickly, thus helping to maintain blood volume and mitigating hypotension [340-342]. The loss of control of this vascular bed after SCI makes individuals particularly susceptible to low blood pressure [53, 60]. It also means that this vasculature can participate in generating reflex episodic hypertension when triggered by sensory stimuli below the level of injury [25, 48, 136].

AD has been described in up to 90% of individuals with tetraplegia and high paraplegia [83, 338, 343], and generally develops sometime after injury, after the resolution of neurogenic shock [344]. This might be a particular concern if it develops after individuals have been discharged from inpatient rehabilitation. In such cases, patient education and awareness are critical. The development of AD seems to involve a
combination of maladaptive anatomical changes [344-346] that distort the interaction between sensory nerves and sympathetic outflow. There may also be increased responsiveness to adrenergic stimulation and synaptic plasticity that contribute to the pressor response [345-349].

AD can occur in response to any afferent stimulus below the lesion level [54], but the most potent triggers are visceral stimuli [343], such as bowel care [84]. The blood pressure rise is secondary to vasoconstriction in resistance and capacitance vessels below the lesion, due to reflex sympathetic activity triggered by afferent input to the isolated spinal cord [54]. Above the lesion level, in regions under supraspinal control, vasodilatation occurs due to marked baroreflex-mediated reductions in sympathetic drive [48]. Since the cardiac vagus nerve does not pass through the spinal cord, it is unaffected by SCI, producing a baroreflex-mediated increase in vagal stimulation of the heart coincident with the high cardiac sympathetic outflow [48]. Many individuals also experience concurrent palpitations due to cardiac arrhythmia (often atrial fibrillation) triggered by the combined high cardiac vagal and sympathetic outflow during AD [69-71].

We believe it is a significant priority to investigate strategies to effectively manage bowel care and minimise AD in people with SCI. Here we sought to gather more information about bowel management practices among individuals with SCI and determine the prevalence of cardiovascular symptoms during routine bowel care.

5.3. Methods

Ethical approval was obtained from the Office of Research Ethics at Simon Fraser University and all research complied with the Declaration of Helsinki [239].

5.3.1. Participant recruitment

Participants were recruited using postcards distributed at local rehabilitation and community centres around Vancouver. Online advertising for the survey was posted on
our institutional website (www.icord.org) as well as discussion forums and online community groups specific to SCI, including: Inspired Spinal Cord Injury Support Community (inspiredsciforum.com); Care Cure Community (sci.rutgers.edu); Spinal Injury Network (spinal-injury.net); Apparelyzed (apparelyzed.com); and SCI BC (facebook.com/SpinalCordInjuryBC).

The convenience sample of participants self-administered either a paper-based (Appendix A.2.) or online survey (http://fluidsurveys.com/s/bowelcare-SCI). To begin the survey, participants gave consent and acknowledged that they have a SCI and are over 18 years old. A total of 101 individuals submitted survey responses. Eighty-one responses were complete.

5.3.2. Questionnaire design

The Bowel care and cardiovascular function after spinal cord injury questionnaire (Appendix A.2.) was designed using the International Bowel Function Basic and Extended Data Sets, developed by a working group including members from the American Spinal Injury Association (ASIA) and the International Spinal Cord Society (ISCoS) [350, 351]. Additional questions were added from another recent community-based bowel survey [352]. Questions about cardiovascular signs and symptoms commonly associated with AD were added from our Cardiovascular symptoms after spinal cord injury questionnaire [64, Appendix A.1] as well as some basic nutrition questions.

5.3.3. Measurements

Respondents self-reported their neurological level of injury. Motor and sensory completeness of injury was determined by respondents' answers to the following questions: 1) Can you feel touch in your anal area; 2) Can you voluntarily tighten your anal sphincter; 3) Can you feel light touch below your lesion level; 4) Can you feel the difference between sharp and dull below your lesion level; and 5) Can you lift your legs against gravity. If the answer to all of these questions was "No", then an individual was considered to have a motor and sensory complete injury.
Basic bowel management information was collected using questions from the International Bowel Function Basic and Extended Data Sets [350, 351] and previous surveys [352]. Five-point ordered Likert scales were used to assess symptoms of AD during bowel care and at other times of the day. The severity of common symptoms of AD were rated during bowel care as “Not experienced”, “Mild”, “Moderate”, “Severe”, and “Very severe”. The frequencies of cardiovascular symptoms were assessed using a range of “Never”, “Rarely”, “Monthly”, “Weekly”, and “Daily”. Where applicable, follow-up narrative responses were grouped by topic. For some analyses, responses were dichotomised into either “Not Experienced” or “Experienced”.

We also asked about symptoms in response to 12 other common AD stimuli and provided an opportunity for individuals to add a category “Other” to identify additional stimuli. Symptoms of orthostatic hypotension (OH) were also recorded. Sixteen common symptoms of OH were assessed using the same frequency range (“Never”, “Rarely”, “Monthly”, “Weekly”, and “Daily”).

5.3.4. Stratification of participants by injury level

For analysis of cardiovascular symptoms, participants were stratified by injury level at or above the seventh thoracic segment (T7) and below T7. Injuries that disrupt the sympathetic control of the vasculature in the splanchnic region make individuals susceptible to AD. The sympathetic outflow to the greater splanchnic nerve, which synapses in the celiac ganglia and ultimately terminates in the splanchnic vasculature – among other targets – originates between T5 and T10 [353]. Therefore, individuals with injuries at T5 or above are particularly susceptible to blood pressure abnormalities, including AD, due to a complete loss of sympathetic regulation of the splanchnic vascular bed. However, due to the broad outflow of preganglionic neurons from multiple spinal levels [353], divergence in the preganglionic-ganglionic sympathetic connections [354], and anatomical variability in greater splanchnic nerve outflow anywhere from T4-T9 to T6-T11 [353], it is possible that injuries at T6 or T7 also have the potential to disrupt descending control of the splanchnic vasculature considerably. This reduces the ability to mobilise blood when necessary, and leaves the decentralised circuitry able to participate in generating the reflex sympathetic vasoconstriction characteristic of AD –
even in lesions below T6 [22]. Because we were relying on individuals’ self-report of their injury level, and not their medical diagnosis, we wanted to be lenient with our cut-offs as we did not want to exclude individuals with AD and lesions at T6 or T7, who may not know their precise level of injury.

5.3.5. Statistical analysis

Data processing and analysis was performed using R (Version 3.0.2) and RStudio (Version 0.98.507). Comparisons of proportions between groups were made using Fisher’s exact test. Interval data were compared using pairwise Wilcoxon rank sum tests, with the Bonferroni correction for repeated tests. Chi-squared tests were used to compare the distribution of AD symptoms and triggers between SCI groups. Post-hoc comparisons were made using pairwise Fisher’s exact tests.

5.4. Results

One hundred and one individuals with SCI completed the survey. Most respondents (89%) were directed from our institutional website (www.icord.org). Respondents primarily originated from Canada (n=52) and the United States (26), with the remainder from Europe (13) and South America (2). The locations of 8 respondents were unknown.

5.4.1. Demographic and injury information

The demographic and injury information of respondents is outlined in Table 5.1. There was a wide range of respondents age (20-68 years), time since injury (1-49 years), and injury level (C2-sacral). A majority of respondents had an injury at or above T7, and the majority of injuries were incomplete (Table 5.1).
Table 5.1. Demographic and injury information of survey respondents

<table>
<thead>
<tr>
<th>Sample size (n)</th>
<th>101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.6 ± 12.5</td>
</tr>
<tr>
<td>Time since injury (years)</td>
<td>13.1 ± 13.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injury levels (spinal segment)</th>
<th>Cervical</th>
<th>35 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>55 %</td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>8 %</td>
<td></td>
</tr>
<tr>
<td>Sacral</td>
<td>1 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injury levels (T7)</th>
<th>At or above T7</th>
<th>64 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Below T7</td>
<td>36 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injury completeness</th>
<th>Complete</th>
<th>33 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incomplete</td>
<td>67 %</td>
</tr>
</tbody>
</table>

5.4.2. General bowel management

A majority of respondents (57%) were dissatisfied with their normal bowel management routine responding: “No, I’m dissatisfied”, or “No, I’m very dissatisfied”, with their current bowel management routine. The long duration for bowel care, its unpredictability, and high incidence of bowel accidents were the most common complaints in the narrative responses associated with this question. The long duration for bowel care was reflected in the responses for total duration of bowel care, where the most frequent duration of bowel care was between 61 and 90 minutes (Table 5.2). Interventions used and other general bowel management information is also shown in Table 5.2.
Table 5.2. General bowel management information

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of day of bowel care</td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>57</td>
</tr>
<tr>
<td>Evening</td>
<td>31</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
</tr>
<tr>
<td>Total duration of bowel care</td>
<td></td>
</tr>
<tr>
<td>0-5 min</td>
<td>8</td>
</tr>
<tr>
<td>6-10 min</td>
<td>10</td>
</tr>
<tr>
<td>11-20 min</td>
<td>17</td>
</tr>
<tr>
<td>21-30 min</td>
<td>19</td>
</tr>
<tr>
<td>31-60 min</td>
<td>15</td>
</tr>
<tr>
<td>61-90 min</td>
<td>24</td>
</tr>
<tr>
<td>&gt; 90 min</td>
<td>7</td>
</tr>
<tr>
<td>Interventions used in bowel care program (multiple responses possible)</td>
<td></td>
</tr>
<tr>
<td>Straining/bearing down</td>
<td>21</td>
</tr>
<tr>
<td>Alter drink/food</td>
<td>28</td>
</tr>
<tr>
<td>Abdominal massage</td>
<td>30</td>
</tr>
<tr>
<td>Touching skin near anus</td>
<td>9</td>
</tr>
<tr>
<td>Digital stimulation</td>
<td>68</td>
</tr>
<tr>
<td>Manual evacuation</td>
<td>47</td>
</tr>
<tr>
<td>Suppositories</td>
<td>34</td>
</tr>
<tr>
<td>Laxatives</td>
<td>30</td>
</tr>
<tr>
<td>Enema</td>
<td>9</td>
</tr>
<tr>
<td>Stool softeners</td>
<td>22</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
</tr>
<tr>
<td>Length of time managing bowel program current way</td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>2</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>14</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>28</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>53</td>
</tr>
</tbody>
</table>

Figure 5.1 compares the impact of different aspects of living with SCI on a scale from one (least effect) to ten (worst effect). The bowel effects of SCI were rated significantly worse than using a wheelchair for mobility (p<0.0001), skin integrity issues (p<0.0001), spasticity (p<0.0001), and bladder effects (p=0.0067). Pairwise comparisons also revealed significantly greater effects of SCI on sexual function than both wheelchair use (p=0.012) and skin effects (p=0.0042), as well as greater effects on pain than skin issues (p=0.047).
Figure 5.1. Impact of different aspects of living with spinal cord injury on quality of life

Note: Respondents were asked to rate each aspect of living with spinal cord injury from 1 (Least effect) to 10 (Worst effect). Solid red line indicates group median; dotted grey line indicates group mode. Asterisk indicates significant difference between indicated aspects (p<0.05).
The impact of bowel care on flexibility and quality of life was apparent. Inflexibility in bowel care was described by 84%, who felt they had to fit their life around their bowel care. Bowel care had a negative impact on their quality of life, for 81% of respondents, including 35% who felt this was a major impact. Figure 5.2 shows the impact of bowel management on aspects of social life and work. A majority of individuals reported that bowel management interfered with their social life (71%) and personal relationships (64%). Just under half of respondents (46%) reported that bowel care stops them from working outside the home.

![Graph showing impact of bowel management](image)

**Figure 5.2.** Impact of bowel management on respondents’ life and activities

### 5.4.3. Cardiovascular symptoms during bowel care

Just under half of respondents (43%) reported experiencing AD at least once since their injury. Ten percent of respondents did not know whether they had ever experienced AD. Of these, half (5%) had injury levels at or above T7, which makes them possible candidates for experiencing AD. All of these respondents experienced several symptoms of AD during their routine bowel care, at least one of which was identified as “Moderate” or “Severe”.

Regardless of whether they self-identified as experiencing AD, 80% of respondents reported at least one symptom of AD during their routine bowel care. Both individuals with injuries at or above T7 and those with injuries below T7 reported symptoms traditionally associated with AD. Figure 5.3 shows the percentage of
respondents with SCI, divided by injury level, who report experiencing AD symptoms during their routine bowel care. More than a quarter of respondents in both groups identified experiencing several of the hallmark symptoms of AD, including goosebumps, spasticity, sweating, headache, general unwellness, flushing, dizziness, or nausea during bowel care. While there was a trend towards higher proportion of individuals with higher level SCI experiencing these symptoms, there was no significant difference in the overall distribution of symptoms between groups (p>0.05).

Figure 5.3. Symptoms of autonomic dysreflexia reported during bowel care in individuals with injuries above and below T7

There was also no clear difference in the severity of these symptoms between groups (Figure 5.4). The most severe symptoms (identified as “Severe” or “Very severe” during bowel care) for individuals with SCI above T7 were sweating, flushing and spasticity, while those with SCI below T7 were spasticity, flushing and uncomfortably fast heart rate.
Figure 5.4. Severity of autonomic dysreflexia symptoms reported during bowel care in individuals with SCI at or above T7 and below T7
As we were particularly interested in cardiac arrhythmias during bowel care, we asked separately about symptoms of palpitations. Heart palpitations, irregular heartbeats or a feeling of fluttering in their chest, during bowel care were reported by 29% of total respondents. When respondents were stratified into groups at and above or below T7, a similar proportion of each group experienced palpitations, suggesting that this symptom is not strictly associated with AD (Figure 5.5).

**Figure 5.5.** Percentage of individuals with SCI above and below T7 who report heart palpitations during bowel care

Thirty-six individuals had injuries at or above T7 and experienced at least one AD symptom triggered by bowel care. We considered these individuals to have AD and the analysis of the following AD-specific questions were conducted on this subset of individuals. The majority of respondents who experienced AD identified more than one trigger of AD (88%). The most frequent number of reported stimuli were six (18%) and ten (15%), out of a possible 13.

Respondents who reported AD-like symptoms with bowel care identified a number of other stimuli that trigger these symptoms (Figure 5.6). In addition to bowel triggers, bladder, pain, high and low temperatures, and spasticity were frequently identified by respondents as AD symptom-inducing stimuli. There was a trend towards different distribution of stimuli for triggering AD-like symptoms between individuals with SCI at or above T7 and those with SCI below T7 (p=0.0585). There was a significant difference between groups in the proportion of individuals who reported bladder triggers (p=0.004, Figure 5.6).
Figure 5.6. Additional stimuli that trigger autonomic dysreflexia symptoms in those with symptoms of autonomic dysreflexia during bowel care

Note: Asterisk (*) indicates significant difference between groups (p<0.05).

AD was reported to interfere with at least one activity of daily living by 56% of respondents with AD. The most frequent activities that AD was described to interfere with were sleep, exercise, activities of daily living, and sexual activity, which were each reported by more than 30% of respondents with AD (Figure 5.7).

There was a positive, but weak, correlation between symptoms of AD and symptoms of orthostatic hypotension (OH) in individuals with SCI at or above T7 (r=0.2908, r²=0.1363, p=0.008, Figure 5.8).
Figure 5.7. **Prevalence of autonomic dysreflexia interfering with common activities**

![Bar chart showing prevalence of autonomic dysreflexia interfering with common activities](chart)

Figure 5.8. **Correlation between symptoms of autonomic dysreflexia and orthostatic hypotension in individuals with SCI at or above T7**

![Scatter plot showing correlation between symptoms](chart)

### 5.5. Discussion

Here we document the impact of routine bowel management on quality of life for individuals living with SCI. Bowel effects of SCI were rated as having a significant effect
on individuals’ lives compared to other aspects such as using a wheelchair, as well as skin, spasticity and bladder effects. Our results suggest that there is significant opportunity to improve bowel management to minimise its impact on quality of life. Our results also show that a significant proportion of individuals experience cardiovascular symptoms during their routine bowel care. The nature and aetiology of these symptoms must be further elucidated. It appears that a significant proportion of individuals experience AD during their routine bowel management. While the long-term consequences of repeated AD remain unknown, there is some evidence to suggest that minimising its severity could be prudent [336, 355].

5.5.1. Bowel management after SCI

When considered compared to other aspects of living with SCI (Figure 5.1), difficulties with bowel management were most frequently ranked among the worst effects. Impaired sexual function was also ranked highly as one of the worst effects of injury. On the other hand, aspects such as skin care, spasticity, and use of a wheelchair were ranked on the lower end, as aspects that have little effect on individuals’ lives. This suggests that these aspects have been managed well in our respondent population – as we know they can be areas of significant importance and concern when they are problematic [356, 357].

Some of the reasons for the major effect of bowel management on quality of life were apparent from the general bowel management responses. A majority of respondents described that there was little or no flexibility in their bowel management routine, so that they have to fit their life around their routine. More than a third of respondents also reported that their bowel management takes more than 60 minutes to complete. Bowel management was identified by more than half of respondents to interfere with social activities, personal relationships and work. Together these responses reveal that bowel care can have significant negative impact on quality of life and participation for individuals living with SCI.
5.5.2. **Autonomic dysreflexia during bowel care**

Both individuals with injuries above and below T7 reported symptoms of AD, suggesting that we must be careful when we associate certain symptoms solely with AD as many of these same symptoms are also identified by individuals who do not experience AD. For example, a similar proportion of individuals with injuries above and below T7 reported experiencing palpitations during bowel care, suggesting that this symptom is not strictly associated with AD. Therefore, there is a need to resolve whether these individuals are in fact experiencing palpitations, clarify individuals’ understanding of palpitations, and ultimately determine the trigger of these symptoms – perhaps they are secondary to something else in individuals with lesions below T7.

While bowel care is one of the most potent triggers of AD, most respondents identified several other stimuli that also cause AD-like symptoms (Figure 5.6). In general, these are similar in individuals with injuries above and below T7. However, the most common stimuli for these symptoms are different: bladder for individuals with SCI at or above T7 and pain for those with SCI below T7. This could give further insight into the different aetiology of AD-like symptoms in those with injuries below T7, and help us to refine our symptom questions to ensure that we are more specifically targeting AD-related symptoms, wherever possible.

The majority of individuals who experienced symptoms of AD also identified more than one stimulus that triggered those symptoms. Therefore, most individuals who are susceptible to AD are likely experiencing AD multiple times a day. Several of these stimuli, such as bowel and bladder care, are unavoidable, and bowel care in particular is a stimulus of long duration. Therefore this is a key target for improved management of cardiovascular sequelae. Furthermore, the long-term effects of these repeated bouts of hypertension have yet to be fully elucidated. We have shown evidence of altered vascular function in animal models after repeated episodes of AD [336]. In extreme cases, reports have identified instances of cerebral vascular accidents, such as haemorrhage, secondary to AD [79, 213, 214]. These hypertensive episodes occur in the face of constitutional hypotension common in those with high-level SCI. The magnitude of this change may particularly challenge the integrity of the endothelium and
vascular wall, which could be more vulnerable after being habitually exposed to low flow. Furthermore, increased arterial stiffness has been documented in individuals with paraplegia [358] which may further contribute to vascular damage during these hypertensive episodes of AD.

The most common activity that respondents reported AD interfering with was sleep. This might seem surprising, as we don’t think of many triggers being present during sleep. However, considering that most respondents reported doing their bowel care first thing in the morning or in the evening, it is possible that colon filling initiates AD ahead of morning bowel care, or evening bowel care triggers AD symptoms that continue unabated – even once the offending stimulus has been removed [359]. In addition, bladder triggers would similarly be peaking in the morning, as the bladder has been filling throughout the night, and in the evening, following intermittent catheterisation before bed. Urine production is also higher during the night than during the day in individuals with tetraplegia, which could exacerbate the bladder stimulus in the night [360]. Together these triggers could combine to interfere with sleep. The disruption of sleep is particularly concerning among individuals with high-level SCI who experience AD, because many of these individuals already experience chronic fatigue related to low resting cerebral blood flow during the day [236-238, 276, 277, 288] and poor sleep is known to further exacerbate fatigue, difficulty concentrating, and excessive daily sleepiness [361].

There was a positive, but weak, correlation between symptoms of AD and symptoms of OH in individuals with SCI at or above T7. One challenge of investigating both AD and OH is that they can each occur symptomatically, despite significant changes in blood pressure and cerebral perfusion [82, 243, 362]. Even in the absence of symptoms, these conditions can be worrying because of their impact on cognitive function (OH) [243] and potential trigger of vascular accidents (AD) [79, 213, 214]. This highlights the challenges of relying on symptom reporting and the need for combination with physiological testing. Another challenge when assessing symptoms is quantifying the severity of symptoms on an ordinal scale. In most cases here we chose to dichotomise the presence or absence of symptoms, so we are not capturing the severity
of symptoms. With more respondents it might be possible to capture the relationship between the severity of AD and OH symptoms.

5.5.3. **Physiological testing during bowel care**

Reports of cardiovascular symptoms would be significantly strengthened in combination with cardiovascular recording during bowel care. While the individual experience of symptoms should not be disregarded, it is important to document the associated cardiovascular changes to corroborate symptoms and determine the physiological correlates of the symptoms. For example, an electrocardiogram would help determine whether an individual’s experience of heart palpitations during bowel care is merely a result of profound brady- or tachycardia, or another more sinister type of arrhythmia.

We are currently in the process of doing cardiovascular testing with a range of individuals with SCI to resolve how symptoms relate to the blood pressure changes and cardiac abnormalities during bowel care. We hope this will allow us to associate particular symptoms with physiological changes and distinguish between harmful pathogenic and unpleasant but harmless symptoms. Furthermore, we suspect that we will also identify individuals who are not symptomatic during bowel care, despite exhibiting significant blood pressure and heart rate changes – so-called *silent* AD [82, 362]. An example trace of an individual with asymptomatic AD triggered by routine bowel care is shown in Figure 5.9. Significant rises in systolic and diastolic blood pressure were experienced despite absence of symptoms. The identification and discussion of silent AD is particularly important because individuals may not take steps to minimise AD if they do not experience warning symptoms.
5.5.4. Mitigating cardiovascular symptoms during bowel care

AD during bowel care is triggered by the potent sensory stimulus from manual stimulation, or the stimulus from stool passing through the rectum. While AD triggered by bowel care may be unavoidable, it is possible that strategies might be used to mitigate the severity of AD. One strategy is to reduce the afferent input using an anaesthetic as part of the bowel care program [363-365]. This strategy is often used as part of inpatient bowel care management, and is recommended for use outside the hospital. However, there is little evidence supporting this practice [364]; none of our respondents reported using lidocaine lubricant as part of their bowel program. Given the high incidence of cardiovascular symptoms reported by respondents in this survey, our next step will be to test whether the use of topical anaesthetic lidocaine reduces the severity of AD in individuals who regularly experience this condition. This testing will be performed as a
double-blind, placebo-controlled trial in individuals who experience AD with bowel management.

5.5.5. Current guidelines for bowel management and autonomic dysreflexia

It is clear from the narrative responses that a significant proportion (57%) of individuals are unsatisfied with their current bowel care management. This highlights possible gaps in bowel management education and raises questions about current guidelines for bowel management, and where individuals with SCI and their caregivers obtain information about this topic. Formal guidelines are available from organisations such as the Paralyzed Veterans of America [331, 366], but these publications can become dated quickly as new medications and equipment arrive on the market. Web-based education material and videos (such as http://www.sci-u.ca/ [367]) serve the need to remain current and provide engaging resources where individuals can easily access them at any time. Activity on online SCI forums also suggests that many people also share and obtain information on bowel care from other individuals with SCI and their caregivers [368]. A combination of formal accessible guidelines and real-time support from health care providers when necessary – either online, over the phone, or in person – would appear to be an ideal combination of approaches. This kind of approach has been successful in managing other SCI-related complications, including pressure ulcers, depression, and hand function [369, 370] – especially for individuals who live far from specialty centres [371]. Ongoing support and education is essential for continued effective bowel care management, especially as changes in gastrointestinal function over time after injury, and with aging, demand ongoing adaptations of routine management protocols.

Our results also demonstrated evidence of missing information relating to AD, with ten percent of respondents unsure of whether or not they experience AD. Of these, half had lesions above T6, making it possible that they might experience AD. Therefore, there is room for improvement for education about identifying signs and symptoms of AD and knowing when to seek additional assistance. For those with AD, current recommendations concerning anaesthesia during routine bowel care are dated, and
provide conflicting advice. According to current clinical guidelines, during the acute management of AD bowel stimuli should be removed as potential underlying causes, using 2% lidocaine gel [372]; however, similar recommendations are not included for individuals with SCI when performing bowel care at home [366]. Others report that topical anesthetic is sometimes necessary for the management of AD during routine bowel care [329], although specific protocol recommendations are lacking. Finally, anaesthetic lubricant is recommended for use during rectal examinations in individuals with a risk of AD [331]. This conflicting advice is noted in the SCI community, with uncertainty about the different techniques and strategies to manage AD when performing routine bowel care at home [368]. Clearer recommendations and additional education are warranted.

5.5.6. Study limitations

Our subject recruitment was performed locally, in Vancouver, at rehabilitation and community centres, and digitally, in SCI forums and through social media. While we achieved a large cross section of individuals with different ages and injury levels, it is likely that our sample does not represent all individuals with SCI. In particular, we likely have a higher representation of individuals who are not happy with their current bowel management routine – making them more likely to share their experiences and seek out information about alternative bowel care management options. This might make them more likely to rank bowel management as particularly problematic compared to other aspects of living with SCI, for example. However, this population would not necessarily be more prone to cardiovascular symptoms during their bowel care, so we believe that the conclusions about cardiovascular symptoms are robust and representative of the SCI population. In any case, we should be mindful of sampling bias when extrapolating our results to the SCI population more generally.

It is possible that some terminology used in the current survey was not described sufficiently clearly. Different people may have interpreted medical language, such as heart palpitations, differently – defined here as a feeling of irregular heartbeats or of “fluttering in your chest”. Clearer explanations of terms might ensure that all respondents are judging by the same criteria. For example a proportion of respondents (10%) were
not sure whether they have ever experienced AD; it is possible that a more thorough explanation of AD might have clarified this for respondents. Based on these results, future studies should describe terminology clearly and also point respondents to additional reading material about the topics in question. This could help improve the reliability of responses and provide reliable sources of information for individuals.

While we did not intend to confuse or worry respondents about AD or other cardiovascular symptoms, it is possible that asking about these symptoms might have raised questions for the respondents. Providing links to literature and other resources might allow individuals to understand their symptoms in the context of their injury and others like them. We intend to disseminate these results to respondents to provide feedback and results of the study and links to education materials for further information.

5.6. Conclusions

Bowel care is an important concern for individuals living with SCI. Difficulties in bowel management can have significant impact on participation and quality of life. A majority of individuals with SCI – both above and below T7 – reported cardiovascular symptoms during routine bowel management. We associate these symptoms with AD in those with high SCI, but do not know the nature of similar symptoms in individuals with low-level SCI. Physiological recording is necessary to determine the aetiology of these symptoms and the severity of any associated signs. In individuals with frank AD, the significant number of recurrent AD stimuli, and its interference with sleep and exercise are important areas for further investigation. Together these results suggest that there is an opportunity to ameliorate bowel care and that improved management of cardiovascular symptoms might be one strategy to consider.
Chapter 6.

Discussion

In this dissertation, I examined secondary cardiovascular and cerebrovascular function in individuals with SCI. I focused on the implications of disrupted autonomic, and particularly sympathetic, nervous system control as a result of SCI. SCI is traditionally discussed in terms of its detrimental effects on the motor and sensory systems, and its effects on the autonomic nervous system are largely unexplored. However, we know from people living with SCI that many of these secondary complications are among the most frustrating, and they are consistently identified as top priorities for recovery and resolution [9, 373]. Therefore, research into the causes, mechanisms and consequences of cardiovascular abnormalities after SCI are greatly needed.

The impact of cardiovascular function on activities of daily living are beginning to drive research, and in this thesis I explored several aspects of cardiovascular function in the context of activities of daily living. I investigated the cardiovascular and cerebral consequences of dynamic seating position, I documented cardiovascular function and symptoms in the early post-injury period, I manipulated breathing and blood gasses to assess cerebrovascular control, and finally, I explored the links between bowel care and cardiovascular symptoms. The results of my work have implications for clinical SCI care, self-management for individuals living with SCI, and for SCI research.

6.1. Assessment of autonomic completeness of injury

Determining the injury to the autonomic nervous system after SCI remains a poorly defined task. In the absence of a gold standard, multiple tests are often used to ensure consistency and comparison with other studies. Accordingly, throughout this
thesis I have used multiple different measurements to assess damage to sympathetic pathways, including supine and seated noradrenaline spillover (Chapters 2 and 4) and LF SAP (Chapters 2, 3, and 4). Our laboratory [21, 64, 89] and others [286, 374-376] have used LF SAP as a measure of damage to sympathetic vasomotor pathways after SCI. In these different studies, the LF SAP has shown to be a robust marker that corroborates measures of noradrenaline and sympathetic skin responses [21, 64, 89]. Furthermore, it has shown to be a reproducible measure in the SCI population [286]. However, the threshold for division between individuals with sympathetic vasomotor control and those without has varied both between these earlier studies, and in this thesis. As we, and others, continue to gather data on a range of individuals with different levels and severities of injury, it is likely that the threshold will continue to evolve until we ultimately determine the most appropriate value. In this thesis, modification of the threshold was made on the basis of individuals with low-level lesions, in whom autonomic function was preserved. More research is needed in the SCI population in order to establish LF SAP thresholds.

The physiological meaning of the absolute LF SAP, and LF SAP variability, warrants clarification. In our experience, in the absence of sympathetic vasomotor control, LF SAP is close to 1 mmHg$^2$ or lower; when sympathetic vasomotor control is preserved, LF SAP is generally around 4 mmHg$^2$ [21, 64, 89]. As seen in Chapter 2, there is often greater variability in LF SAP when sympathetic control is present. However, once LF SAP is above a certain threshold, it is not clear that greater variability confers any additional physiological benefits. Functionally, it seems it is the presence or absence of variability in LF SAP that is a key indicator of sympathetic vasomotor function. Therefore, LF SAP is challenging to correlate with other functional measures, as those with autonomically-complete SCI cluster around the very low end, and those with incomplete lesions, and controls, show greater spread. However, we have previously used LF SAP as a continuous variable that correlates with functional measures of blood pressure control in animal models of SCI [210]. Considering LF SAP as a continuous variable may also help the field as we move towards establishing clear threshold values for evidence of sympathetic vasomotor control.
In the absence of a gold standard, and as we continue to clarify the magnitude of LF SAP that describes the difference between preserved and abnormal sympathetic control, the measurement of plasma noradrenaline spillover remains a popular alternative to assess global sympathetic function [377]. Ideally, supine noradrenaline levels are obtained as well as the levels in response to a sympathetic stimulus, such as an orthostatic stress [64]. Noradrenaline levels are routinely measured in clinical labs, which facilitates this assessment for research purposes. However, this protocol necessitates a venous line in order to minimize the effect of venipuncture, which itself can stimulate noradrenaline levels. Other considerations relating to the use of noradrenaline as a marker include the rate of clearance and the fact that it is a more global measure than one that relates specifically to vasomotor function.

6.2. Implications for clinical care and self-management

6.2.1. Managing fatigue after SCI

Fatigue is a common secondary complication associated with SCI [277]. A majority of individuals living with SCI experience fatigue that is severe enough to limit participation in activities of daily living [277] and individuals with fatigue are less likely to participate in employment, social interactions, and community activities [236]. The specific contributors to this severe and disabling fatigue are unclear. However, we know that fatigue has been associated with low resting blood pressure in the able-bodied population [287], and that low blood pressure and OH result in low cerebral blood flow and orthostatic symptoms of dizziness [378]. Therefore, constitutive hypotension and OH likely contribute to fatigue in the SCI population [53].

In Chapter 2, I demonstrated the cardiovascular and cerebrovascular effects of dynamic changes in wheelchair seating positions. With a suitable wheelchair, such as the Elevation™ wheelchair tested in Chapter 2, individuals can use a lowered position to bolster their blood pressure and prevent OH, when necessary. However, not all individuals experience symptoms when they are hypotensive, making it difficult to recognise low blood pressure. Indeed, several individuals we tested experienced
hypotension throughout testing in the seated position (average blood pressure=85-90/50 mmHg), without reporting any symptoms of presyncope. This shows a remarkable capacity of the cerebrovascular system to function at levels that most able-bodied individuals would find intolerable because they would be at or below the lower limit of cerebral autoregulation, where consciousness begins to be lost. It also demonstrates the challenge of self-identifying hypotension when symptoms are not present. However, even without symptoms, there is mounting evidence that hypotension and cerebral hypoperfusion should be avoided, including documented attention deficits and other mild cognitive impairments in hypotensive individuals with SCI [244, 293, 379, 380]. Therefore, there is a strong rationale to increase education about hypotension, symptoms, and positional counter-manœuvres, and potentially to encourage self-monitoring of blood pressure at home.

6.2.2. Implications for self-management of blood pressure

Chronic management of cardiovascular dysfunction focuses primarily on managing symptoms to maximise functional independence and quality of life. Particularly for individuals with high-level autonomically-complete injuries, long-term cardiovascular management remains a fine balance between mitigating hypotension without exacerbating autonomic dysreflexia-induced hypertension. Self-management is an important component of this approach; achieving this balance relies heavily on individuals’ being able to identify their symptoms of OH and AD. However, my research demonstrates that symptoms alone are not always sufficient to determine blood pressure abnormalities. In Chapter 2, we tested several individuals who were asymptomatic while seated, even with profound OH; in Chapters 3 and 5, many individuals with low-level lesions described experiencing hallmark symptoms of AD, yet it is unlikely that these were caused by frank AD. Therefore, these surrogate indicators often used to identify autonomic impairments are insufficient for discriminating between those who are, and are not, experiencing them. Therefore, portable cardiovascular monitoring devices such as blood pressure cuffs and heart rate monitors may be useful for some individuals to monitor their physiological signs. Recording may not always be necessary, but could help individuals identify and learn specific symptoms associated with recorded changes in blood pressure.
Appropriate identification of episodes of AD is essential when it dictates decisions about pharmacological management. A common blood pressure management approach is to provide long acting methods to counter hypotension, such as compression garments, blood volume increases, or $\alpha$-adrenergic activation [227, 381], and equip individuals with short-acting approaches to deal with episodic hypertension (such as $\alpha$-adrenergic antagonists (nifedipine or prazosin) or ACE-inhibitors (captopril) [382, 383]). Therefore, the identification of AD is critical to initiate these short-acting pharmacological methods.

Portable cardiovascular monitoring devices may also help guide the targeted prescription of cardiovascular management approaches. In practice, the selection of non-pharmacological and pharmacological approaches to manage blood pressure can be a lengthy exercise in trial and error. Continuous portable blood pressure and heart rate recording during use of new prescriptions could facilitate this exercise.

6.2.3. Ongoing bowel management and education

The results in Chapter 5 demonstrated that a majority of respondents (57%) were unsatisfied with their current bowel management practices. Furthermore, the impact of bowel management on individuals’ opportunities for social engagements, employment and general activities of daily living was profound: more than two-thirds reported that bowel management interfered with their social life and about half of respondents (46%) reported that bowel care stops them from working outside the home. This suggests that there are significant opportunities for more follow-up and ongoing gastrointestinal consultation after SCI to assist with bowel management. Long-term follow-up is common in bladder care, with annual or biannual urodynamics evaluation to assess urinary dysfunction and quality of life related to bladder management [384, 385]. Bladder dysfunction and renal failure were, and continue to be, a significant cause of death in patients with SCI, making this practice critical [386-389]. However, it is clear that bowel management also significantly negatively impacts quality of life and individuals with SCI could serve to gain from increased focus and care directed towards this subject.
Bowel management is a potent trigger of AD and yet, in Chapter 5, my results showed that about 10% of respondents indicated that they did not know whether or not they experience AD. Half of these individuals had high-level SCI, making them potential candidates for AD. This demonstrates that there is a continued education gap between the clinical and research knowledge and the community – even among those that are engaged enough to complete an online survey on the subject. Furthermore, even among individuals who have well-established and successful bowel care routines, practiced over many years, such as the example trace shown in Figure 5.9, there is evidence that people are unaware of AD. With appropriate monitoring and education AD can be recognised and managed. Therefore, continued bowel care follow-up could conceivably include an element of targeted education about AD. In addition, beat-to-beat blood pressure and heart rate recording could be adopted into regular bowel care follow up appointments to identify AD and ensure that it is being managed appropriately.

Aging with SCI further complicates management of secondary complications, which also tend to occur at a higher rate with advancing age [288]. Bowel care is a particular concern with aging; changes associated with menopause, normal physiological aging, and long-term bowel management contribute to increased bowel care needs [288, 390-392]. These concerns further highlight the need for long-term bowel care consultation and clinical care to provide information and support self-management and quality of life after SCI.

6.2.4. Implications for acute autonomic function testing

International standards for documenting autonomic function after SCI have been established, and are slowly beginning to be adopted in rehabilitation settings [132, 393-395]. However, at present these guidelines are heavily reliant on patient self-awareness and knowledge about the autonomic consequences and symptoms of SCI. They do not include quantitative assessment of physiological autonomic function. This is problematic from what I have shown in Chapters 2, 3 and 5, where individuals’ symptoms do not always match their physiological reality. Therefore, simple quantification of autonomic function will be an important addition to these guidelines. In terms of cardiovascular control, this could be achieved with an orthostatic challenge, such as the sit-up test, or
by monitoring the beat-to-beat blood pressure and heart rate and quantifying the frequency oscillations using spectral analyses.

Without reliable *quantification* of autonomic function, it will be difficult to assess changes over time with the current standards. In addition, there is little guidance about when the autonomic testing should occur. My results in Chapter 3 suggest that in the very early post-injury period, many individuals show abnormal autonomic function – even those with low-level SCI without frank damage to autonomic pathways. This suggests that early autonomic function testing should occur at or after four weeks post-injury - well after the acute effects of trauma and surgery are dissipated, and resolution of neurogenic shock [396].

### 6.2.5. Implications for cerebrovascular management

In Chapter 4, I assessed the cerebral reactivity to changes in $O_2$ and $CO_2$ after SCI. Individuals with autonomically-complete SCI showed similar cerebrovascular reactivity to changes in $CO_2$ compared to individuals with autonomically-incomplete SCI. However, those with autonomically-complete SCI demonstrated an abnormal cerebrovascular response to hypoxia, failing to increase blood flow velocity in hypoxic conditions. This reduced responsiveness could result in periods of hypoperfusion if these individuals experience conditions of hypoxia, for example during periods of sleep apnea. Sleep apnea is common after SCI [397], and is particularly prevalent in people with tetraplegia [321]. Rehabilitation care after SCI often includes assessment of sleep; however, a recent study showed that many people with SCI who have identified sleep disordered breathing remain untreated [320]. My results in Chapter 4 suggest that more aggressive testing and management of OSA might be warranted, to ensure that cerebral oxygenation is not compromised by hypoxia and impaired cerebral blood flow regulation.

The failure to modify cerebrovascular reactivity means individuals with autonomically-complete SCI have a strong response to changes in $CO_2$, similar to individuals without SCI. Together with reduced blood pressure and diastolic blood flow (Chapter 3), and poor cerebral autoregulation [64], maintained sensitivity to $CO_2$ could create conditions that essentially shut down cerebral vessels and significantly
hypoperfuse the brain. This would be especially relevant in a seated position, when P_{ET}CO_{2} decreases particularly in individuals with high-level SCI [64].

My research also contributes some mechanistic insight into the role of extrinsic sympathetic innervation of the cerebral vasculature. From the results in Chapter 4, the loss of extrinsic sympathetic control seems not to significantly alter the cerebrovascular response to changes in CO_{2}. This supports the previous study that did not observe any frank changes in reactivity to CO_{2} after SCI [123]. However, my research is strengthened by the assessment of autonomic-completeness (by LF SAP and noradrenaline levels) of the participants with SCI, without which it was difficult to make a strong conclusion. The conclusions suggest that autonomic-completeness may play a more significant role in the response to hypoxia.

6.2.6. Changing demographics of SCI

The changing demographics of SCI to an older population have been noted nationally [2]. While the incidence of traumatic SCI remains highest in younger populations (15-29 years) there is an increasing incidence in the 45-49 year old range, reflecting the age profile of the Canadian population [2, 398]. In this research, in the acute study in Chapter 3, I also saw a significant number of older individuals sustaining SCI. In general, individuals who sustain a SCI when they are older than 50 years of age have poorer functional outcomes and complete SCI among this cohort results in particularly high mortality [391, 399]. Furthermore, this age group tends to be burdened with additional pre-existing comorbidities and secondary complications not seen in younger individuals with comparable injuries [399, 400].

These changing demographics have implications for both clinical management and research. From a research perspective, there are two main challenges associated with the changing demographics of SCI. The first relates to the differences in how individuals of different ages respond to injury. Having a bimodal distribution makes it challenging to form conclusions about physiological result of injury versus effect of age. It also complicates the recommendations for care, which might be significantly influenced by age. The heterogeneity of SCI as one “condition” is further diversified by
this wide range of ages. A second major challenge with the increase in SCI among older adults is dissociating the effects of SCI from the pre-existing comorbid conditions that are more common in this population. The heterogeneity of an already heterogeneous condition can quickly become overwhelming. For example, an autonomically-complete SCI on a background of congestive heart failure, or diabetic neuropathy, significantly complicates the cardiovascular management of such patients, and makes research conclusions and generalisations particularly challenging. However, avoiding the study of such patients would be to exclude a significant portion of individuals who are now sustaining SCI. The reality of our changing demographics and their comorbid conditions will be increasingly important to consider in clinical management guidelines and in future research as our baby boomers age and the obesity epidemic continues to grow in this cohort [401, 402].

6.3. Implications for research

6.3.1. Heterogeneity of SCI

As a clinical condition, SCI is heterogeneous. Variability both along the neuraxis and in the completeness of damage to the spinal cord at the injury level results in functional deficits unique to each individual. Motor and sensory recovery patterns among individuals with incomplete SCI are similarly diverse and contribute additional variability [403]. This heterogeneity can make traditional research approaches of grouping and comparing groups quite challenging. There is a balance to be found between stratifying individuals based on their unique physiological variables and combining heterogeneous groups to create group sizes that are powerful enough to detect differences, if present. Neurological studies are often underpowered [404], as properly powered studies require very large sample sizes [405]. To deal with this heterogeneity, clinical trial design to ensure suitable stratification is the focus of substantial research [403, 406]. In Chapter 3, my research documents the natural changes in cardiovascular variability during standard clinical care, so that ultimately further improvements, or recovery, from clinical therapies might be judged against this intrinsic capacity for improved function.
Chapter 3 demonstrates the variability of cardiovascular control after SCI, which adds an additional aspect of variability to an already heterogeneous condition. Furthermore, unlike motor and sensory function, for which there are accepted standards for assessment and quantification, cardiovascular autonomic function is difficult to measure, and there is no gold-standard among the SCI community on how to quantify cardiovascular function – or autonomic function more generally. Throughout this thesis I have used different measures of autonomic function to discriminate function and provide meaningful markers of cardiovascular dysfunction.

Furthermore, there may be an interaction between these different aspects of recovery and variability. Namely, individuals who regain some mobility and are able to mobilise early – whether using a wheelchair or ambulating – may also improve cardiovascular function, or prevent further deconditioning. Several of the participants studied in Chapter 3 were ambulatory by three to six months post-injury. This mobilisation and activity likely contributed to improved cardiovascular control in these individuals. However, in spite of a wide range of neurological injuries and severities, in Chapter 3, I documented a significant reduction in LF SAP in almost all individuals with SCI in the very early period after injury. By one month after injury, there was a separation between two groups, which was maintained in the months after injury.

6.3.2. Magnitude and duration of blood pressure changes

One of the challenges in characterising and comparing blood pressure changes is the variation in how changes can be described, and whether these differences are related to their pathophysiology. For example, there is debate about whether the critical component in OH is the absolute value of how low blood pressure goes, or the magnitude of change from baseline [407]. Furthermore, from a cumulative burden perspective, it is unclear whether a short period of extremely low blood pressure is more detrimental to the end organ than a longer period of a slightly less extreme hypotension. Conversely, when blood pressure is elevated from baseline, in periods of AD, there are similar questions about the relative importance of the magnitude of change, the absolute blood pressure, and the duration for which hypertension is sustained. Furthermore, constitutive hypotension in individuals with high-level autonomically-complete SCI might
result in structural adaptations to low flow that make them more vulnerable to damage during the periods of extreme hypertension associated with AD. Furthermore, it is unclear whether the repeated exposure to AD associated with unavoidable activities of daily living such as bladder and bowel care contribute to poor cardiovascular outcomes, or what are the long-term consequences of repeated AD. There is preclinical evidence of vascular effects of repeated AD that suggest minimising its severity and frequency might be prudent [336].

The association of blood pressure changes with pathophysiology should have implications for both clinical treatment targets and for research. In research, the present strategy seems to be to document and report multiple parameters (absolute magnitude, maximum change, average change, duration), which hopefully facilitates generalisability and comparisons between research groups. Ultimately, it would be preferable to be able to determine the most pernicious parameters associated with AD or OH. Clinically, without beat-to-beat blood pressure recording during procedures such as cystometry, bowel management, or sperm retrieval, we don’t often know the exact physiological changes that are occurring. However, given that both OH and AD are often documented to be asymptomatic despite profound changes in blood pressure [64, 82, 244, 362], it seems prudent to record beat-to-beat blood pressure wherever feasible to determine the true magnitude and duration of the blood pressure changes.

The clinical relevance of blood pressure changes is another important consideration when putting the results of this thesis into context. There is natural variability in the healthy cardiovascular system [157], and healthy able-bodied individuals routinely experience blood pressure changes relating to their physiological state throughout the day (sleeping, waking, standing, sitting, exercising). A 5 or 10 mmHg drop in systolic blood pressure is unlikely to trigger any clinically relevant symptoms in normotensive individuals. However, a similar magnitude blood pressure change may be more relevant in individuals who are already hypotensive. Further hypotension could trigger cerebral hypoperfusion, symptoms of presyncope, and potentially reduce blood pressure below the limits of cerebral autoregulation – resulting in more pronounced changes in cerebral blood flow with changes in pressure [233].
6.3.3. SCI treatments and their effects on cardiovascular function

Cardiovascular outcomes are gradually beginning to be included among outcomes in preclinical trials characterising the effects of SCI and potential therapeutic targets [408, 409]. Despite the importance of cardiovascular and other secondary complications to individuals living with SCI, autonomic consequences are slow to be adopted into the assessment of clinical therapeutic approaches [132, 410]. This is partly explained by the complexity of autonomic function testing [7], and the difficulty in standardising quantification. Similar problems also plague the assessment of trunk muscle preservation in individuals with SCI, which is also complex [411].

One approach that might facilitate the translation of results and testing from the preclinical to the clinical domain is an adoption of similar assessment techniques in each domain. We have recently shown that spectral analyses are feasible in animal models of SCI, and can detect alterations in cardiovascular autonomic function in animals with SCI [210]. Rodents with high-level SCI, unlike those with low-level SCI, experience resting hypotension, OH and AD, as well as altered HRV and BPV [210, 344]. Furthermore, the frequency markers of autonomic dysfunction, such as a reduction in LF SAP, in these animals are similar to the clinical population [210]. The use of similar assessments both at the bench and the bedside should facilitate translation research.

It is also important that potential treatments that ameliorate some aspects of SCI don’t exacerbate the secondary cardiovascular consequences. Certain preclinical treatments for SCI, such as intermittent hypoxia, might augment spontaneous recovery and certain functions [412, 413], but they also have the potential to worsen spinal ischemia and, as seen in Chapter 4, hypoxia may also risk hypoperfusion of the cerebral tissue due to impaired cerebral responses to hypoxia. In this case, a multi-faceted approach, considering effects on motor, sensory, and autonomic function will be critical for clinical and preclinical trials to move closer to reality.
6.3.4. **Cardiovascular variability and ability to respond appropriately to stressors**

In resting conditions, healthy physiological systems tend to show variability originating in complex dynamics from multiple control systems operating on different time scales [414]. This variability confers an ability to respond and adapt to multiple different kinds of perturbations or stressors [414]. In the cardiovascular system, alterations in sympathetic and parasympathetic activity account for the majority of the short-term variations in beat-to-beat blood pressure and heart rate, while hormonal and temperature related regulation act on longer time scales [414]. These different contributions can also be explored in the frequency domain, where high-frequency (HF) oscillations are predominantly vagally-mediated, while low-frequency (LF) oscillations are predominantly sympathetically-mediated [21]. The slower acting contributions of hormonal and thermoregulatory control are reflected in the very low frequency (VLF) domain [21, 187].

Following autonomically-complete SCI, variations in certain frequency bands are reduced more than others. Blood pressure variability in the LF range in particular is associated with sympathetic nerve activity and function [21]. In this thesis, we have observed stressors of positional and chemical nature, as well as perturbations from activities of daily living, including bowel care. The reduced blood pressure variability in the LF range in individuals with autonomically-complete SCI was associated with a poorer ability to respond to the orthostatic challenges associated with seating, and seating in an elevated position. Other physiological changes that decrease cardiovascular variability, such as aging and hypertension, reduce complexity in heart rate and blood pressure and also seem to blunt the response to physiologic stressors, such as a reduction of vasomotor sympathetic responsiveness to orthostasis [414-416].

6.3.5. **Integrating research and clinical practice**

The translation and implementation of findings from research to clinical practice is a slow process. One of the challenges in more closely integrating research and clinical practice is the inconsistency between a statistically significant change and a clinically meaningful change – whether the change is judged to be of value to people living with
the disorder [417]. In asking applied questions, such as how wheelchair positioning affects blood pressure and cerebral blood flow in Chapter 2, I tried to use the experience of individuals living with SCI to drive and direct my research approach. Patient reported outcomes and quality of life metrics are also gaining influence in both the clinical and research worlds [283, 418, 419]. In Chapter 5 my aim was to identify gaps in care management and knowledge, as identified by individuals living with SCI. I believe this approach will help us guide research to be most meaningful and also bring research closer to clinical practice.

Another challenge of combining research and clinical practice is the sheer number of tasks that clinicians need to complete in their practice. In order to integrate research into practice, as researchers, we must provide realistic proposals in terms of what health care providers could actually incorporate into their busy workflow [420]. Therefore, simple assessments of function are necessary. This is particularly challenging in the context of the autonomic nervous system, with its diffuse anatomy and broad functions. In Chapter 3, and throughout this thesis, I use spectral analyses of blood pressure to determine autonomic completeness of injury. This technique uses beat-to-beat blood pressure – a fairly simple measurement to acquire clinically. Certainly continuous beat-to-beat blood pressure recording during rehabilitation, even if only for half an hour, could inform cardiovascular management of patients and identify those particularly in need of blood pressure support. In particular, this technique may be useful in identifying cardiovascular dysfunction in individuals without the hallmark features of damage to the cardiovascular pathways – such as low resting blood pressure. In Chapter 3, this technique identified several individuals with incomplete (AIS D) injuries as having damage to autonomic pathways. With the incidence of SCI including older adults and individuals with complex co-morbidities and existing cardiovascular dysfunctions it will be increasingly difficult to identify individuals at risk of cardiovascular events. Spectral analyses of blood pressure variability may be one way to do so.
6.4. Implications for exercise and sport after SCI

My results also have suggestions for exercise after SCI. Blood pressure maintenance during exercise can be challenging for individuals with SCI, and exercise-induced hypotension is common [421, 422]. The results in Chapter 2 demonstrate the benefits of a lowered seating position to bolster blood pressure and improve stroke volume in a static seated position. It is likely that the benefit of this position would be even more apparent during exercise. Body movement and dynamics during wheeling may accentuate the differences in cardiovascular parameters between positions. The lowered position provides improved ergonomics while wheeling and individuals tend to lean forward to move the center of gravity forward [247]. This would further compress the abdomen and increase venous return to the heart [248]. Therefore, the functional cardiovascular benefits of the lowered position might be enhanced during exercise.

The differences in ability to control blood pressure between autonomically-complete and -incomplete SCI seen in Chapter 2 highlight the varied challenges that individuals with SCI face when exercising. Exercising with a low blood pressure and low maximal heart rate due to altered or absent sympathetic control of the heart [234, 423, 424] is quite different from a normal blood pressure and increased heart rate and associated increased cardiac output and venous return. Indeed, this is part of the rationale that is being used to propose the addition of autonomic testing and classification to the current Paralympic classification system [425, 426]. The proposal aims to level the cardiovascular playing field in the same way that individuals are given a motor score based on their level of function [427]. However, there is an added challenge of not having a gold standard to assess cardiovascular autonomic function. To date, the combination of neurological level and sympathetic skin responses (SSR) have been used with some success in this population [426]. However, the time and equipment associated with SSR testing are such that beat-to-beat blood pressure recording and spectral analyses might provide a simpler alternative [21].

Exercise and physical training might also improve aspects of blood pressure regulation (as discussed above). Additional benefits for individuals who engage in exercise and sport after SCI may include improving physical capacity, body composition
changes and functional capabilities [428]. These benefits could influence mobility and independence as well as the traditional cardiovascular benefits of exercise in the able-bodied population. However, it is not clear whether these traditional training effects of exercise have similar effects to the able-bodied population. There is accumulating evidence specifically from studies in people with SCI that physical exercise improves aerobic capacity and muscular strength [428, 429] and increases metabolic rate [430], just as we would expect. Cardiovascular health benefits, such as reduced arterial stiffness [431] have also been documented.

6.5. Limitations

6.5.1. Limitations of research tools

Most research tools have some limitations and it is important that we are aware of these limits and temper our conclusions appropriately. Cardiovascular recording is vulnerable to all of the physiological stressors that can activate the sympathetic nervous system – in addition to the stimuli of interest. It is important to minimise extraneous stimuli that might activate or depress the cardiovascular system during testing. One way that we minimised additional stressors is by not wearing lab coats during testing, which is known to elevate blood pressure clinically [432-434]. As much as possible we ensured that participants were warm, comfortable and well hydrated throughout testing. In the acute study, wherever possible, we performed testing in individuals’ homes, while they were supine on their sofa or bed, to minimise the stress of being tested in a clinical lab setting and the patient burden of traveling to participate in research. We believe that all of these measures served to reduce the additional stimuli that can activate the cardiovascular system and ultimately give us more confidence in interpreting our results.

Transcranial Doppler (TCD) ultrasound, while widely used as a measure of cerebral blood flow, must be interpreted with caution. This method uses the measurement of blood velocity as a surrogate of blood flow with the key assumption that arterial diameter remains constant. As long as the artery does not change diameter, the relationship between velocity and flow remains constant. Previous MRI research supported the assumption that arterial diameter remains constant during changes in
However, more recent MRI studies show that there is measurable dilation of the MCA during significant hypercapnia [257, 258] and constriction during hypocapnia [257] – therefore, velocity may underestimate flow in hypercapnia and overestimate flow in hypocapnia. However, within the physiological range (plus or minus 5 mmHg $P_{ET\text{CO}_2}$, such as in Chapter 4) there is little change in MCA diameter, at least based on the current resolution of the MRI [435]. Furthermore, during larger changes in $P_{ET\text{CO}_2}$ during end-tidal forcing in Chapter 4, CO$_2$ manipulation was applied equally, and both groups achieved the same ranges of CO$_2$. Therefore, we are confident in our data and the comparisons made between groups.

Secondly, TCD is typically used to insonate the MCA, due to its simple access through the transtemporal window. Often the MCA is the only vessel insonated, with the assumption that the anterior vessels are representative of the vasculature in the brain. However this assumption has recently been challenged by research showing posterior vessels respond differently to certain physiological stimuli, such as CO$_2$ [436, 437]. This may require future studies to insonate both anterior and posterior vessels to make generalizations about the cerebral vasculature. For now, the majority of laboratories continue to focus on the MCA and the most information has been obtained about the behaviour of this vessel – making it the target of our investigations as well.

6.5.2. Research participation and sampling bias

All individuals participated in our research voluntarily, knowing that their participation would likely not bring them any individual benefit. Some people participated out of interest in their own physiology and others to help improve care and knowledge for future individuals who sustain similar injuries. It is important to acknowledge this self-selection when we generalise our conclusions broadly. However, we do not expect that the individuals who did participate in these studies are systematically different physiologically to those who do not choose to participate in research. In our acute study, we missed out on some of the sickest patients, including individuals who were using a ventilator, as medical treatment clearly takes priority over research in this early medically fragile period after injury. In the bowel care study, it is possible that we were more likely to recruit individuals who were dissatisfied with their current bowel care practices and
seeking assistance in this area. Despite this, in both cases we were able to recruit participants with a wide range of neurological injury levels and severities, from whom we can draw some conclusions about the population more generally.

6.5.3. Sample sizes and statistical methods

Individuals with SCI can be a challenging population to study. We were quite pleased to have seven to ten participants in each of our SCI groups in our experimental studies in Chapter 2 and 4. Obtaining these group sizes represents a significant achievement, and a gives us confidence in our results in these studies. The results of Chapter 3 represent interim results that should be considered to be pilot data. These pilot results suggest that there are two distinct groups – individuals with autonomically-complete and -incomplete SCI – based on their LF SAP. Further evidence is clearly warranted to ensure that this relationship is robust in individuals over time. In particular, as we move forward with this project it will be important for us to increase our retention to capture data from all subjects at all time points. To date, a significant majority of the participant attrition was beyond our control; the nature of working at tertiary acute SCI centre with a large catchment area means that people tend to return to their communities to complete their long-term rehabilitation.

Within individual variables, post-hoc tests were corrected to control the family-wise error rate. However, we did not correct the error rates between unrelated variables across each study. Therefore, we interpret our results with caution. Nevertheless, we believe that the recommendations made on the basis of our results reflect our interpretation on the basis of multiple different outcome measures all pointing towards these conclusions: for cardiovascular recording during wheelchair selection, and for greater sleep testing to assess the incidence of hypoxia in the face of the blunted responses to hypoxia. As a result, we feel that these recommendations are robust and are unlikely to be significantly altered by a modest increase in Type I error from the repeated comparisons made in these studies.
6.6. Areas for future research

Secondary complications of SCI remain a pressing concern for individuals living with SCI [9, 133]. These complications can further limit independence, reduce quality of life and add to the daily burden of living with SCI. It is critical that these priorities are realised by the research community and that we continue to focus more of our efforts toward these priorities.

Cardiovascular and cerebrovascular complications can be among the more sinister secondary complications of injury, yet they can also be less overt, with individuals not experiencing symptoms despite extreme variability. However, there is mounting evidence that even asymptomatic OH and AD can be associated with adverse outcomes and pathophysiological blood pressure changes [82, 244, 293, 362, 379, 380]. This makes education and monitoring critical. With greater access to handheld monitoring devices and advancing health technologies, I am hopeful that we will see more monitoring integrated into individual self-management and care.

When symptoms are present we, as researchers, need to be more discerning in determining the sources or triggers of those symptoms. The results in Chapters 3 and 5 demonstrate that symptoms alone do not provide sufficient evidence to determine whether individuals are experiencing AD or OH; even the classic symptoms of AD were documented in individuals with very low-level lesions, who are unlikely to experience this condition. Conversely, in Chapter 3, in the acute period after injury, symptoms of light-headedness and dizziness were common, and more likely associated with the trauma of injury, or deconditioning, than positional hypotension. Ideally, the combination of symptoms assessments and physiological recording can give us more confidence in our identification of these conditions and enable us to stratify patients appropriately.

Age is an important and underexplored aspect of SCI and associated secondary complications. In Canada, there is an increasing incidence of individuals sustaining injuries later in life [2, 398]. Furthermore, SCI seems to accelerate aging [288, 438]. These observations warrant longitudinal studies to further investigate the natural course of secondary complications and their relationship with aging [288]. Such studies, where
the variables (age, age at injury, and duration of injury) are associated with each other make the dissociation of confounding factors complex, and will demand multicentre approaches to ensure sufficient power [288]. Careful documentation of cardiovascular function over time may help to clarify the pathophysiology of the high incidence and severity of cardiovascular disease in the SCI population [13, 439]. In particular, the identification of which cardiovascular events are associated with worse outcomes could help direct care and management of cardiovascular and cerebrovascular complications after SCI.

Self-management of secondary complications is gaining momentum as a priority to minimise rehospitalisation and maximise quality of life after SCI [440, 441]. Key aspects specific to cardiovascular and cerebrovascular complications relate to education about signs and symptoms of common conditions, as well as identifying corrective and preventative actions, and equipping individuals with appropriate pharmacological and non-pharmacological tools to manage their blood pressure [381, 382, 419]. The ability to monitor cardiovascular function in real time is closer to reality with the increase of affordable wearable technological devices. Continuous biological tracking and quantification, including heart rate and blood pressure measurement, increase accessibility to calculate metrics such as HRV. Furthermore, wearable technologies have the potential to capture a large amount of data that would otherwise go undocumented, which could also allow us to accelerate research and engage users more directly in the research process. Future directions in this area of research will hopefully also be able to leverage this new data resource as a tool to get a clearer picture of cardiovascular function after injury.

6.7. Final thoughts

The autonomic repercussions of SCI are widespread and the management of these secondary complications demands substantial time and effort. Accordingly, research efforts in this area are imperative and have the potential to significantly improve quality of life for individuals living with SCI. In this thesis I quantified blood pressure and cerebral blood flow changes that commonly occur during routine activities of daily living. My results show that autonomic dysfunction has significant ramifications on blood
pressure control and quality of life after SCI. The results have implications for clinical care, self-management, and research. Above all, the results highlight the importance of assessing autonomic function and considering damage to autonomic pathways when making treatment decisions and research stratification. Cardiovascular symptom education and identification was recognised in several studies as a key area for improvement. Finally, it is essential that we continue to take guidance from individuals living with SCI to help us continue to focus our research efforts on their priorities for recovery and management.
References


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Appendix A.

Questionnaires

1. Cardiovascular symptoms after spinal cord injury questionnaire
2. Bowel care and cardiovascular function after spinal cord injury questionnaire
CARDIOVASCULAR SYMPTOMS AFTER SPINAL CORD INJURY
QUESTIONNAIRE

Thank you for taking the time to complete this questionnaire. Please answer all the questions. This questionnaire should not take longer than 15 minutes of your time to complete. If you would like help to complete the questionnaire, please ask one of the study investigators who will be pleased to assist you.

Section A – General Information
1. Identification number Date DD/MM/YYYY
2. Date of birth DD/MM/YYYY
3. Date of injury DD/MM/YYYY

Section B – Questions about irregular heart beats
1. Do you ever experience palpitations, irregular heart beats, an irregular pulse, or a feeling of “fluttering in your chest”?
   Yes ☐ No ☐
2. How often do you experience this?
   Daily ☐ Weekly ☐ Monthly ☐ Rarely ☐ Never ☐

Section C – Questions about autonomic dysreflexia
Autonomic dysreflexia refers to increases in blood pressure that occur in response to a sensory stimulus below the level of a spinal cord injury. The sensory stimulus may be something that would normally be expected to be painful e.g. a bump, or non-painful e.g. a full bladder. The stimulus does not need to be perceived to cause autonomic dysreflexia.
1. Have you ever experienced autonomic dysreflexia since your injury?
   Yes ☐ No ☐ Don’t know ☐
If yes, how many times?
   Once only ☐ 1-3 times ☐ 4-7 times ☐ More than 8 times ☐
2. How often do you experience the following symptoms of autonomic dysreflexia?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound headache</td>
<td></td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Nasal congestion</td>
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<tr>
<td>Goosebumps</td>
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<td>Blurred vision/visual sensitivity</td>
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<tr>
<td>Visual tunneling</td>
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<tr>
<td>Facial flushing</td>
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<tr>
<td>Profuse sweating</td>
<td></td>
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<tr>
<td>Difficulty breathing</td>
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<tr>
<td>Spasticity</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Shortness of breath/chest tightness</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Uncomfortable fast heart rate</td>
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<tr>
<td>Uncomfortable slow heart rate</td>
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<tr>
<td>General unwellness</td>
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<tr>
<td>Seizure</td>
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<tr>
<td>Other (please specify)</td>
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</table>

3. What sorts of things trigger these symptoms?

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
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</thead>
<tbody>
<tr>
<td>Bladder trigger</td>
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<tr>
<td>Bowel trigger</td>
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<tr>
<td>Sexual activity</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Pressure sores</td>
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<tr>
<td>Spasticity</td>
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<tr>
<td>Ingrown nails</td>
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<td></td>
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<tr>
<td>Fracture</td>
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<tr>
<td>Tight clothes/devices</td>
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<tr>
<td>Menstrual cramps</td>
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<tr>
<td>High/low temperatures</td>
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<tr>
<td>Blood clot</td>
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<tr>
<td>Other (please specify)</td>
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</tbody>
</table>

4. Has autonomic dysreflexia ever interfered with your ability to participate in the following activities?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
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<tr>
<td>Work</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Sexual activity</td>
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<tr>
<td>Rehabilitation</td>
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<tr>
<td>Household chores</td>
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<tr>
<td>Driving</td>
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<tr>
<td>Social activities</td>
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<tr>
<td>Sleep</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other (please specify)</td>
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</tbody>
</table>
5. Have you ever used AD to boost your sports performance?
Yes ☐  No ☐  N/A ☐  Prefer not to answer ☐

Section D – Questions about orthostatic hypotension

Orthostatic hypotension refers to decreases in blood pressure that occur when in an upright (sitting or standing) position. It is sometimes associated with fainting or dizziness.

1. Have you ever fainted prior to your injury?
Yes ☐  No ☐  
If yes, how many times?
Once only ☐  1-3 times ☐  4-7 times ☐  More than 8 times ☐

2. Have you ever fainted since your injury?
Yes ☐  No ☐  
If yes, how many times
Once only ☐  1-3 times ☐  4-7 times ☐  More than 8 times ☐

3. How often do you experience the following symptoms WHEN UPRIGHT, and NOT in conjunction with autonomic dysreflexia?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
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<tr>
<td>Fainting/Blackouts</td>
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<tr>
<td>Lightheadedness</td>
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<tr>
<td>Blurred vision</td>
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<tr>
<td>Visual Tunneling</td>
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<tr>
<td>Profuse sweating</td>
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<tr>
<td>Profound tiredness/lethargy</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Shortness of breath</td>
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<tr>
<td>Palpitations</td>
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<td>Uncomfortable fast heart rate</td>
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<tr>
<td>Uncomfortable slow heart rate</td>
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<tr>
<td>Extreme pallor</td>
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<tr>
<td>Seizure</td>
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<tr>
<td>Other (please specify)</td>
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</tbody>
</table>
4. What sorts of things trigger these symptoms?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural change in the morning</td>
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<tr>
<td>Sitting still in a wheelchair</td>
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<tr>
<td>Being in a warm room</td>
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<tr>
<td>Drinking alcohol</td>
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<tr>
<td>Stopping exercise</td>
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<td></td>
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<tr>
<td>After meals</td>
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<td></td>
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<tr>
<td>After bathing</td>
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<tr>
<td>Blood sampling/sight of blood</td>
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<tr>
<td>Physiotherapy</td>
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<tr>
<td>Other triggers (please specify)</td>
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</tbody>
</table>

5. Has orthostatic hypotension ever interfered with your ability to participate in the following activities?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
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</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Sexual activity</td>
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<tr>
<td>Rehabilitation</td>
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<tr>
<td>Household chores</td>
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<tr>
<td>Driving</td>
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<tr>
<td>Social activities</td>
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<tr>
<td>Other (please specify)</td>
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</table>

Section E – Questions about fatigue

Place an “x” on each of the following lines to indicate how you are feeling RIGHT NOW. For example, suppose you have not eaten since yesterday. Where would you place your “x” on the line below?

Not at all hungry                  | Extremely hungry

You would probably place your “x” closer to the extremely hungry end of the line. This is where I put it:

Not at all hungry                  | Extremely hungry

Now please complete the following items:

I am feeling:

1. Not at all fatigued | Extremely fatigued
2. Not at all tired    | Extremely tired
3. Not at all exhausted | Extremely exhausted

Thank you for completing this questionnaire.
BOWEL FUNCTION AFTER SPINAL CORD INJURY QUESTIONNAIRE

Section A: Participant information/demographics

Age _______ How long have you been living with a spinal cord injury? _______years _______months

1. What site on your spinal cord is injured? (Circle)
   C1  C2  C3  C4  C5  C6  C7  T1  T2  T3  T4  T5  T6  T7  T8  T9  T10  T11  T12  L1  L2  L3  L4  L5  Sacral

2. Can you feel touch in your anal area?
   □ Yes
   □ No

3. Can you voluntarily tighten your anal sphincter?
   □ Yes
   □ No

4. Can you feel light touch below your lesion level?
   □ Yes
   □ No

5. Can you feel the difference between sharp and dull touch below your lesion level?
   □ Yes
   □ No

6. Can you lift your legs against gravity?
   □ Yes
   □ No

8. What assistive devices do you use most often in your daily life?
   □ Motorized wheelchair
   □ Manual wheelchair
   □ Crutches
   □ Cane
   □ None
   □ Other

Section B: Questions about your normal bowel routine

1. Are you satisfied with your bowel management routine?
   □ Yes, very satisfied
   □ Yes, satisfied
   □ No, I’m dissatisfied
   □ No, I’m very dissatisfied

   If you checked No, please briefly explain why:

2. What steps do you use to empty your bowel? Check all that you use:
   □ Normal defecation/straining/bearing down to empty
   □ Drink/food before bowel management
   □ Massaging or rubbing abdomen
   □ Touching the skin around the anus
   □ Digital stimulation – putting a finger inside the anus and circling
   □ Manual evacuation – using a finger to remove stool from the bowel
   □ Suppositories – what kind and how many?
   □ Laxatives – what kind and how much?
   □ Enemas – what kind?
   □ Stool softeners
   □ Other steps. Please explain
3. How long have you been managing your bowel routine this way?
- ☐ Less than 6 months  ☐ Less than 1 year  ☐ Up to 5 years  ☐ Longer than 5 years

4. How often do you perform your bowel care?
- ☐ Three times or more per day
- ☐ Twice daily
- ☐ Once daily
- ☐ Not daily but more than twice every week
- ☐ Twice every week
- ☐ Once every week
- ☐ Less than once every week, but at least once within the last four weeks

5. How are you normally positioned during your bowel care?
- ☐ Bed
- ☐ Toilet chair/Commode
- ☐ Raised toiled seat
- ☐ Other, specify

6. How much do you usually drink each day?
- ☐ ½ litre (about ½ quart)
- ☐ 1 litre (about 1 quart)
- ☐ 1-2 litres
- ☐ More than 2 litres

7. Do you take any other medications that might affect bowel function?
- ☐ No
- ☐ Not sure
- ☐ Yes, anticholinergics ( Ditropan / Hyzone XL, Vesicare, Detrol, Toviiaz)
- ☐ Yes, opiates ( methadone, codeine, etc)
- ☐ Yes, antidepressants ( Tricyclics: Elavil, Amitriptyline, Nortriptyline, Desipramine)
- ☐ Yes, other, specify: ********

8. Do you regulate your diet to help with bowel management? (For example, by taking fibre supplements or eating certain fibre-rich foods?)
- ☐ No
- ☐ Yes – please explain briefly

9. Do you require assistance to perform your bowel care?
- ☐ Require total assistance
- ☐ Require partial assistance, including with cleaning
- ☐ Require partial assistance; cleaning done independently
- ☐ Independent in tasks but need adaptive devices or special setting (e.g. bars)
- ☐ Use toilet independently; do not need adaptive devices or special setting

10. What is the average time that you require for bowel care?
- ☐ 0-5 min
- ☐ 5-10 min
- ☐ 11-20 min
- ☐ 21-30 min
- ☐ 31-60 min
- ☐ More than 90 min
- ☐ Unknown

11. Breaking down the events and intervals of defecation:
   a) Average time from initiation of bowel care to the time that stool comes out:
      ☐ _______ minute(s)
      ☐ Not applicable
      ☐ Unknown

   b) Average time during bowel movement that stool intermittently or continuously comes out with or without assistance:
      ☐ _______ minute(s)
      ☐ Not applicable
      ☐ Unknown

   c) Average time spent waiting after last stool passes before ending bowel care:
      ☐ _______ minute(s)
      ☐ Not applicable
      ☐ Unknown

12. At what time do you usually do your bowel care?
- ☐ Morning
- ☐ Evening
- ☐ Other: ********

2
13. How flexible is your bowel management routine? Please check one box
- Very flexible – I often change the time or frequency at which I manage my bowel
- Quite flexible – I can delay management or later the timing if I want to
- Not very flexible – I don’t usually change my routine unless it’s unavoidable.
- Not flexible at all – I will not go to activities if they clash with my bowel management time

14. Do you wear a pad or plug to manage bowel accidents:
- Every day
- Not every day but at least once per week
- Not every week but at least once per month
- Less than once per month
- Never

15. How are you aware of the need to defecate:
- Direct sensation
- Indirect sensation (for e.g. abdominal cramping or discomfort, abdominal muscle spasms, spasms of lower extremities, perspiration, headache, chills)
- None
- Unknown

16. How often do you experience pain during bowel care:
- Daily
- Not every day but at least once per week
- Not every week but at least once per month
- Less than once per month
- Never
- Unknown

17. How often do you experience abdominal bloating or discomfort (anytime – not only during bowel care):
- Daily
- Not every day but at least once per week
- Not every week but at least once per month
- Less than once per month
- Never
- Unknown

18. How often do you experience respiratory discomfort (shortness of breath/difficulty in taking a deep breath due in part to a distended abdomen):
- Daily
- Not every day but at least once per week
- Not every week but at least once per month
- Less than once per month
- Never
- Unknown

19. If you had to estimate your frequency of fecal incontinence:
- Two or more episodes per day
- Once daily
- Not every day but at least once per week
- Not every week but at least once per month
- Once per month
- Less than once per month
- Never
- Not applicable
- Unknown

20. Does fecal incontinence alter your lifestyle:
- Lifestyle altered each day
- Lifestyle altered at least once per week but not every day
- Lifestyle altered more than once per month but not every week
- Lifestyle altered once per month
- Lifestyle altered less than once per month
- Lifestyle not altered
- Not applicable
- Unknown

21. What is the overall impact of bowel dysfunction on your quality of life:
- Major impact
- Some impact
- Little impact
- No impact
22. How does bowel management fit into your life? Please check one box beside each statement

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>I fit my life around my bowel management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel management stops me from working outside my home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managing bowels interferes with personal relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel management stops me staying away from home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My bowel management is a problem to me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel management interferes with my social life</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23. How much does bowel management affect your life compared to other aspects of spinal cord injury? Please give the following items a score between 1 and 10, where 10 is the worst effect and 1 the least. Circle X if an item does not apply to you.

<table>
<thead>
<tr>
<th>Least effect</th>
<th>Worst effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing my bladder</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Changes in sexual function</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Using a wheelchair</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Taking care of my skin</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Managing my bowel</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Living with chronic pain</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Living with spasticity</td>
<td>X 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

Section C: Questions about cardiovascular symptoms

1. During your bowel routine, do you ever experience any heart palpitations, irregular heartbeats or a feeling of “fluttering in your chest”?

   Yes ☐ No ☐
   If yes, how often do you normally experience this?
   Daily ☐ Weekly ☐ Monthly ☐ Rarely ☐ Never ☐

2. How would you rate the following symptoms during your normal bowel routine?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Very severe</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Not experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goosebumps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision/visual sensitivity</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Visual tunnelling</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Facial flushing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Profuse sweating</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### How would you rate the following symptoms during your normal bowel routine? (continued)

<table>
<thead>
<tr>
<th>Difficulty breathing</th>
<th>Very severe</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Not experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath/chest tightness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Uncomfortable fast heart rate</td>
<td></td>
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<tr>
<td>Uncomfortable slow heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General unwellness</td>
<td></td>
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</tr>
<tr>
<td>Seizure</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Other (please specify)</td>
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</tbody>
</table>

### Section D: Questions about autonomic dysreflexia

Autonomic dysreflexia refers to increases in blood pressure that occur in response to a sensory stimulus below the level of a spinal cord injury. The sensory stimulus may be something that would normally be expected to be painful e.g. a bump, or non-painful e.g. a full bladder. The stimulus does not need to be perceived to cause autonomic dysreflexia.

1. Have you ever experienced autonomic dysreflexia since your injury?
   - Yes [ ]
   - No [ ]
   - Don’t know [ ]
   - If yes, how many times? Once only [ ]
   - 1-3 times [ ]
   - 4-7 times [ ]
   - More than 8 times [ ]

2. How often do you experience the following symptoms?

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dizziness</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Goosebumps</td>
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<tr>
<td>Blurred vision/visual sensitivity</td>
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<tr>
<td>Visual tunnelling</td>
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<td></td>
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<tr>
<td>Facial flushing</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Profuse sweating</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Shortness of breath/chest tightness</td>
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<tr>
<td>Chest pain</td>
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<td></td>
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<tr>
<td>Palpitations</td>
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<td></td>
</tr>
<tr>
<td>Uncomfortable fast heart rate</td>
<td></td>
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<tr>
<td>Uncomfortable slow heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General unwellness</td>
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<tr>
<td>Seizure</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
3. What sorts of things trigger these symptoms?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder trigger</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel trigger</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sexual activity</td>
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<td></td>
<td></td>
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<tr>
<td>Pain</td>
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<td></td>
<td></td>
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<tr>
<td>Pressure sores</td>
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<td></td>
<td></td>
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<tr>
<td>Spasticity</td>
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<td></td>
<td></td>
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<tr>
<td>Ingrown nails</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tight clothes/devices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual cramps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High/low temperatures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood clot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Has autonomic dysreflexia ever interfered with your ability to participate in the following activities?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household chores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Have you ever used AD to boost your sports performance?

Yes ☐ No ☐ N/A ☐ Prefer not to answer ☐

Section E: Questions about orthostatic hypotension

Orthostatic hypotension refers to decreases in blood pressure that occur when in an upright (sitting or standing) position. It is sometimes associated with fainting or dizziness.

1. Have you ever fainted prior to your injury?

Yes ☐ No ☐ Don't know ☐

If yes, how many times? Once only ☐ 1-3 times ☐ 4-7 times ☐ More than 8 times ☐

2. Have you ever fainted since your injury?

Yes ☐ No ☐ Don't know ☐

If yes, how many times? Once only ☐ 1-3 times ☐ 4-7 times ☐ More than 8 times ☐
3. How often do you experience the following symptoms WHEN UPRIGHT, and NOT in conjunction with autonomic dysreflexia?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fainting/Blackouts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightheadedness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual tunnelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profuse sweating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profound tiredness/lethargy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Uncomfortable fast heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomfortable slow heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme pallor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

4. What sorts of things trigger these symptoms?

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder trigger</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural change in the morning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting still in a wheelchair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being in a warm room</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stopping exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After meals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After bathing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sampling/sight of blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Has orthostatic hypotension ever interfered with your ability to participate in the following activities?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household chores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section F: Questions about fatigue

1. Place an “x” on each of the following lines to indicate how you are feeling RIGHT NOW.

Not at all fatigued ——————————————————————————— Extremely fatigued

Not at all tired ——————————————————————————— Extremely tired

Not at all exhausted ——————————————————————————— Extremely exhausted

Section G: Questions on hydration and fluids

1. What is your fluid intake each day?
   □ about 500 mL (about ½ quart) □ 1-2 litres (between 1-2 quarts)
   □ 1 litre (about 1 quart or 34 oz) □ More than 2 litres (more than 2 quarts)

2. How much caffeine do you usually drink each day, on average? (Including coffee, tea, soda)
   □ None □ 1 cup/ can □ 2 cups/cans □ 3 cups/cans □ 4 cups/cans □ 5 or more cups/cans

3. How much alcohol do you usually drink each day, on average? (1 unit = 12 oz (350 mL) beer, 5 oz (150mL) wine, 1.5 oz (44 mL) liquor)
   □ None □ 1 unit □ 2 units □ 3 units □ 4 units or more

4. If you had to estimate your average daily urine output (24 hours), would it be:
   □ < 1000 mL □ 1000 mL □ 2000 mL □ 3000 mL □ 4000 mL □ 5000 mL or more

5. Do you ever restrict your fluid intake because of bladder control problems or concerns?
   □ No □ Yes □ Rarely □ Sometimes □ Often

6. Do you take any diuretics as part of your medications? Diuretics are sometimes called water pills as they increase the amount of urine that you produce. (For example, Lasix or HTCZ (hydrochlorothiazide)).
   □ No □ Yes □ Not sure

Thank you very much for taking the time to complete this questionnaire.