Cardiovascular autonomic control after spinal cord injury: comprehensive investigations into classification and care

by

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Abstract

Over 86,000 Canadians live with the consequences of a spinal cord injury (SCI). Injury to spinal autonomic pathways can lead to profound cardiovascular autonomic dysfunction. Key areas of concern identified by individuals living with SCI relate to continence and cardiovascular dysfunction. Conditions that result from autonomic dysfunction, such as autonomic dysreflexia (sudden extreme hypertension) are of particular concern. This thesis examined the cardiovascular autonomic consequences of SCI and their relationship to bowel care, the most potent stimulus for dysreflexia, and a key factor that negatively impacts quality of life after SCI. To assess cardiovascular autonomic control, first a quantitative marker of autonomic dysfunction following SCI had to be identified. In Aim 1 (Chapter 3), cardiovascular dysfunction during, and beyond, the first year of injury (n=63) was assessed using a novel quantitative non-invasive marker of cardiovascular autonomic control. From here, a randomized double-blind placebo-controlled crossover clinical trial to determine the effect of topical afferent blockade (lidocaine) on dysreflexia severity during bowel care was conducted (n=13). Aim 2 (Chapter 4) provides evidence that, contrary to current clinical guidelines, topical lidocaine prolongs bowel care, worsens dysreflexia, and increases cardiovascular symptoms. Despite bowel care concerns, past research shows that individuals do not change bowel care practices, highlighting knowledge translation gaps concerning evidence-based bowel management strategies. To address this, in Aim 3 (Chapter 5), semi-structured interviews (n=13) were used to examine the barriers and facilitators to changing bowel care. The largest influences on changing bowel care and potentially relevant intervention options were identified. Finally, during dysreflexia profound sympathetic stimulation may increase risk for cardiac arrhythmia. Aim 4 (Chapter 6) evaluated susceptibility to arrhythmia in a rodent-model of SCI, the impact of the sympathomimetic drug dobutamine on arrhythmia risk, and the potential mitigating effect of exercise training. SCI increased susceptibility to cardiac arrhythmia, with dobutamine further increasing susceptibility in high-level SCI. Exercise training ameliorated markers of arrhythmia risk during dobutamine. The research conducted in this thesis uses a translational and patient-orientated approach to bridge the gap between physiological understanding and meaningful improvement in the clinical setting for individuals living with cardiovascular and continence implications of SCI.

Keywords: cardiovascular dysfunction, spinal cord injury, bowel care, autonomic dysreflexia, cardiac arrhythmia

Land Acknowledgement

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To my 21-year-old self, a girl interrupted, a wonderful life nearly lost.

To my parents, for everything.

And to you, the reader. May this work spark curiosity in you as it has so dearly in me.

"It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat."

– Theodore Roosevelt

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List of Key Acronyms

AD	Autonomic dysreflexia
AIS	ASIA Impairment Scale
AR	Autoregressive
ASIA	American Spinal Injury Association
BCT	Behaviour change technique
BCT Tv1	Behaviour Change Technique Taxonomy Version 1
BCW	Behaviour change wheel
BPV	Blood pressure variability
CBF	Cerebral blood flow
COM-B	Capability, Opportunity, Motivation – Behaviour
CVD	Cardiovascular disease
C_W	Arterial Windkessel compliance
DAP	Diastolic arterial pressure
DESD	Detrusor-external sphincter dyssynergia
ECG	Electrocardiogram
FFT	Fast Fourier Transform
GI	Gastrointestinal
HDL	High density lipoproteins
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
ICORD	International Collaboration On Repair Discoveries
ISAFSCI	International Standards to document remaining Autonomic Function after Spinal Cord Injury
ISCoS	International Spinal Cord Society
ISLAGIATT	It Seemed Like A Good Idea At The Time
LF	Low frequency
LMN	Lower motor neuron
MAP	Mean arterial pressure
MoD	Mode of delivery
MoDTv0	Mode of Delivery Taxonomy Version 0
MSNA	Muscle sympathetic nerve activity
NBD	Neurogenic bowel dysfunction

NE	Norepinephrine
OH	Orthostatic hypotension
PABAK	Prevalence-adjusted bias-adjusted Kappa
PWD	P-wave duration
Q	Cardiac output
QTc	Heart rate corrected QT interval
QTVI	QT variability index
RAAS	Renin-angiotensin-aldosterone system
R_P	Estimated peripheral resistance
RRI	R-R interval
SAP	Systolic arterial pressure
SCI	Spinal cord injury
SCI-BC	Spinal Cord Injury British Columbia
SSR	Sympathetic skin response
SV	Stroke volume
TDF	Theoretical domains framework
TFG	Transfer function gain
T_{peak}-T_{end}	T-peak to T-end interval
TPR	Total peripheral resistance
UMN	Upper motor neuron
VLF	Very low frequency
Z_O	Aortic characteristic impedance

Chapter 1

Introduction

1.1 Spinal cord injury in Canada

Approximately 86,000 Canadians are living with the devastating consequences of a spinal cord injury (SCI) [1], with 44,000 (51%) of individuals having sustained their injury as a result of trauma (traumatic SCI) [1] (**Figure 1.1**). Of those with a traumatic SCI, 60% of injuries result in tetraplegia and 70% of injuries are incomplete lesions of the spinal cord [2]. Young adults aged 19-35 years are most likely to sustain a traumatic SCI, and males account for a large majority (79%) of all injuries [2]. Given that Canada's population is ageing, and the demographics of SCI in Canada are believed to be shifting, it is believed that in coming decades, more injuries will occur from falls in older populations [1].

With increasing advances in acute management of SCI, life expectancy has greatly increased following injury. However, these advances come at an economic cost, associated with both the acute and chronic phases of SCI, and are exacerbated by the burden of secondary complications for those living with SCI [1]. The lifetime economic burden for an individual with SCI is estimated at $1.5-3 million, depending on the severity of the injury [3]. Extending beyond the financial costs, the consequences of motor, sensory, and autonomic loss on quality of life are profound.

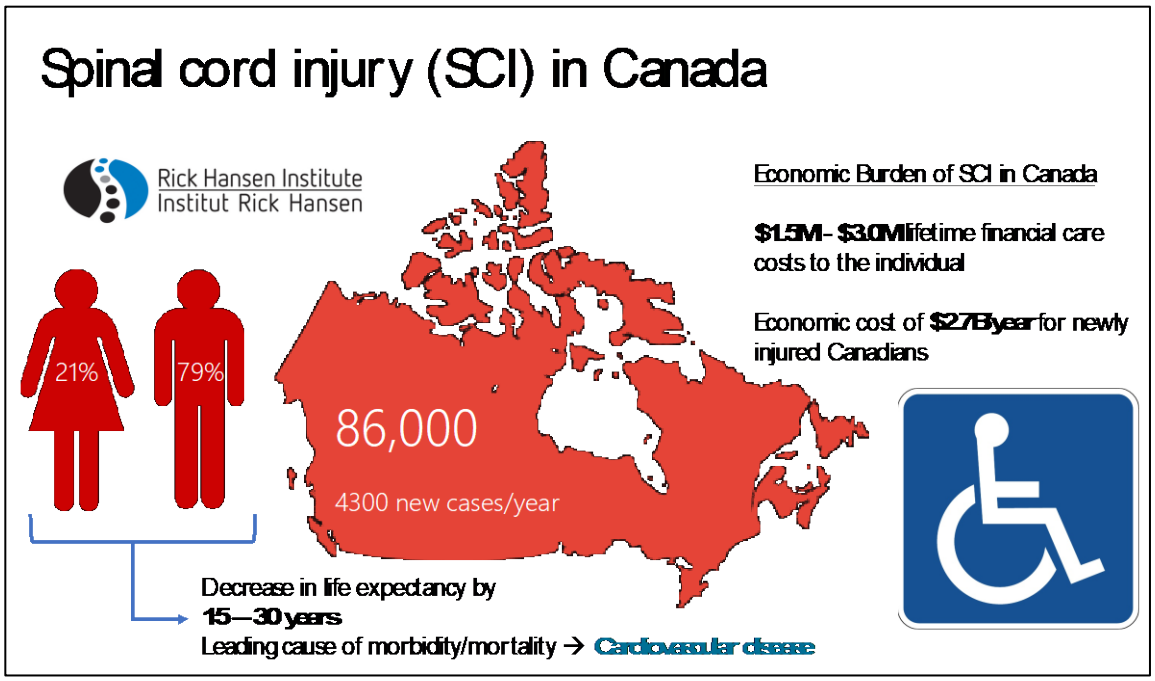

Figure 1.1 – SCI Demographics in Canada.
SCI is disproportionately acquired in males, and life expectancy is significantly reduced in the SCI population. Similarly, there is a significant cost to both the individual and economy that can be attributed to high care costs and secondary health concerns. Adapted from [2].

1.2 Overview of autonomic dysfunction after SCI

Along with permanent impairment to motor and sensory function, SCI has a profound impact on spinal autonomic pathways (**Figure 1.2**). These pathways are responsible for regulation of heart rate (HR), blood pressure, temperature, respiration, urinary and bowel control, renal function, gastrointestinal (GI) activity, and sexual function [4]. This widespread autonomic dysfunction after SCI is due to disruption of sympathetic (descending) spinal pathways [5].

The overarching and devastating effects of autonomic impairments following SCI have been recognized as a leading cause of dissatisfaction for individuals with SCI [6]. Individuals with SCI have also prioritized the need for investigations to develop an understanding and an eventual amelioration of the consequences of autonomic dysfunction [6]. Thus far, this priority has only recently been recognised in the research community.

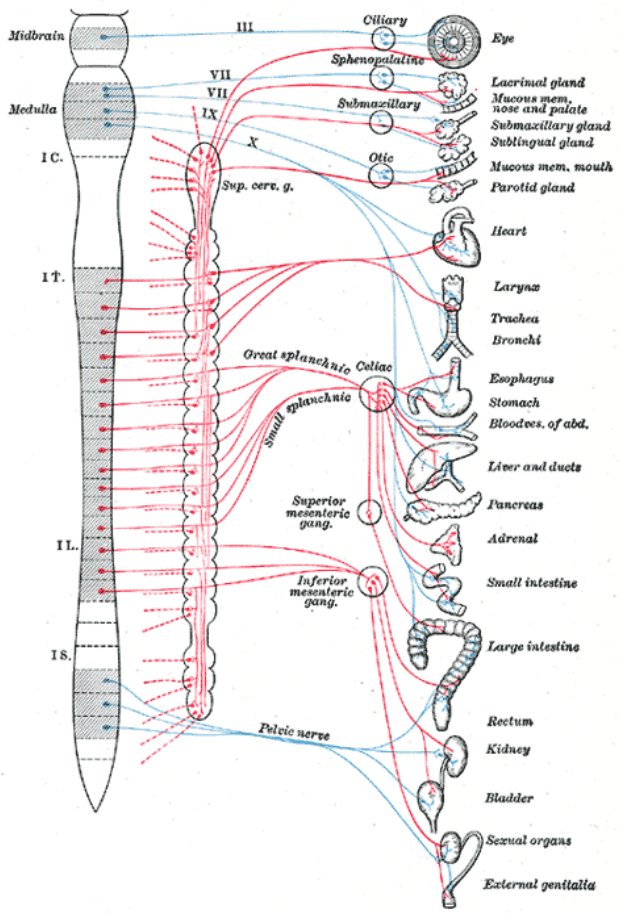

Figure 1.2 – The autonomic nervous system.
The autonomic nervous system includes both sympathetic (red) and parasympathetic (blue) subdivisions. Following SCI sympathetic and sacral parasympathetic outflow is impaired, dependent on the spinal level of injury. However, supraspinal components of the parasympathetic nervous system, such as the vagus (cranial nerve X) are unaffected by spinal injury. Used with permission from [7].

1.2.1 Cardiovascular dysfunction

Interruptions to the sympathetic autonomic (descending) pathways can lead to disturbances in cardiovascular control following injury, the degree of which is directly related to the level and severity of the SCI. Typically, individuals with lesion levels at or above the sixth thoracic level (T6) experience greater cardiovascular dysfunction because of interruption of the sympathetic outflow to the heart and key vascular resistance and capacitance bed in the splanchnic region. Accordingly, cardiovascular disease (CVD) is the leading cause of morbidity and mortality in chronic SCI (longstanding SCI of at least 1 year; SCI is considered sub-acute when close >1 year post-injury) [8]. Investigations into

the mitigation and understanding of the progression of CVD in individuals with SCI should be a research priority.

Metabolic syndrome is prevalent in SCI populations, and is a marker of CVD risk [9,10]. Metabolic syndrome is characterized by low levels of high density lipoproteins (HDL), elevated triglycerides, elevated fasting blood glucose levels, hypertension, and abdominal obesity [9–11]. In the general population, metabolic syndrome is associated with a higher prevalence of CVD and mortality [11]. This is also the case in the SCI population, and there are reports that the disease process is exacerbated in those with SCI [9].

Orthostatic intolerance

The most pronounced cardiovascular complication following SCI is orthostatic hypotension (OH) [12]. OH is characterized as a drop in systolic arterial pressure (SAP) by ≥20mmHg or diastolic arterial pressure (DAP) by ≥10mmHg within 3 minutes of standing or 60° head-up tilting, with or without symptoms [13].

OH is caused by the inability of the body to compensate for the gravitational shift of blood volume when moving into an upright position. The subsequent venous pooling and capillary filtration diminish venous return, resulting in a decrease in stroke volume (SV) and cardiac output (Q). In high level SCI, this is exacerbated by the inability to vasoconstrict the splanchnic vasculature, that already results in supine hypotension in this population. This diminished Q leads to a decrease in cerebral blood flow (CBF), and often manifests classic symptoms of OH, such as light-headedness, dizziness, pre-syncope (near-fainting), and syncope (fainting) [13]. In addition to OH, a decrease in CBF has also been linked to increases in diabetes mellitus [14], fatigue [15], and arterial stiffening [16] in able-bodied individuals. Cerebral hypoperfusion has also been linked to cognitive deficits and fatigue in both able-bodied and SCI populations [14,17].

Autonomic dysreflexia

In addition to these *hypo*tensive episodes, another manifestation of impaired spinal autonomic injury is acute *hyper*tensive episodes, known as autonomic dysreflexia (AD). AD is characterized by paroxysmal hypertension in response to sensory stimuli below the level of injury [18] (**Figure 1.3**). AD is caused when the stimulus (noxious or non-noxious) elicits a sympathetic reflex, resulting in massive widespread vasoconstriction of the

splanchnic vascular bed, and other vessels below the level of injury, leading to a dangerously large increase in blood pressure [18–20]. This increase in blood pressure leads to baroreflex-mediated reduction in HR through sympathetic withdrawal above the level of injury and increased vagal tone. AD classically presents with large elevations to blood pressure with bradycardia, which is atypical of hypertensive responses seen in able-bodied populations.

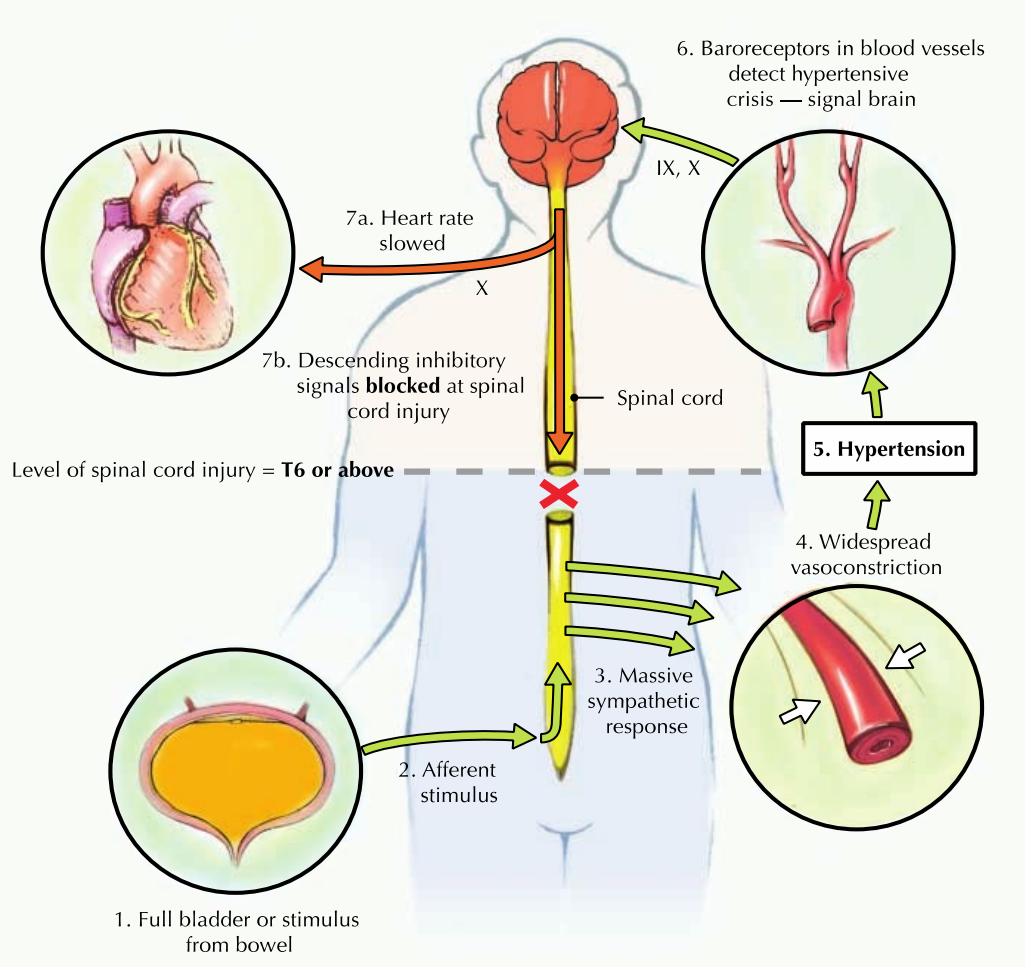

Figure 1.3 – Mechanism of autonomic dysreflexia.
AD occurs as the afferent stimulus (shown as a distended bladder), triggers a peripheral sympathetic response, resulting in vasoconstriction and subsequent hypertension. This rise in blood pressure cannot be attenuated as descending sympathetic withdrawal signals are blocked at the level of the spinal cord injury. Adapted from [18]. Used with permission.

The increase in blood pressure seen in AD is sudden and sustained until the sensory stimuli is removed. Such instances occur daily for individuals with SCI at or above T6 and can be triggered by a variety of different afferent stimuli. Typical causes include a distended bladder or bowel, care routines, pressure sores, infections, and external stimuli

[18]. AD can present clinically with symptoms including sweating above the level of injury, nausea, profound headache, facial flushing, and blurred vision [18]. However, AD can also present asymptomatically [21] and has been linked to cognitive impairments [17,22,23]. AD, along with OH, evolves post injury [24], and represents one of the largest autonomic complications following SCI. Another concern of the disrupted blood pressure regulation after SCI relates to the impact of repeated bouts of profound hypotension and hypertension, often many times per day, on overall vascular health and cognition [22].

Cardiac arrhythmias

In addition to the profound hypertension associated with AD, there are also reports that the excessive sympathetic discharge is proarrhythmogenic [25]. In addition, cardiac arrhythmia can also occur in isolation after SCI due to the profound cardiac dysfunction that accompanies high level injuries. The disruption to the sympathetic outflow to the heart results in unopposed parasympathetic activity, which has been linked to bradycardia, asystole, and cardiac arrhythmias [26]. Indeed, bradyarrhythmias are well documented in the acute stages of SCI [27–29]. However, arrhythmias have also been seen during episodes of AD, where the extreme hypertension coupled with the dysregulation of the descending spinal pathways leads to an increase in the spatial dispersion of ventricular repolarization [25,30] (**Figure 1.4**). It is not yet known if the transient arrhythmias experienced during AD have any effect on the progression of CVD in the chronic phase of SCI.

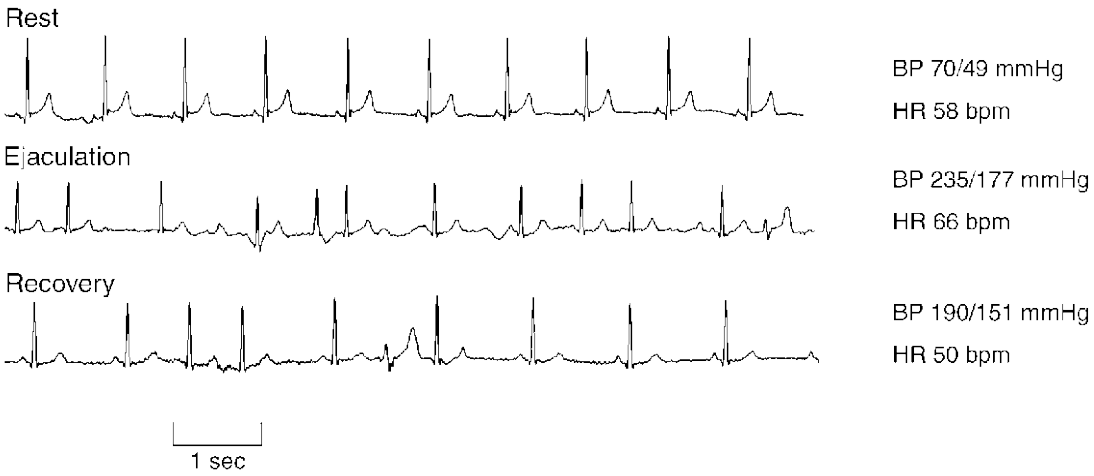

Figure 1.4 – Cardiac arrhythmia seen during AD caused by vibrostimulation for sperm retrieval

Marked AD was experienced during the procedure (see blood pressure and HR on right hand side) with provoked rhythm disturbances. Abbreviations: BP, blood pressure; HR, heart rate. Adapted from [31]. Used with permission.

Indices of arrhythmia risk (P-wave duration [PWD], a marker of atrial arrhythmia risk; Tpeak- Tend [T_{peak}-T_{end}] mean and variability, markers of transmural dispersion of repolarisation; heart rate corrected QT interval [QTc], reflecting the duration of repolarization; and QT variability index [QTVI], a marker of ventricular arrhythmia risk) provide quantitative markers of susceptibility to cardiac arrhythmia. Typically, increases in these parameters indicates a greater arrhythmia risk.

Exercise intolerance

Another concern after SCI is the relationship between cardiovascular dysfunction and exercise intolerance [32]. The loss of motor function can prove limiting to exercise following SCI [33]. However, the autonomic consequences of SCI during exercise are also widespread – notably lung function, HR and blood pressure responses to exercise are impaired [8,33–35]. Lung function is impaired after SCI [8,35,36], and is related to injury severity [34] and decreased exercise capacity in the SCI population [34]. Since exercise is integral in the mitigation of CVD, impaired lung function could impact the progression of CVD in the chronic phase of injury.

Moreover, autonomically-impaired athletes have blunted cardiovascular responses to exercise, due to disruption of descending control of sympathetic outflow to the heart and vasculature [33]. This results in blunted HR and blood pressure responses

to exercise, and post-exercise hypotension, leading to exercise intolerance [33]. Research examining the relationships between exercise intolerance and cardiovascular autonomic function after SCI is lacking.

Although OH, AD, and arrhythmias are acute events, they can be experienced often and are believed to lead to early onset of CVD [11,27,33,37]. Not only is exercise intolerance a barrier to quality of life, given the known health benefits of exercise, there is a growing body of evidence to suggest that exercise training post-SCI is beneficial to cardiovascular health [33,38]. Whether the benefits of exercise extend to improvements in autonomic function after SCI remains unclear.

1.2.2 Bladder and bowel dysfunction

The aforementioned manifestations of cardiovascular dysfunction are often triggered by daily tasks carried out by individuals with SCI. A common precursor to some of these cardiovascular abnormalities is bladder and bowel dysfunction [4]. As with all autonomic dysfunctions following SCI, problems with urinary and bowel control stem from the disruption of the sympathetic spinal pathways. Parasympathetic and motor pathways in the sacral circuity are also disrupted, notably the pudendal nerve which controls both external urethral and anal sphincters.

Not only are bladder and bowel problems of particular concern in relation to quality of life, they may also exacerbate other concerns for those with SCI. Of particular concern is their ability to provoke AD, as the most potent triggers of this condition are visceral stimuli. Persons at risk for AD (injury at or above T6) can experience AD with or without symptoms during bowel care. Many of these individuals require interventions to trigger defecation that are often particularly potent triggers for AD; since bowel care is a regular and unavoidable trigger for AD in susceptible individuals, bowel care represents a key target for treatment or preventative strategies to ameliorate AD.

SCI also results in neurogenic bladder activity. Facilitation and inhibition of normal micturition requires the coordination of the sacral micturition centre (S2-S4), the pontine micturition centre, and the cerebral cortex [39]. Depending on the level of neurological insult, bladder dysfunction can either result in the preservation or dissolution of bladder tone. Suprasacral lesions result in a loss of reflexive micturition and an atonic bladder with

urodynamics testing commonly showing detrusor-external sphincter dyssynergia (DESD) [40]. DESD relates to four major problems: (1) inadequate or excessive detrusor function; (2) inadequate or excessive sphincter function; (3) dyssynergy between detrusor and sphincter actions; and (4) impaired bladder sensation [39]. The uncoordinated contractions seen in DESD during micturition result in high voiding pressures, residual urine volume, and urinary incontinence which, if untreated, will manifest as upper tract deteriorations and renal failure [39]. Conversely, sacral lesions exhibit highly compliant and acontractile bladders with sphincters retaining some fixed tone. Urinary tract infections, urinary and renal stones, and renal impairment are common complications of bladder dysfunction in SCI [39].

Bowel impairments after SCI are primarily related to the impact of injury on GI function, as the sympathetic pathways are responsible for motor coordination of GI motility [41]. This disruption is highly dependent on the level of injury and is known as neurogenic bowel dysfunction (NBD). NBD can be further classified as upper motor neuron (UMN) dysfunction or lower motor neuron (LMN) dysfunction, depending on whether the injury level is above or below the conus medullaris (L1), respectively [41]. UMN lesions maintain reflex activity in the sacral segments of the cord. Accordingly, UMN lesions result in a loss of voluntary control of the bowel, with a preservation of reflexive defecation. This often results in a spastic sphincter leading to constipation and fecal retention which requires intervention (either chemical or mechanical) to trigger defecation and evacuate the bowel [42]. This is known as a hyperreflexive bowel. While LMN lesions also result in a loss of voluntary control of the bowel, they are accompanied by a lax external sphincter, resulting in both constipation and a high frequency of fecal incontinence. This is caused by a loss of sacral reflexive circuitry, which is responsible for the reflexive bowel seen in UMN NBD. This is also known as an areflexive bowel.

Both UMN and LMN NBD require an individualized approach to bowel management. This means that bowel programs and bowel care routines differ largely from person to person. The most common approaches to bowel routines are digital stimulation (to produce a reflexive defecation) and manual evacuation [43]. Other common management approaches include the use of suppositories, laxatives, abdominal massage, and enemas, among others [42]. There is a general lack of knowledge regarding current bowel care practices in the community setting. It is not clearly understood how individuals

choose to alter their routine, and if care routines used in the community are the same as prescribed in rehabilitation.

Bowel and bladder management after SCI

In a recent questionnaire-based study by our lab group [43] of 287 community-dwelling individuals, bowel management strategies described were multifactorial and complicated. Respondents most commonly used a multi-step approach to bowel management (70%), with 58% using three or more methods to achieve their bowel care. This is consistent with previous studies [44,45]. An increase in the number of approaches used to complete bowel care had a negative impact on quality of life through increases in the time taken to complete bowel care, as well as more severe symptoms of AD. An infographic review of common bowel care approached based on the results of this survey (**Figure 1.5**) was prepared in conjunction with our community partner, Spinal Cord Injury British Columbia (SCI-BC).

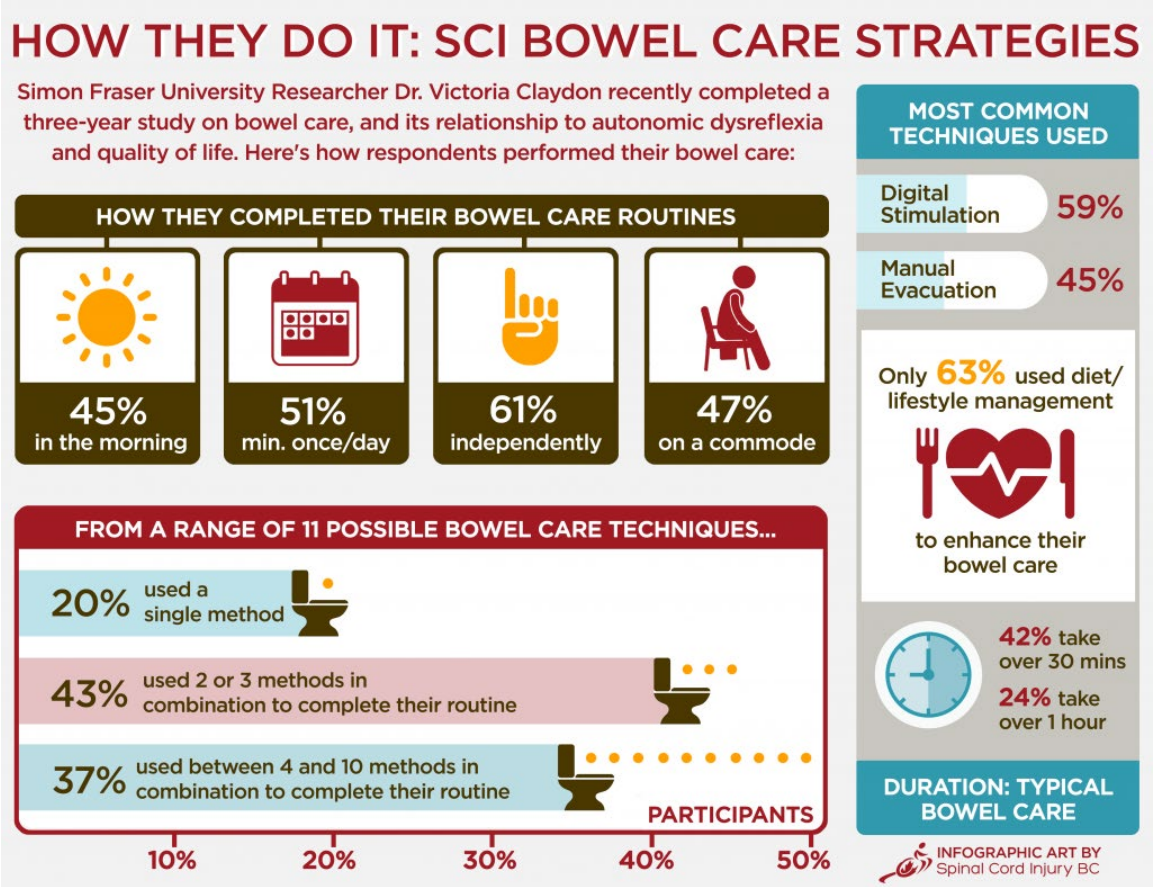

Figure 1.5 – Bowel care management approaches after SCI.
This infographic aimed at integrated knowledge translation within the SCI community summarizes the results of our recent survey concerning bowel management approaches [43] for individuals with SCI. Abbreviations: SCI, spinal cord injury. Adapted from [46]. Used with permission.

Fecal incontinence was a common concern, and has been reported previously [44]. As might be expected, [47,48] this was particularly the case for those with a LMN bowel disorder and areflexive bowels. However, despite concerns about incontinence, it was no longer significantly associated with quality of life when potential confounding factors were considered. This does not necessarily mean that minimising fecal incontinence is not an important target for improvement of quality of life; rather that these relationships are complex and not independent of other factors such as age, duration of injury and level of injury. This is underscored by the large number of narrative responses targeting fecal incontinence as a concern.

Fatigue was a common concern, with high levels of fatigue reported, particularly in younger individuals. Fatigue was strongly associated with the severity of OH, presumably through hypotension and cerebral hypoperfusion [49–54]. Surprisingly, in the specific

context of bowel care, fatigue was a secondary predictor of quality of life through its association with severity of AD. This might reflect the association between AD and OH [55], which often manifests symptomatically as fatigue [56].

In our sample [43], 71% of individuals reported intentional fluid restriction because of bladder management concerns, with 49% of individuals using fluid restriction "sometimes or often". Younger individuals were more likely to employ fluid restriction. We considered whether this might impact the time to complete bowel care or severity of symptoms of AD, based on the theoretical risk of worsening constipation. We found that fluid restriction was associated with the severity of AD, but not the time to complete bowel care. In addition, fluid restriction was strongly related to the severity of OH and fatigue reported, presumably through hypovolemia [55]. These data highlight the need to consider a holistic approach to the management of bladder and bowel care after SCI, enhancing bladder care to prevent fluid restriction and optimizing bowel care to reduce symptoms of cardiovascular dysfunction.

Current clinical guidelines suggest that a bowel routine is problematic if it exceeds one hour in duration [57]. According to this definition, one-quarter of our respondents had problematic routines (a further 18% had typical bowel routines that exceeded 30 minutes) [43]. Given the strong association between the duration of bowel care routines and quality of life, these data suggest an urgent need to investigate and implement bowel management approaches that decrease the time to complete routine bowel care. In our analyses, the bowel management approaches most associated with long bowel care routines were use of suppositories and digital stimulation; in those able to use normal defecation (bearing down) the time to complete care was shorter.

1.2.3 Associations between bowel care and cardiovascular dysfunction

From the same dataset described above [43], of those most at risk for experiencing cardiovascular dysfunction after SCI, 74% reported at least one symptom of AD during bowel care and 32% described symptoms compatible with cardiac arrhythmia. Severity of symptoms of AD during bowel care in individuals at risk for cardiovascular dysfunction in this sample can be seen in **Figure 1.6** [43]. The most common symptoms reported were goosebumps, spasticity, sweating, flushing, a feeling of unwellness, and headache – very

typical symptoms associated with AD [18,58–60]. In those who experienced symptoms of AD during bowel care, episodes of AD were also commonly triggered during other activities of daily living, most notably bladder care and pain, suggesting most individuals who are susceptible to AD are experiencing multiple episodes per day. Many of these stimuli, such as bladder and bowel care, are unavoidable, and bowel care in particular is a stimulus of long duration. Therefore, it is likely that improvement of AD is a target, not only for improving the impact of bowel care on quality of life, but also for improved management of cardiovascular sequalae. The long term effects of repeated bouts of AD have yet to be fully elucidated, but there is evidence of altered vascular function in animal models of AD [61], and there are case reports of cerebrovascular accidents and hemorrhage secondary to AD [59,62,63]. These hypertensive episodes often occur in conjunction with constitutional hypotension and OH, as noted by survey respondents, and the impact of these large swings in blood pressure may particularly challenge the integrity of the endothelium, vessel wall, and cardiac function [64].

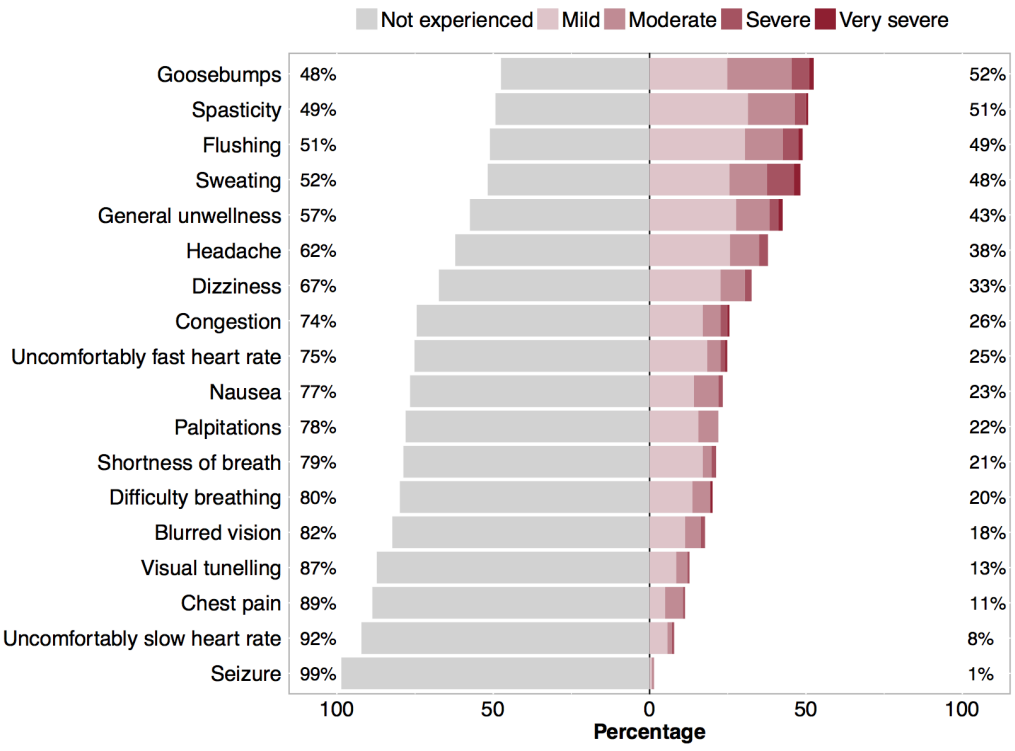

Figure 1.6 – Severity of symptoms of autonomic dysreflexia during bowel care in individuals with SCI considered at risk for cardiovascular dysfunction.

Each symptom was classified according to its perceived severity. Abbreviations: SCI, spinal cord injury. Adapted from [43]. Used with permission.

Although we were primarily interested in the relationships between AD and bowel care, it was interesting that AD was reported by our respondents to interfere with other common activities, including sleep, exercise, normal daily activities, and sexual function (**Figure 1.7**) [43]. Many of these triggers are well known [59,60] and underscore the need to find effective management strategies for AD [60]. However, the association between AD interfering with sleep has not been reported previously to our knowledge. This may seem surprising because we do not think of many triggers for AD being present during sleep. However, considering that most respondents reported conducting their bowel care first thing in the morning or in the evening, it is possible the colon filling initiates AD ahead of morning bowel care, or that evening bowel care triggers symptoms of AD that continue unabated – even once the offending stimulus has been removed [65]. Furthermore, bladder triggers for AD may also be peaking over the night as the bladder progressively fills following evening bladder care prior to bed. Urine production is also higher in the night than the day in individuals with high-level lesions, which could further exacerbate the nocturnal bladder stimulus [66]. Together these triggers could combine to exacerbate AD and 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 profound fatigue related to low resting CBF during the day [49–54], and poor sleep is known to further exacerbate fatigue, difficulty concentrating, and excessive daytime sleepiness [56].

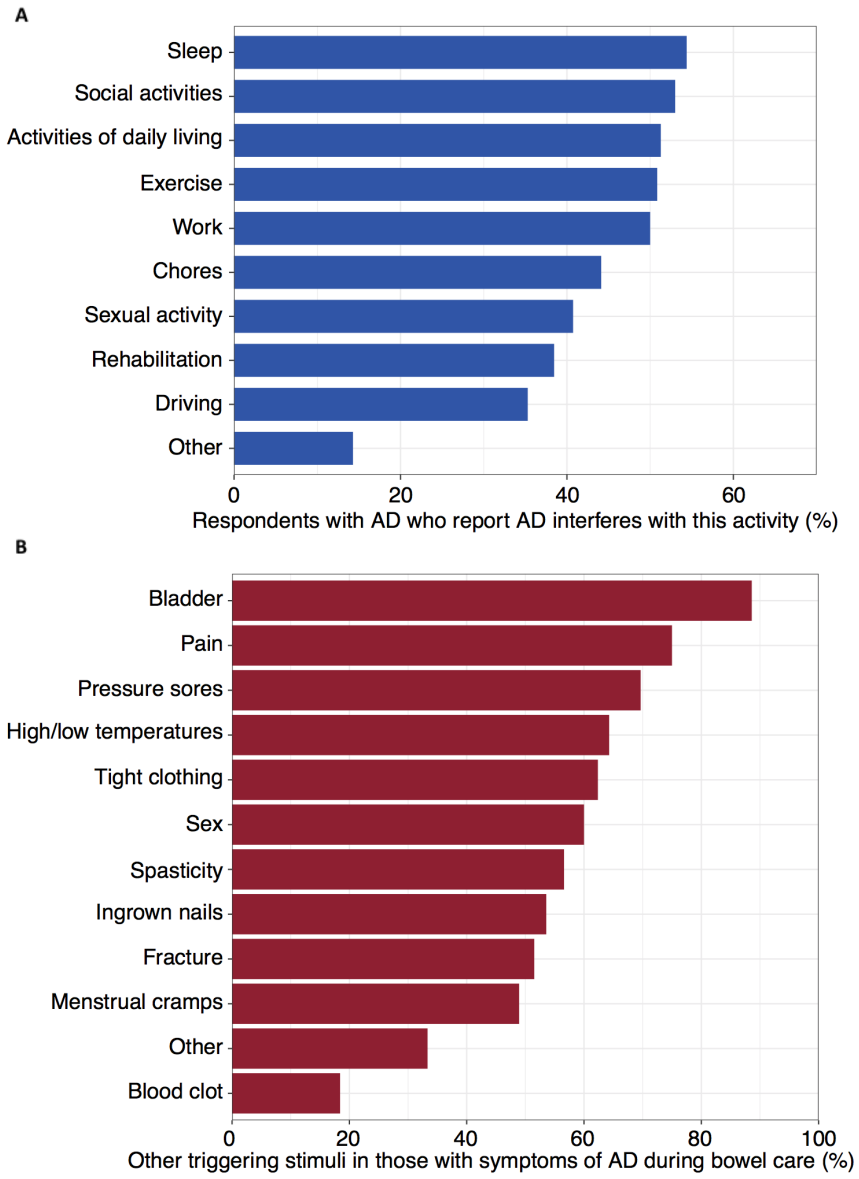

Figure 1.7 – Influence of AD outside of bowel care.
(A) Prevalence of autonomic dysreflexia interfering with common activities. (B) Additional stimuli that trigger autonomic dysreflexia symptoms in those with symptoms of autonomic dysreflexia during bowel care. Abbreviations: AD, autonomic dysreflexia. Adapted from [43]. Used with permission.

Most individuals (88%) in our survey [43] were aware of AD and whether they had experienced it. This suggests that education strategies in this area have largely been effective. However, a number of respondents with lesion levels placing them at risk for AD did not know if they had it, despite describing symptoms of AD during their bowel care [43]. This suggests there is still some room for improvement in education about the risk profile, identifying signs and symptoms of AD, and when to seek additional assistance for

AD management. More generally, although AD awareness was high in this sample, AD was described as impacting quality of life and interfering with activities of daily living, suggesting education and resources concerning the *management* of AD are a priority for those living with SCI [43]. Those who were particularly likely to experience severe symptoms of AD were those who were younger, with more complicated bowel care routines, and those for whom bowel care takes a long time. It is probable that the longer duration and magnitude of the afferent stimulus for AD during more complex and longer duration routines underlies the more severe symptoms of AD, highlighting the need to ameliorate symptoms in these individuals, either pharmacologically, or behaviourally, through reductions in the time to complete bowel care and decreases in the number of stimuli used.

In terms of reducing the severity of AD pharmacologically, one approach has been to mitigate the afferent stimulus using anaesthetic lubricants during bowel care. However, guidelines regarding use of topical anaesthesia to minimise AD during known triggers, such as during bowel care, are conflicting [57,67–69], and this is noted in the SCI community, with uncertainty about the different techniques and strategies to manage AD when performing bowel care at home [69,70]. Clearer recommendations and additional education are warranted.

Additionally, symptoms of OH, including light-headedness, dizziness, and lethargy were also reported by a significant proportion (93%) of our survey respondents [43]. Triggers for these symptoms included positional changes and sitting, such as those needed to perform bowel care. These symptoms can further compound the challenges that individuals with SCI face in their daily lives, work, and leisure activities, and were strongly associated with fatigue [17,71]. There is mounting evidence that hypotension is not a benign condition, and that hypotension and associated cerebral hypoperfusion should be avoided, including documented attention deficits and other mild cognitive impairments in hypotensive individuals with SCI [71]. Therefore, there is a strong rationale to increase education about hypotension, symptoms, and positional counter manoeuvres, and potentially to encourage self-monitoring of blood pressure at home [71,72]. These measures should be targeted to those most at risk - individuals with high level lesions and younger individuals with SCI. In particular, given that 71% of individuals reported intentionally restricting their fluid intake because of concerns with bladder management

[43], the holistic management of bladder and bowel function and the importance of adequate fluid intake should be stressed.

1.2.4 Gastrointestinal dysfunction

As previously mentioned, sympathetic pathways responsible for the motor coordination of GI motility, when impacted by SCI, result in bowel dysfunction [73]. Moreover, strategies for bowel emptying, such as digital stimulation and manual evacuation of stool, provide the most potent triggers for AD [74]. In addition to bowel dysfunction, several GI abnormalities and pathologies are common in SCI in both the acute phase (related to neurogenic shock) and the chronic phase of injury. Dysphagia is common in SCI (22.5% to 41%), with severity of impairment related to level of injury [75–77]. Gastric emptying is also delayed following SCI [41]. The increase in time to empty is directly related to level of injury and duration since injury, with increases in both resulting in an increase of gastric emptying [41]. Other common GI complications include fecal impaction, c ulcers, megacolon, small bowel dilatation, and hemorrhoids [78].

1.2.5 Sexual dysfunction

Sexual function following SCI is also determined by level and severity of injury. Male sex organs are innervated by three separate sets of nerves; the pelvic nerves (parasympathetic), the hypogastric nerves (sympathetic) and the pudendal nerves (somatic). Normal sexual function sees the coordination of systems responsible for erection, orgasm, and ejaculation. However, after SCI, coordination of these independent systems is impaired [79]. Erection is achieved when the arterioles that supply the erectile tissue of the corpus cavernosum are dilated. This occurs through norepinephrine (NE) inhibition (inhibition of vasoconstriction) and cholinergic activation (vasodilatation) via inhibition of NE and increasing nitric oxide release, both of which contribute to vasodilation. Similar to bowel function, UMN and LMN lesions behave differently. Reflexogenic (response to touch) erections, though often insufficiently rigid or poorly sustained, are achievable in 95% of males with complete UMN SCI, while psychogenic erections are often not [80]. The reverse is true for LMN lesions. Regardless, because of the coordination involved with ejaculation, anterograde ejaculation is not possible in SCI without the use of electroejaculation or vibrostimulation therapies [81]. These sperm

retrieval therapies can be a potent trigger for AD in susceptible males and thus add to the burden of autonomic injury [31,81].

It should be noted that SCI predominately effects males (79%) and therefore literature on sexual function following SCI is dominated by males. Coupled with the societal misrecognition of normal female sexual function beyond reproduction, there is little (in comparison) research aimed at improving female sexual function following SCI [82]. The literature that exists contains small sample sizes and is largely survey-based data. Nonetheless, SCI has been shown to impair both arousal and orgasm in women [82]. However, despite sexual dysfunction, the largest sexual concerns for women with SCI relate to problems associated with urinary and bowel accident (provoked by vaginal or anal penetration during intercourse) and concerns around sexual activity provoking AD [80–82]. Despite having no effect on fertility, sensory loss associated with SCI has been shown to be problematic during gestation and childbirth [83]. Childbirth is also a potent trigger for AD [84].

Of note, the resolution of cardiovascular changes accompanied with sex may take longer than pre-injury, especially in the presence of AD [85]. This evidence underscores the need for proper management and mitigation of AD throughout its myriad of triggers.

1.2.6 Impaired thermoregulation

In addition to bladder, bowel, GI, and sexual functioning, thermoregulation is also impaired after high-level SCI and can be attributed to alterations in body composition, circulation, energy expenditure, sweating, and shivering responses [33,86–88]. These alterations are caused by changes to sudomotor, vasomotor, and pilomotor function as a result of disruption to afferent and efferent pathways. Changes in thermoregulation are, in part, influenced by alterations in autonomic control. After injury there is a significant loss of muscle mass, which can be attributed to impaired mobility and increased sedentary time. This changes the proportion of fat free mass, resulting in increased adiposity [89]. This increased fat mass changes heat conductance, causing high thermal resistance [86]. Additionally, changes to mobility and body composition decrease an individual’s basal metabolic rate [86].

In addition to compositional changes, impaired afferent and efferent signalling further exacerbates thermoregulatory control. Acutely, ‘quad fever’ (a condition where body temperature is elevated and unrelated to fever, infection, or other likely cause) typically presents in the first few weeks following injury [88,90]. Chronically, impaired blood pressure control and resting hypotension leads to decreased arterial diameter below the level of injury [86]. A decrease in arterial diameter changes thermoregulatory processes mediated by vasodilation, as a decreased arterial diameter will result in a decreased heat transfer between the core and periphery. Additionally, impaired sudomotor function decreases the ability of individuals with SCI to sweat below the level of lesion, predisposing to increased core temperature [86]. These processes predispose individuals to a higher risk of heat stress. Conversely, the loss of afferent signals from peripheral cold sensors impairs an individual’s ability to increase body temperature through shivering [86,91]. Much like sweating, shivering can only occur above the level of lesion. Impaired heat transfer, sudomotor and shivering responses explains the higher incidence of hyperthermia and hypothermia in SCI populations compared to able bodied populations, with level-dependent severity [33,91].

These vasomotor, sudomotor, and compositional changes influence, and are influenced by several other secondary complications after SCI including those beyond the scope of autonomic dysfunction. Of note to this thesis, it is important to recognise the inherent interplay of these autonomic-specific dysfunctions after SCI.

1.2.7 The interplay of autonomic dysfunction after SCI

The impact of SCI on numerous interrelated autonomic systems has a profound effect on physiological functioning. These aforementioned complications occur concurrent to each other and many other conditions with widespread impacts on numerous interrelated aspects of physiological functioning. There is an inherent interplay between direct and potent triggers of autonomic dysfunction and the several systems regulated by different branches of the autonomic nervous systems. In a broad classification of autonomic processes, SCI can be seen to affect cardiovascular function, bladder and bowel processes, as well as both GI and sexual functions [92] and thermoregulation. The impact of SCI on GI motility can lead to bowel impaction [68,78], which serves as a potent trigger for AD, and can result in a cascade of cardiovascular events. Likewise, sex can serve as a potent trigger for AD for both males and females [31,79,81,82]. Additionally,

women have reported sexual penetration as a potential trigger for accidental defecation (much like the effects of direct digital stimulation) [81] showing a relationship between the different classifications of autonomic dysfunction described above. SCI often presents with motor spasm [54] which also has the potential to severely impact both GI and sexual function and can be a trigger for AD.

Although the entire complexity of autonomic dysfunction extends far beyond the scope of this thesis, it is important to contextualize these investigations. Improvements to autonomic dysfunction investigated in my work has the potential to extend far beyond the potential immediate benefits. Improvements to autonomic dysfunction would inevitably lead to an increase in quality of life – surveys have shown that individuals with SCI prioritize the need for improved autonomic control before motor and sensory function [6].

1.3 Assessment of autonomic injury after SCI

While there are a wide range of autonomic function tests available for both clinical and research settings, not all are appropriate for use assessing autonomic injury after SCI. Given the motor and sensory deficits that are present after injury, and the medically intensive nature of the acute management of SCI, the tests employed must be practical in addition to being highly specific, sensitive, and clinically informative. The methods for the quantitative assessment of autonomic function after SCI outlined below are applicable given the realities of living with an SCI. The use of these tests is practical and informative without being cumbersome, which should be a consideration for the standardization of the quantification of autonomic function testing after SCI for both individuals with SCI and clinicians.

1.3.1 Quantification of autonomic function after SCI

Sympathetic skin response

A common non-invasive assessment of sympathetic autonomic activity is the evaluation of sympathetic skin responses (SSR). SSR tests use electrical stimulation to activate sympathetic sudomotor activity by provoking both pre- and post-ganglionic sympathetic sudomotor pathways in addition to supraspinal sudomotor control [93,94]. An absence of sudomotor activity indicates disruption of either central or peripheral sympathetic signaling, and such the results of this test are binary, indicating either a

presence or absence of response. It has been shown that the absence of SSR is seen during the presence of AD, underscoring the usability of this technique to assess autonomic function after SCI [31]. It is important to note that while this test assesses cholinergic sympathetic function, its results are often extrapolated to address adrenergic function as well [94]. Despite its usability [31,94–96], this test has several limitations, most notably that test ambiguity proves to be challenging as there is no clear result if tests are atypical in any way (largely due to its binary scoring). In addition, it is more typical that palmar or plantar recordings are performed, further limiting the usability of this test to clearly determine the extent of autonomic injury. This technique also assumes that no efferent impairment (e.g., peripheral neuropathy) is present. Given the high prevalence of diabetes in individuals with SCI [54], the utility of this test within this population should be considered.

Muscle sympathetic nerve activity

It is also possible to take direct recordings of sympathetic nerve activity. Muscle sympathetic nerve activity (MSNA) uses a single non-bioreactive (usually tungsten) electrode to directly record sympathetic nerve activity [97,98]. Recordings are quite commonly acquired in the peroneal (fibular) nerve, although any peripheral nerve that can easily be accessed and is sizable enough to support the electrode can be used [98,99]. These recordings allow for the quantification of sympathetic bursts (both magnitude and frequency), which can be compared at baseline and during sympathetic challenge [98,100]. This test requires considerable technical skill to ensure quality MSNA sampling. In addition, any underlying autonomic pathophysiology is difficult to characterize from MSNA. MSNA Is most commonly conducted in the peroneal nerve but can be performed in the radial, median, or ulnar nerves [98–100], which, in the case of some individuals with SCI, could allow for MSNA recordings to capture sympathetic nerve activity both above and below the level of injury. However, much like SSR, the absence of assessment in the trunk region limits the specificity of this test to determine the extent of autonomic injury after SCI. Interestingly, direct recording of vagal nerve activity is currently being explored using this same approach [101]. It is possible that these investigations, in combination with comprehensive sympathetic function testing, can provide insights into the mechanism of vagal predominance commonly seen after severe impairment to descending sympathetic pathways after SCI.

Plasma norepinephrine

A more clinically relevant assessment of sympathetic activity after SCI is the evaluation of circulating plasma NE [29,102–104]. During activation of the sympathetic nervous system, NE "spills over" into the plasma from sympathetic nerve activity regulating peripheral resistance [105,106]. In healthy able-bodied individuals, circulating levels of NE are largely reflective of post-ganglionic NE spillover [106]. Intensity-dependent increases in plasma NE are seen with graded sympathetic stress, while sympathetic inhibition reveals large decreases in plasma NE [107]. Given that high-level SCI results in severe autonomic impairment and interrupts neural signal transmission to efferent pre-ganglionic sympathetic fibers, high-level SCI results in low circulating plasma NE levels that do not increase in the face of sympathetic challenge [29,55,103]. However, this test is invasive and not without its limitations. This test provides an indication of global autonomic function that, while informative, is limited in its specificity in SCI populations. Additionally, levels of plasma NE are related to both the spillover from post-ganglionic fibers *and* its eventual clearance and reuptake [105–107]. While plasma NE has been correlated with other markers of sympathetic function, alone it is not informative enough for the assessment of sympathetic impairment after SCI.

Heart rate and blood pressure variability

Within the cardiovascular system, the integration of multiple control systems results in significant variability in both blood pressure and HR recordings. Inherent variability is a strong indicator of proper control system integration, underscoring the homeostatic principles needed to maintain, adjust, and adapt these cardiovascular parameters [108]. Both short-term (5-10 minutes) and long-term (24-hour) assessment of both HR and blood pressure variabilities can be informative in the assessment of autonomic function [109–111]. Additionally, the assessment of fluctuations within beat-to-beat measures of HR and blood pressure has shown to be predictive of a range of clinical measures of sympathetic impairment after SCI [29].

The very low (VLF), low (LF), and high (HF) frequency oscillations within both HR variability (HRV) and blood pressure variability (BPV) relate to specific physiological processes and phenomena [109,112–114]. Through the use of autoregressive (AR) spectral analyses (Chapter 2) the relative contributions of these three major frequencies as well as the total power of HRV and BPV can be quantified. The magnitude of these

powers in addition to the location of the central frequency within each frequency band can provide useful information in the assessment of autonomic function after SCI [109].

Of these major frequency bands, VLF oscillations in both HRV and BPV (<0.03 Hz human, <0.1Hz rats) are least understood. In HRV, VLF is thought to be influenced primarily by renin-angiotensin-aldosterone system (RAAS) [115,116] activity in addition to baroreflex-mediated changes to blood pressure. The absence of VLF HRV has been directly linked to all-cause mortality [117]. VLF oscillations in BPV are likely a reflection of myogenic vascular function, mediated by voltage-gated L-type calcium channels, in response to spontaneous perturbations in arterial blood pressure [110,118]. VLF BPV has also been linked to other factors influencing changes to the vasculature including RAAS, thermoregulatory control, and circulating catecholamines [115,119–122].

LF oscillations (0.05-0.15Hz human, 0.4-1.2Hz rats) in BPV reflect vasomotor activity. These rhythmic oscillations have commonly been referred to as Mayer waves [123,124] and are believed to be both centrally and peripherally mediated [125,126]. In BPV, LF oscillations directly reflect sympathetic modulation of the vasculature [111,124,127,128]. Blunted or absent LF BPV reflects impaired cardiovascular autonomic control [129]. There is compelling evidence that BPV can provide a discrete marker of autonomic completeness after SCI [29]. Previous research has shown a strong correlation between plasma NE levels and LF SAP after SCI [29]. Low levels of adrenergic activity are positively correlated with low or absent LF SAP. As LF SAP directly relates to the sympathetic control of the vasculature, this gives further rise to the use of LF BPV as a simple non-invasive alternative to measure sympathetic function after SCI [29]. In HRV, LF oscillations reflect both parasympathetic and sympathetic function as LF HRV is driven by LF BPV through baroreflex-mediated changes in cardiac sympathetic and vagal tone [130,131].

HF oscillations (0.2-0.3Hz human, 1.2-3.0Hz rats) in both BPV and HRV are largely a consequence of respiratory activity [29,114]. Efferent vagal activity is the major contributor to HF HRV, reflecting the vagal influence on cardiac sinus arrhythmia [132–134]. As such, HF HRV is largely reflective of cardiac parasympathetic activity [109]. Additionally, HRV LF-to-HF ratio provides an indication of sympathovagal balance, however, the usability of this metric is debated, with many studies reporting largely overstated conclusions [135]. In regard to BPV, HF oscillations are associated with the

intrathoracic pressure changes associated with the mechanisms of respiration [133]. Baroreflex integration of HR changes induced by cardiac sinus arrhythmia also influences HF BPV [136,137].

1.3.2 Current classification of autonomic function

In 2012, the American Spinal Injury Association (ASIA) and the International Spinal Cord Society (ISCoS) released the first guidelines for scoring autonomic function following SCI [138]. Although this is an improvement to the pre-existing impairment scale (which previously only assessed motor and sensory function) this new addition fails to accurately quantify autonomic function following SCI. We, like the Autonomic Standards Committee responsible for the creation of the International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI), recognize that there is no current clinical standard with which to accurately and quantitatively identify the degree of autonomic dysfunction after injury. Despite its high priority for individuals with SCI, improvements to autonomic control, specifically cardiovascular dysfunction, are lacking and thus a key area for research.

1.4 Impact of bowel management and quality of life

In addition to previous reports on the priorities for individuals with SCI [6], we have documented the profound impact of routine bowel management on quality of life for a large sample of community-dwelling individuals with SCI [43]. Our results suggest there is significant opportunity to improve bowel management to minimize its impact on quality of life. It was clear that a significant proportion of individuals (78%) felt their current bowel management was a problem to them. When compared to other aspects of SCI, difficulties with bowel management were more frequently rated as been one of the worst effects of living with SCI. Impaired sexual function and bladder concerns were also ranked as severe consequences of injury, highlighting the impact of autonomic dysfunctions in general on quality of life after SCI. Living with chronic pain was also ranked as a significant concern. However, aspects such as skin care, spasticity and use of a wheelchair were rated as having much lower effects on individual's lives. This suggests that these aspects have been well managed within this population – they can be areas of significant importance and concern when they are problematic [139,140].

Some of the reasons for the major effect of bowel management on quality of life were highlighted by respondents to our survey [43], with the majority commenting that there was little or no flexibility in their bowel management routine (57%), meaning they had to fit their life around their bowel care (85%). Bowel management was identified as interfering with social activities (70%), personal relationships (60%), as well as staying (62%) and working (41%) away from home (**Figure 1.8**).

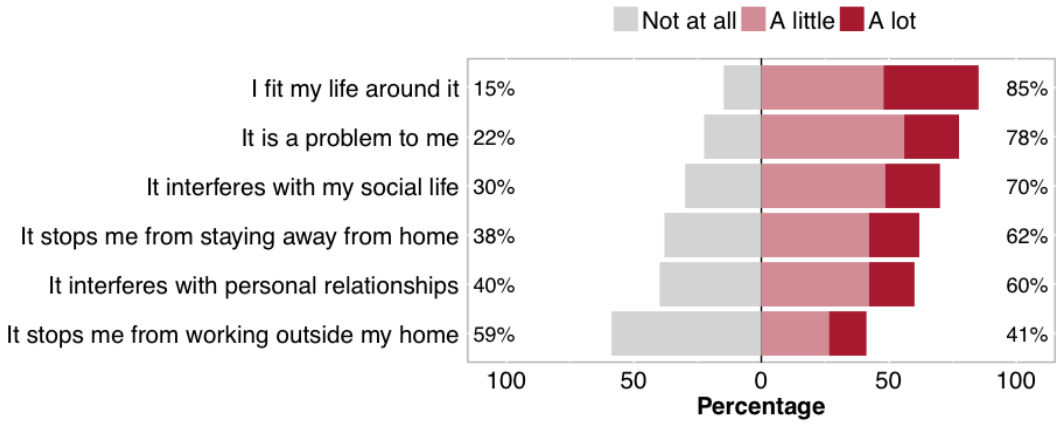

Figure 1.8 – Impact of bowel management on respondents' life and activities.
Individuals with SCI report that bowel care has a profoundly negative effect on quality of life, interferes with their personal and social life, and prevents them working or staying away from home. Adapted from [43]. Used with permission.

What is perhaps most surprising is that, despite the clear concerns raised by the majority of survey respondents about their bowel care, most (71%) have not made any changes to their bowel routine for at least 5 years [43]. These data highlight gaps in bowel management education and raise questions about current guidelines for bowel managent, and where individuals with SCI and their caregivers obtain information about this topic. Formal guidelines are available from agencies such as the Paralyzed Veterans of America [57,74], but these publications can become dated quickly as new medications and equipment arrive on the market. Web-based education material and videos serve the need to remain current and provide engageing and accessible resources [141]. Activity on online SCI resources suggest many people also share and obtain information on bowel care from individuals with SCI and their caregivers [69]. A combination of formal accessible and up-to-date guidelines, with real-time support from health care providers and trained peer counsellers when necessary (either online, over the phone or in person) would seem an ideal combination of resources to provide advice and support for bowel care. This kind of approach has been sucessful in manageing other SCI complications,

including pressure ulcers, depression and hand function [142,143]. Ongoing support and education is essential for continued effective bowel care management, especially as changes in GI function occur over time after injury and with aging, demanding ongoing adaptaions to routine management protocols.

The findings from this survey [43] are consistent with past studies that have also found a decrease in quality of life due to bowel management [44,45]. However, our analysis discovered primary and secondary predictors not yet mentioned in the literature. The primary predictors of a severe impact of bowel care on quality of life after adjustment for confounds were a longer time to complete bowel care, and severe symptoms of AD (**Figure 1.9**). Secondary predictors were high level injuries, more complicated bowel care routines, and more severe fatigue. As noted above, optimising bladder care to limit fluid restriction and so improve fatigue, and implementing strategies to reduce both the time taken to complete bowel care and the number of approaches need to complete bowel care would be key targets to improve quality of life of reduce the severity of AD. Adjunct therapy to further ameliorate symptoms of AD may also be of benefit.

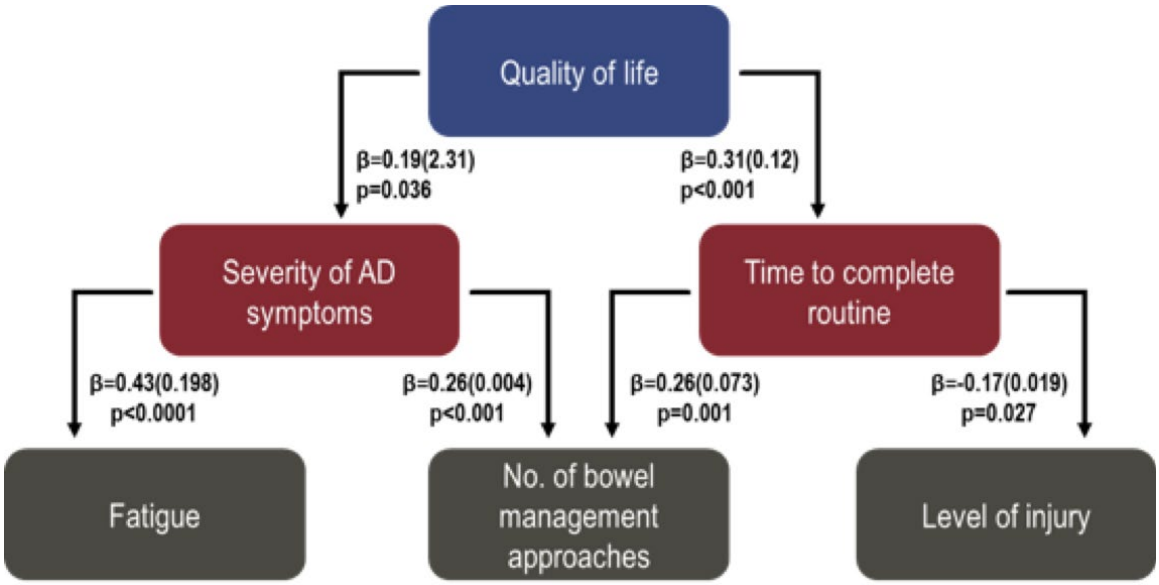

Figure 1.9 – Primary and secondary factors influencing quality of life.
Relationships are expressed as ß (standard error). Primary predictors are shown in red boxes and secondary predictors in grey boxes. Adapted from [43]. Used with permission.

Bowel care and symptoms of cardiovascular dysfunction are a significant concern for individuals living with SCI, with a profound impact on quality of life [43]. Despite these

concerns, most individuals are not making changes to their bowel care, highlighting gaps in bowel management education, and raising questions about current guidelines for bowel management. These data demonstrate the need for better information and resources about this topic for individuals with SCI and their caregivers.

1.5 The need for evidence-based qualitative methods in intervention development

There is overwhelming evidence to suggest that SCI research must shift to focus on outcomes relevant and important to individuals living with SCI [144]. To do so, there is a call for the increased use of mixed methodology. The introduction of qualitative research methods will increase the likelihood that the complex issues facing individuals with SCI can be identified and addressed, as qualitative methods allow for a deeper contextual understanding into the lived experience of SCI [145,146]. Most poignant to this thesis work, qualitative methods into behaviour change allows a deeper understanding of aspects of living with an SCI that cannot be fully captured by quantitative methods. These findings can then inform future studies, allowing researchers to address the most prevalent barriers to care. Additionally, people with SCI urgently need, but lack access to, evidence-based health promotion interventions that respect their unique challenges and barriers to health behaviour change [147–149].

1.5.1 The need for theory-based interventions aimed at behaviour change

Evidence-based qualitative methods and theories can be used to elucidate the factors that influence one's behaviour (**Table 1.1**). Leveraging these factors will inform intervention design, making future quantitative investigations both relevant and feasible. The systematic application of behaviour change theory can be employed to better understand behaviour, as the use of evidence-based behaviour change theory is advantageous when designing, testing, and implementing behaviour change interventions [150]. When used appropriately, evidence-based behaviour change theories increase the relevancy of interventions [151–153]. However, until recently, many behaviour change interventions were developed devoid of theory and frameworks, often using the "It Seemed Like A Good Idea At The Time" (ISLAGIATT) Principle [150,154]. The absence of theory and framework in these interventions results in variable effectiveness [155,156]. This

approach makes it unknowable as to *why* the intervention was effective or not and does not allow for improvements to intervention effectiveness nor does it allow for advances into behaviour change research [150]. To address these issues, recent work has focused on the synthesis of behaviour change frameworks to distill a framework that provides both a theoretical basis and evidence-based conceptual clarity [150,157,158]. Table 1.1 defines the common terminology used in behaviour change research, as described by Michie [150].

Table 1.1 – Common terminology used in behaviour change research.

Term	*Description*
Behaviour	Anything a person does in response to internal or external events. Actions may be overt and directly measurable, or covert and indirectly measurable; behaviours are physical events that occur in the body and are controlled by the brain.
Behaviour change intervention	An activity or co-ordinated set of activities that aims to get an individual or population to behave differently from how s/he or they would have acted without such an action
Behaviour change technique	An active component of an intervention designed to change behaviour. The defining characteristics of a behaviour change technique are that it is observable, replicable, irreducible, a component of an intervention designed to change behaviour and a postulated active ingredient within the intervention.
Construct	Objects, events, characteristics, or processes
Framework	A conceptual scheme
Intervention function	Functions served by an intervention targeting factors that influence behaviour. In the Behaviour Change Wheel these are defined broadly on the basis of labels and descriptors previously used in the literature.
Model	A specification of a set of elements or constructs and inter-relations between them that represent an object or system in the world outside of itself. It can be used to predict, explain or simply describe a set of events or phenomena.
Target behaviour	The behaviour targeted either for change (in the context of intervention design) or to be understood (in the context of understanding an implementation problem)."
Taxonomy	A classification of constructs (e.g. objects, events, characteristics, processes etc.), typically involving hierarchical associations between categories.
Theory	A model (or set of models) that aims to explain and predict phenomena

Adapted from [150].

The behaviour change wheel

The Behaviour Change Wheel (BCW) (**Figure 1.10**) provides the much-needed clarification among the abundance of overlapping constructs and theories within behaviour change research [157]. The BCW was developed through the systematic review and synthesis of 19 behaviour change frameworks and provides a theory-based method for intervention development [157]. The BCW provides conceptual clarity as it synthesizes several theoretical constructs, accounting for redundancy and relevancy . This framework includes a theory-driven, evidence-based three-stage process for intervention development: (1) understanding the behaviour; (2) identify intervention options; (3) identify content and implementation options [159]. To first understand behaviour (stage 1) the behaviour must first be identified, and a behavioural analysis and diagnosis conducted (see Chapter 2, General Methodology). This behavioural analysis should aim to deepen the understanding of factors influential to the target behaviour or desired outcome, in particular assessing the capability (psychological or physical), opportunity (physical or social), and motivation (automatic or reflective) serving as barriers or facilitators to engaging in the target behaviour [150,157,159]. Collectively, these three interacting determinants of behavioural analysis are integral components to the Capability, Opportunity, Motivation – Behaviour (COM-B) Model for intervention development. The COM-B Model forms the innermost ring of the BCW (**Figure 1.8**) [157].

In order to identify intervention options, the components of the COM-B model have been linked to nine intervention functions and seven policy categories using the BCW [157]. These intervention functions found in the mid-layer of the BCW have been linked to commonly used behaviour change techniques (BCT, the active components of an intervention) that can be utilised in interventions to improve effectiveness of the results. Descriptive taxonomies of BCTs and their usage has been extensively published, most notably the Behaviour Change Technique Taxonomy Version 1 (BCT Tv1) [160]. The BCT Tv1 is a structured taxonomy of 93 distinct BCTs which offers a reliable method for the specification, interpretation, and implementation of these active components of interventions [160,161]. Once intervention functions have been identified using the BCW, appropriate BCTs can be identified to be used within the intervention [150,160]. In addition, the outer layer of the BCW consists of seven policy categories that can be used to deliver the intervention functions [150].

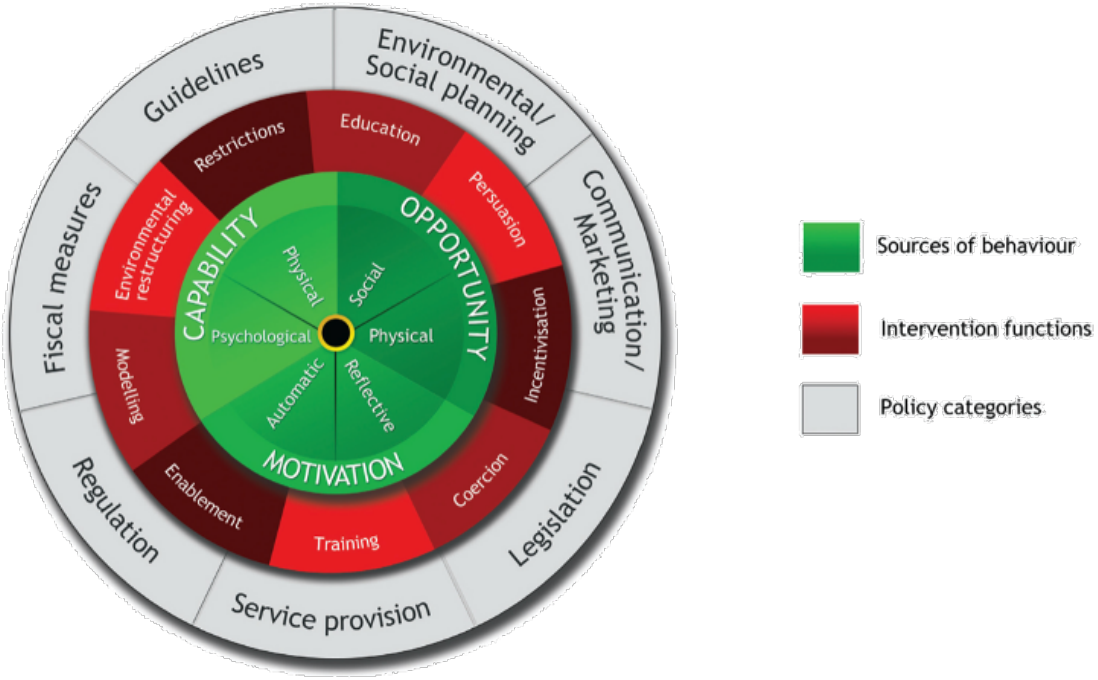

Figure 1.10 – The Behaviour Change Wheel
The BCW uses the Capability, Opportunity, and Motivation – Behaviour model framework (green circle) to understand behaviour. The components of the COM-B model have been linked to nine intervention functions (red; broad methods for intervention) and seven policy categories (grey; methods for enacting intervention functions). Adapted from [150,162]. Used with permission.

To more closely assess how barriers and facilitators influence behaviour, the COM-B model can be further expanded into fourteen domains using the theoretical domains framework (TDF) (**Figure 1.11**) [163,164]. The TDF is an integrative framework with 14 domains, produced from the synthesis of over 80 constructs across 33 psychological theories, to broadly understand the influences of behaviour [150,164]. These 14 domains of the TDF include knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory, attention, and decision processes; environmental context and resources, social influences, emotion, and behavioural regulation. The TDF has been linked to the COM-B Model through expert consensus [163]. By mapping barriers and facilitators of behaviour into TDF domains, interventions can be tailored through the BCW to create relevant, informed interventions.

Figure 1.11 – The Theoretical Domains Framework.
There are 14 domains (yellow circle) of behaviors which can be broadly grouped (center, green circle) into those that influence an individuals' capability (both physical and psychological), opportunity (considering both social and physical factors) and motivation (incorporating both automatic and reflective components) to make a behavior change. Abbreviations: Soc, social influences; Env, environmental context and resources; Id, social/professional role and identity; Bel Cap, beliefs about capabilities; Opt, optimism; Int, intentions; Goals, goals; Bel Cons, beliefs about consequences; Reinf, reinforcement; Em, emotion; Know, knowledge; Cog, cognitive and interpersonal skills; Mem, memory, attention and decision processes; Beh Reg, behavioral regulation; Phys, physical skills. Adapted from [163]. Used with permission.

Together the BCW and the TDF provide a systematic method to link behavioural outcomes to both invention functions and policy categories (**Figure 1.12**). As noted above, individuals with SCI are not making changes to their bowel care practices, despite high levels of dissatisfaction. The use of behaviour change theory, in particular, the BCW and the TDF can guide investigations into the barriers and facilitators to changing bowel care providing information that will inform interventions into mitigating profound effect bowel care has on quality of life.

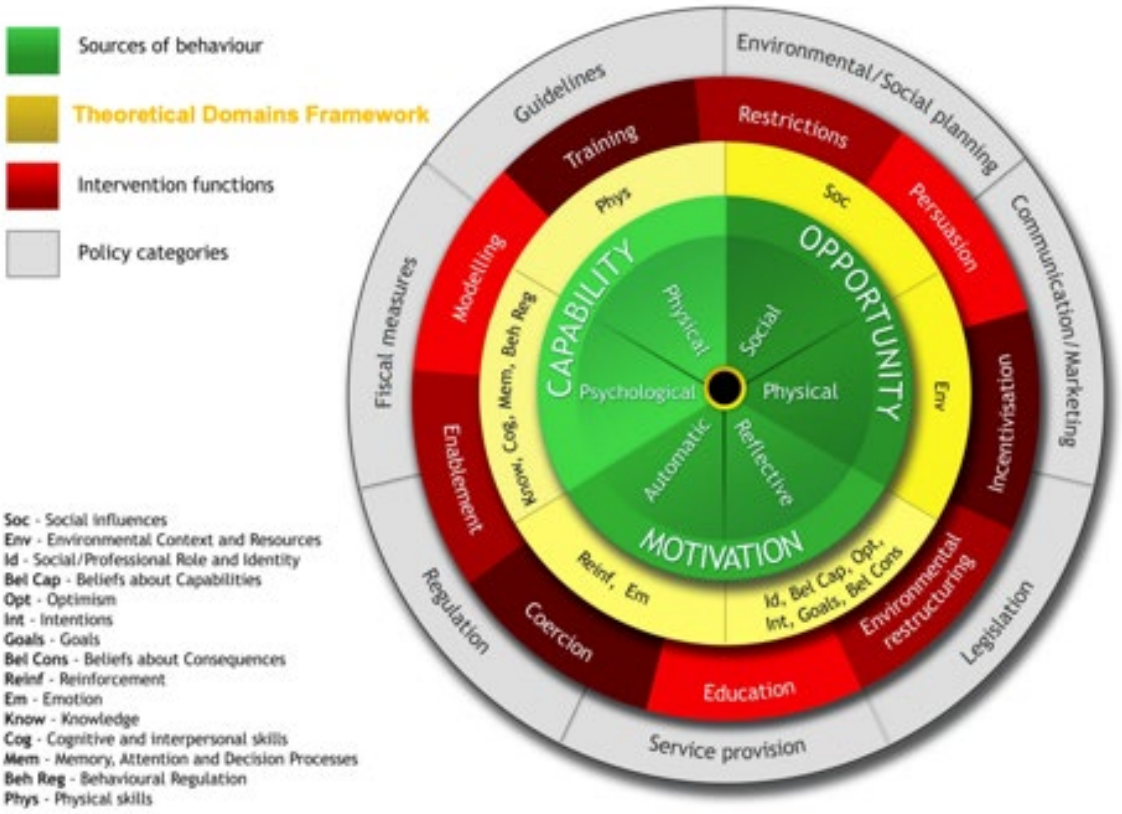

Figure 1.12 – The behaviour change wheel and theoretical domains framework
There are 14 domains (yellow circle) of behaviors which can be broadly grouped (green circle) into those that influence an individuals' capability (both physical and psychological), opportunity (considering both social and physical factors) and motivation (incorporating both automatic and reflective components) to make a behavior change. Once barriers and facilitators for modification have been identified, such as a novel bowel management approach, it can then be modified using the approaches identified (red circle) such as education, incentivisation, or enablement, and translated into novel healthcare policies (grey circle). Abbreviations: Soc, social influences; Env, environmental context and resources; Id, social/professional role and identity; Bel Cap, beliefs about capabilities; Opt, optimism; Int, intentions; Goals, goals; Bel Cons, beliefs about consequences; Reinf, reinforcement; Em, emotion; Know, knowledge; Cog, cognitive and interpersonal skills; Mem, memory, attention and decision processes; Beh Reg, behavioral regulation; Phys, physical skills. Adapted from [163]. Used with permission.

1.5.2 Knowledge-to-action framework

Intervention development should also be guided by an established knowledge-to-action framework originally developed to provide conceptual clarity regarding the key elements of the knowledge translation process [165,166]. The framework divides this complex and dynamic process into two interacting phases: knowledge creation and action (**Figure 1.13**). This framework has been adopted by Canadian funding agencies as part of their effort to increase knowledge translation activities [165].

In the knowledge creation phase, evidence from primary research studies is distilled and refined using dynamic knowledge syntheses to create knowledge products or tools. These tools are then translated and applied via the action cycle. Given that current guidelines exist, while being continually evaluated, regarding appropriate bowel care strategies for people with SCI (knowledge creation) [57,74], the development of theory-based interventions may help ensure these guidelines are adopted by target audiences (forming an action cycle). Stage three of intervention development is a key component of the action cycle [150,159].

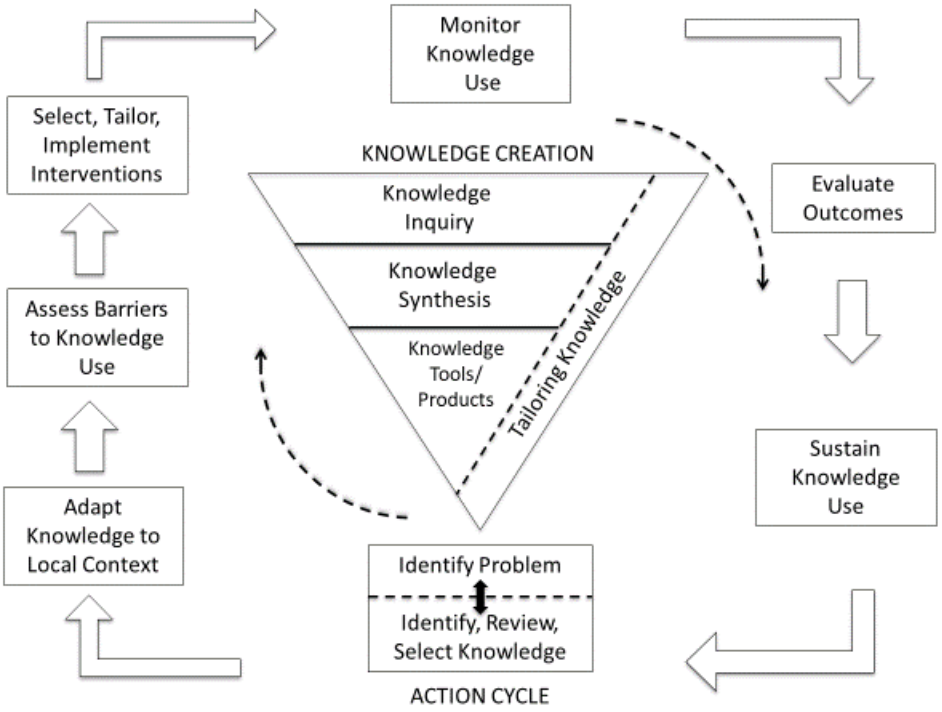

Figure 1.13 – The knowledge to action cycle
In the knowledge creation phase (center triangle), evidence from primary research studies is synthesized and tailored to identify problems to address. These tools are then translated and applied via the action cycle. Adapted from [166]. Used with permission.

1.5.3 The importance of using an integrated knowledge translation approach

Knowledge translation is a dynamic and iterative process. The knowledge creation phase of the knowledge-to-action framework (creation, distillation, and dissemination of knowledge) does not guarantee evidence-based decision making [165,166]. Integrated knowledge translation is an approach to research that engages research users as equal partners alongside researchers throughout the entire research process, resulting in

research that is applicable, useful and translatable to end-users [167]. While integrated knowledge translation is increasingly being considered a gold-standard knowledge translation approach, there are few studies that examine the translation and implementation of health research in SCI, and few examples of knowledge translation interventions that aim to change evidence-based practice and improve health outcomes [168]. SCI researchers and research users have expressed concern that, rather than working in partnership, often individuals with SCI are asked only to endorse and legitimize research programs over which they have little real control. Recently, SCI researchers and community partners co-developed the first integrated knowledge translation guiding principles for conducting and disseminating SCI research in partnership with research users [144]. The eight guiding principles include that all partners: (1) develop and maintain relationship based on trust, respect, dignity, and transparency; (2) share in decision making; (3) foster open, honest, and responsive communication; (4) recognise, value, and share their diverse expertise and knowledge; (5) are flexible and receptive in tailoring the research approach to match the aims and context of the project; (6) can meaningfully benefit by participating in the partnership; (7) address ethical considerations; and (8) respect the practical consideration and financial constraints of all partners [144]. To avoid tokenism and ensure health research is applicable, useful and translatable to end-users of SCI research, enhanced integrated knowledge translation partnerships need to be prioritized.

1.6 Thesis outline and project aims

This thesis aims to assess and classify cardiovascular autonomic dysfunction following SCI, in addition to investigating both current clinical care guidelines and the barriers and facilitators to effecting change in common care routines. These findings are aimed at increasing the ability to accurately diagnose cardiovascular autonomic injury while evaluating both how current care guidelines perform, and the best approaches to enhance care. In addition to this introductory chapter and an overview of general methodology (Chapter 2), this thesis includes four experimental chapters (Chapters 3-6) and a general discussion outlining major findings, thesis limitations, and future directions (Chapter 7). This thesis was written primarily as independent manuscripts. The experimental chapters were undertaken as singular, yet complementary projects. Their placement in this thesis was meant to guide the reader as to their rationale for undertaking.

However, these manuscripts can be read in isolation and are not contingent on reading in order. The general discussion (Chapter 7) explores their findings in relation to each other. Below is a description of aims for each experimental chapter, in addition to publication and author information. With regards to publication and authorship, portions of this introductory chapter were taken from:

Inskip JA*, **Lucci V-EM***, McGrath MS, Willms R, Claydon VE. (2018). A community perspective on bowel management and quality of life after spinal cord injury: the influence of autonomic dysreflexia. *J Neurotrauma*; 35(9):1091–1105.

***Contributed equally**

1.6.1 Chapter 3

A longitudinal assessment of autonomic function during the acute phase of spinal cord injury: use of low frequency blood pressure variability as a quantitative measure of autonomic function

This chapter aimed to assess cardiovascular dysfunction during, and beyond, the first year following SCI. We evaluated whether cardiovascular dysfunction in the acute phase of injury is predictive of long-term cardiovascular health. This work was peer-reviewed and published:

Lucci V-EM, Inskip JA, McGrath MS, Ruiz IA, Lee R, Kwon BK, et al. (2020). A longitudinal assessment of autonomic function during the acute phase of spinal cord injury: Use of low frequency blood pressure variability as a quantitative measure of autonomic function. *J Neurotrauma*;13:1–13.

1.6.2 Chapter 4

Clinical recommendations for use of lidocaine lubricant during bowel care after spinal cord injury prolong care routines and worsen autonomic dysreflexia: results from a randomised clinical trial

This chapter aimed to determine whether use of a topical anesthetic (lidocaine) ameliorates cardiovascular changes triggered by bowel care. We also evaluated whether lidocaine use has a negative impact on the duration of the bowel routine through impaired reflex defecation with afferent blockade, in addition to its effect on perceived symptoms of

cardiovascular dysfunction following SCI. An account of this work has been peer-reviewed and published:

Lucci V-EM, McGrath MS, Inskip JA, Sarveswaran S, Willms R, Claydon VE. (2020). Clinical recommendations for use of lidocaine lubricant during bowel care after spinal cord injury prolong care routines and worsen autonomic dysreflexia: results from a randomised clinical trial. *Spinal Cord;* 58(4):430–40.

1.6.3 Chapter 5

Barriers and facilitators to changing bowel care practices after spinal cord injury: a theoretical domains framework approach.

This chapter aimed to examine barriers and facilitators to making changes to optimize bowel care for individuals with SCI, and identify preferred formats for disseminating bowel care guidelines. This work has been assessed by co-authors and is currently a manuscript in preparation:

Lucci V-EM, McKay R, McBride CB, McGrath MS, Willms R, Gainforth HL, Claydon VE. *In preparation*. Barriers and facilitators to changing bowel care practices after spinal cord injury: a theoretical domains framework approach.

1.6.4 Chapter 6

Markers of susceptibility to cardiac arrhythmia in experimental SCI and the impact of sympathetic stimulation and exercise training.

This study aimed to examine the effects of high-level (T2; at risk for AD) and low-level (T10; not at risk for AD) SCI on ECG parameters using a rodent model. Additional aims examined the impact of dobutamine (a sympathomimetic drug used as a proxy for AD) on electrocardiographic parameters in these animals, and whether exercise training initiated after injury affected these responses. This work has been reviewed by co-authors and, at the time of writing, is prepared for imminent submission:

Lucci V-EM, Harrison EL, DeVeau KM, Harmon KA, Squair J, Krassioukov A, Magnuson DSK, West CR, Claydon VE. *In preparation.* Markers of susceptibility to cardiac arrhythmia in experimental SCI and the impact of sympathetic stimulation and exercise training.

1.7 Research position and approach

In addition to the concepts outline above, it is important to note my position as a researcher. This approach is common in qualitative research but lends itself well to my position as an SCI researcher throughout this thesis.

I am neither an individual living with SCI, nor a caregiver for someone with an SCI, and as such I recognise that I do not have first-hand knowledge of the unique challenges after SCI, their implementation, and impact on other aspects of life. However, having researched this area extensively, interacted with individuals living with SCI both socially and professional, having witnessed and discussed several aspects of daily care, I have been provided a unique perspective to appreciate the sensitivity and the importance of this work.

My central training as a cardiovascular physiology researcher has been from a largely positivist school of thought, holding firm to the belief that the reality of quantitative research is singular, tangible, and objective [169]. However, parts of this thesis (Chapter 5) have taken a pragmatic approach [145,169]. The reality of SCI is that every individual's circumstance is unique. One of the largest hurdles in SCI research stems from the inherent heterogeneity of SCI. Combined with the research questions I have asked in Chapter 5, this deviates from a belief that experiences conform to a single truth and calls for a pragmatic approach, whereby several truths can be determined through the use of a systematic approach to the data [170]. Pragmatism focuses on research utility when solving practical, "real world" problems, and also calls for flexible investigative techniques and cross-disciplinary collaboration [170]. These aspects of pragmatism lend well to both our integrated knowledge translation approach and the reality of living with an SCI.

Chapter 2

General methodology

This chapter explores the methodology used in subsequent experimental chapters. Here the reader will find in-depth descriptions for both quantitative and qualitative methods employed in this thesis work.

2.1 Quantitative methods

2.1.1 Finger plethysmography for the evaluation of non-invasive beat-to-beat blood pressure

Continuous beat-to-beat blood pressure recordings are essential for the proper evaluation of cardiovascular reflex control. Intra-arterial blood pressure measurement is the current gold-standard for continuous blood pressure management. However, this method is invasive and not favourable for most translational clinical research [171]. As such, continuous *non-invasive* beat-to-beat blood pressure through using finger photo-plethysmography is a common surrogate for intra-arterial blood pressure. This technique has been extensively validated for use in clinical research [172,173].

Based on the principles of Peñàz [174], this technique for non-invasive beat-to-beat blood pressure recording uses infrared photo-plethysmography combined with volume clamping (**Figure 2.1**). In this method, an inflatable cuff is placed on the intermediate phalanx of the third digit. On opposing sides of the cuff lies a light source and an infrared detector. As light is emitted from the light source, the detector senses changes in light absorption by the blood during systole and diastole. Volume clamping (controlled by the inflatable cuff via a rapid servo-controller system that integrates the light transmission) allows for the diameter of the artery to be kept constant irrespective of changes in arterial pressure with each successive heartbeat [175]. Keeping the finger in this state of “vascular unloading” means the pressure within the cuff is then equal to the arterial pressure in the finger [176]. This finger pressure is then reconstructed using validated algorithms to determine the brachial pressure, given that the systemic pressure gradient require accounting for pulse wave amplification to reconstruct the brachial waveform from the finger waveform [173].

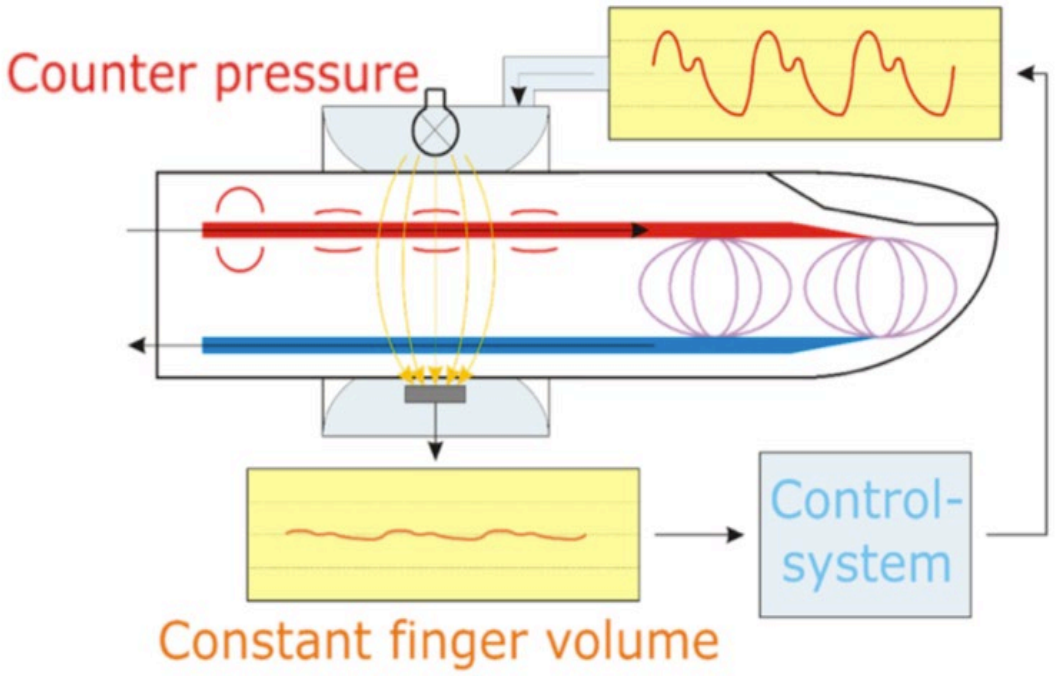

Figure 2.1 – Finger plethysmography with volume clamping
The infrared light source detects the diameter of the blood vessels while the inflatable bladder maintains a constant diameter of the blood vessels. The counter pressure within the cuff is equal to the arterial pressure in the finger, which is then converted into brachial arterial pressure using a servo-control system. Adapted from Prof Bondi, CC BY SA 3.0, 2012. Licensed as CC BY SA.

The continuous blood pressure recordings in this thesis were taken using Finometer Model 2 *Midi* (Finapress Medical Systems B.V., Amsterdam) and sampled at a collection frequency of 200Hz. Unlike the Model 1 (Finometer Pro), the Midi does not use return-to-flow calibration [173]. However, the use of this device allowed for these studies to be conducted within the community and its portability was essential. Calibration was conducted both internally using Physiocal [177] (an algorithm that recalibrates the set-point to reduce measurement drift over time) and externally using a manual brachial blood pressure measurement with a sphygmomanometer. Calibration was performed during baseline recordings. Any discrepancies between manual recording and continuous recording were noted and accounted for in offline analyses. Hydrostatic pressure changes in the hand relative to the heart were accounted for by a height correction unit [172].

Hemodynamic estimations using Modelflow

Modelflow, a pulse contour analysis algorithm included in Finometer software, was used in this thesis to determine Q and SV [178]. This model estimates these components of aortic flow using three elements; aortic characteristic impedance (Z_o), arterial

Windkessel compliance (C_w) (both derived from aortic pressure-area relationships) and estimated peripheral resistance (R_p; ratio of average pressure to average flow) [178]. This model is designed so that Z_o and C_w are non-linearly dependent on pressure. Participant demographics (age, sex, height, and weight) refine values for Z_o and C_w, while R_p is determined from the current beat to estimate the successive beat. Flow can be simulated through modelling these parameters using measured pressures of R_p [178]. Integration of the model during systole accurately quantifies SV [179–181]. Q is then determined as the product of SV and HR, which is derived from successive pressure waveforms. Total peripheral resistance (TPR) can then be determined as the product of mean arterial pressure (MAP) and Q. This model assumes that the participant has a normal aorta and a properly functioning aortic valve and has been validated through the use of thermodilution [178].

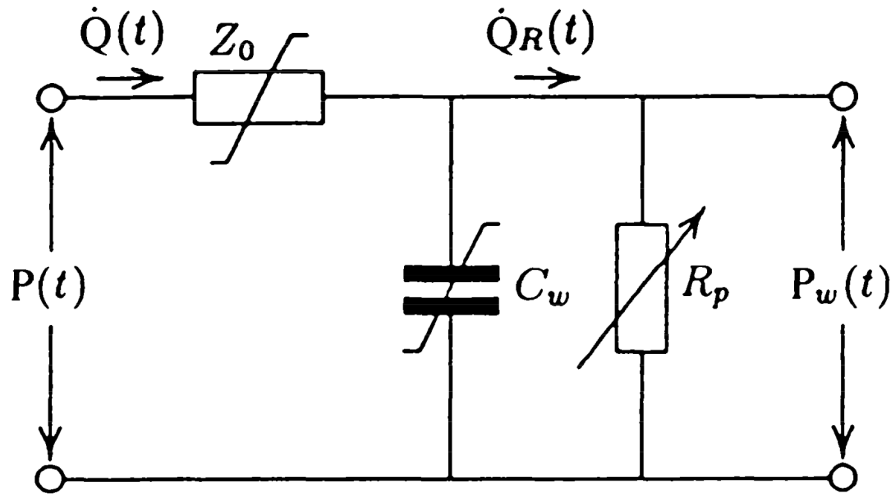

Figure 2.2 – Diagram of 3-element model used in Modelflow
Z_0 and C_w, have nonlinear, pressure-dependent properties, varies with time (symbolized by arrow). Abbreviations: Z_0, characteristic impedance of proximal aorta; C_w, windkessel compliance of arterial system; R_p, total systemic peripheral resistance. Q(t), blood flow as function of time; P(t), arterial pressure waveform; P_w(t), windkessel pressure. Adapted from [178]. Used with permission.

2.1.2 ECG interval detection for the assessment of cardiac arrhythmia risk

Electrocardiogram (ECG) recordings were all taken using a 3-lead (lead II) configuration. As lead II views the conducting system, and shows a prominent p-wave where the mean electrical axis is normal, this view was most informative for risk detection [182]. Risk detection was conducted using customized software [30] (LabView 2010,

National Instruments). This customized software mathematically detects elements of successive ECG characteristics from R-spike to R-spike. The R-spikes are determined from the ECG by taking the maximum amplitude of the derivate of the ECG signal from the point of zero slope. Next, the T peak is determined from the maximum value of the third order polynomial applied to a selection of data preceding the R-spike, while the T end is determined from the point of intersection for two regression lines, one starting at T peak, and the other starting from a specified location after T peak. Q was determined from the minimum value of the 3rd order polynomial applied to a selected section of data preceding the R-spike. Using the detection of Q as reference, P peak, P start, P end were all located in the same manner as for T-wave parameters. Selections of data considered for parameter determination differs between human and rodent ECGs, both of which were assessed in this thesis. Table 2.1 outlines the windows of data considered for the relevant ECG parameters.

Table 2.1 – Selections of data used for ECG parameter detection

Parameter	Human ECG	Rat ECG
Length back from R to find Q	50ms	12ms
Window to find Pstart back from R	200-100ms	70-50ms
Window to find Pend back from R	110-60ms	60-40ms
Window to find T_{peak} forward from R	200-300ms	7-20ms
Length forward from T_{peak} to find T_{end}	200ms	40ms

Note: R, ECG R spike; Pstart, start of P-wave; Pend, send of P-wave; Tstart, start of T-wave; Tend, end of T-wave. Abbreviations: ECG, electrocardiogram.

After determining the location of these sites for each successive heart beat, lengths of parameters can be determined; including R-R interval (RRI) for the assessment of HR, P-wave duration (PWD) to assess atrial repolarisation as a surrogate for p-wave dispersion, and Tpeak – Tend interval (T_{peak}-T_{end}), and Q-T interval (QT) as an index of transmural dispersion of repolarization. QT was corrected for HR (QTc) using Bazett's

formula where $QTc(ms) = \frac{QT(ms)}{\sqrt{RR\ (ms)}}$, with QT and RR indicating the length of the QT and RR intervals in milliseconds, respectively [183].

Variability analyses

The variability for each ECG interval parameter was determined using AR spectral analyses. QT variability index (QTVI), a marker of ventricular arrhythmia risk, was determined by the following formula [30,184]:

$$QTVI = log\ 10\ \frac{\left(QT_v/{QT_m}^2\right)}{\left(RR_v/{RR_m}^2\right)}$$

where v and m denote the variability and mean, respectively. Typically, QTVI is a negative number [30,184]. The more positive (closer to zero) the QTVI, the greater the risk for ventricular arrhythmia [30,184].

2.1.3 Spectral analysis

As outlined in Chapter 1, investigations into the frequency domain characteristics of cardiovascular parameters can elucidate both sympathetic and parasympathetic control and offer explanations into their relative contributions. Offline analysis of continuous cardiovascular parameters for the evaluation of HRV and BPV can be analysed in the frequency domain using power spectral analysis [185,186]. To do so, continuous measures of either HR or blood pressure are first converted to a time series of successive beats, then occasional ectopic beats are removed by linear interpolation of adjacent normal beats, and significant trends are removed by subtracting the best polynomial function fitted to the data using low pass filtering [186,187]. Data are then processed by either a fast Fourier transform (FFT) or an AR analysis [109]. FFTs transform time series into the frequency domain after dividing the signal into its constituent x and y vectors. AR, rather, fits a model to the data. Once fitted successfully, a Fourier-like transformation converts the signal into the frequency domain. Using either approach results in the identification VLF, LF, and HF frequency bands. The central frequency, as well as both absolute and percent power at each frequency domain, are determined by computation of the residuals [188].

For any given range of data, but especially true for shorter recording durations, AR provides a better spectral resolution than FFT [109]. AR is also more favourable given its greater ability to distinctly outline frequency bands with reduced noise compared to FFT [109]. However, using AR requires proper model selection prior to running the spectral analysis. Model selection can be difficult and requires more experience to execute properly.

2.1.4 Cross spectral analysis

Baroreflex function is commonly evaluated to further assess the relationship between SAP and RRI. With the loss of descending sympathetic control after high-level SCI, there is a downstream impact on baroreflex integration resulting from the inability to properly relay neural signals responsible for blood pressure control. Cross spectral analyses was used to determine cardiovagal baroreflex sensitivity through the assessment of RRI and SAP time series as a function of frequency following established procedures [29]. These analyses asses the relationship between the two variables, as SAP (as a system input) provokes changes to RRI (system output) through baroreflex integration. To do so, bivariate AR cross-spectral analyses (model order 15) were fitted to time series to model the vector of discrete values of both variables as a linear sum of subsequent activity [112]. At a given frequency this technique quantifies the frequency-related squared coherence, phase shift (degrees), and transfer function gain (TFG) between the two variables [129]. Phase can be converted to time delay in seconds by the following formula:

$$delay\ (s)\ =\ phase\ (deg)\ \left(\frac{frequency\ (Hz)^{-1}}{360}\right).$$

Coherence (range 0 – 1) represents the proportion of covariance between SAP and RRI with 0 indicating no relationship between the two measures, and 1 indicating complete interdependence. A coherence ≥0.5 represents a statistically significant relationship between the two signals, and therefore values are only accepted where coherence ≥0.5 [185]. TFG reflects the sensitivity of system outputs (i.e. HR) when responding to changes in system inputs (i.e. blood pressure). TFG in the LF range signifies the baroreflex activity, while the gain of the HF range signifies sensitivity to intrathoracic pressure changes with respiration.

2.2 Qualitative methods

2.2.1 Questionnaires

Self-reported measures of cardiovascular symptoms after SCI (Chapter 3) and cardiovascular symptoms after bowel care (Chapter 4) were collected using custom questionnaires [189,190]. These questionnaires were adapted from previously published work [43] and can be found in Appendix A.

2.2.2 Behavioural analysis

The qualitative research in this thesis employed the use of theories and frameworks outlined in Chapter 1. Recent investigations into behaviour change use these frameworks to develop the most practical and relevant interventions available [191–194]. The aspects of analysis relevant to this thesis work are outlined below.

Semi-structured interviews

As in quantitative approaches, qualitative investigations into implementation and behaviour change must consider and select the most appropriate study design for the research question. It is suggested studies make use of interviews as the primary data collection tool when little is known about the implementation problem, as is the case in the work described in this thesis [164]. Semi-structured interviews make use of open-ended questions, probing prompts, and theoretically driven inquiries, lending themselves well to gathering a deep understanding of the participant's experience. The use of semi-structured interviews allows researchers to explore the research question in greater detail, therefore collecting richer data [164]. Most often, these interviews are recorded and transcribed verbatim. When used in theory-informed research, semi-structured interviews aimed at gathering a greater understanding of the target behaviour provide abundant insight into the content needed for interventions [164].

This thesis makes use of semi-structured interviews guided by the TDF, which recommends at least 10 interviews, with an additional three interviews that are appraised for the presence of new themes. If new themes emerge, 3 additional interviews are conducted until no new themes immerge (for a minimum of 13 interviews) [164]. The TDF

has also been used extensively to guide other research designs, highlighting the utility of this framework in guiding a myriad of investigations [158,161,194–196].

The TDF interview data can be analysed deductively (top-down, content analysis). Each domain can then be inductively analysed (bottom-up, thematic analysis) to assess for emerging themes. When used together, deductive and inductive analyses summate to form an abductive reasoning approach [150]. Together, these analyses deepen the understanding of the research question and provide a behavioural diagnosis for the target behaviour.

To begin this procedure and identify the factors influencing the target behaviour, excerpts of interview text containing both barriers and facilitators to the target behaviour must be extracted from the interview transcript. As outlined in TDF guidelines, it is common practice this is done by two coders, who independently extract the transcript items corresponding to a pre-determined definition of what qualifies as a barrier or facilitator to the target behaviour [164].

Deductive analysis of barriers and facilitators

Deductive (or content) analyses are initially conducted to group the extracted barriers and facilitators into their respective TDF domains. Text should be coded into the most appropriate domain independently by each coder, for both barriers and facilitators. It is possible that some content may be mapped to more than one TDF domain, which is acceptable [163,164]. Given that disagreements in coding can initially be quite common, coders must meet regularly, discussing and resolving any differences in the coding approach. In doing so, the coders develop a coding manual which not only informs the reliability of the coding going forward, but the reproducibility of the work. In the event that the two coders cannot reach a consensus, an expert coder (someone identified as having extensive knowledge of TDF coding) external to the analysis is consulted [164]. TDF domains with definitions and association constructs can be found in Table 2.2

Table 2.2 – TDF domains with definitions and associated constructs

TDF Domain	Definition	Constructs
Skills (physical, cognitive and interpersonal)	An ability or proficiency acquired through practice	Skills; Skills development; Competence; Ability; Interpersonal skills; Practice; Skills assessment
Knowledge	An awareness of the existence of something	Knowledge (including knowledge of a condition/scientific rationale); Procedural knowledge; Knowledge of task environment
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives	Memory; Attention; Attention control; decision making; Cognitive overload/tiredness
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions.	Self-monitoring; breaking habit; action planning; self-regulation
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting. Identity.	Professional identity; Professional role; Social identity; Identity; Professional boundaries; Professional confidence; group identity; leadership; organisational commitment
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	Self-confidence; Perceived competence; Self-efficacy; Perceived behavioural control; Beliefs; Self-esteem; Empowerment; Professional confidence
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Optimism; Pessimism; Unrealistic optimism; Identity
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation	Beliefs; Outcome expectancies; Characteristics of outcome expectancies; Anticipated regret; Consequents
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way. Enthusiastic commitment/intention.	Stability of intentions; Stages of change model; Transtheoretical model and stages of change
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Goals (proximal/distal); Goal priority; Goal/target setting; Goals (autonomous/controlled); Action planning; Implementation intention
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus.	Rewards (proximal/distal, valued/not valued; probable/improbable); Incentives; Punishment; Consequents; Reinforcement; Contingencies; Sanctions

TDF Domain	Definition	Constructs
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	Fear; Anxiety; Affect; Stress; Depression; Positive/negative affect; Burn-out
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour. Social environment.	Environmental stressors; Resources/material resources; Organisational culture/climate; Salient events/critical incidents; Person x environment interaction
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours. Persuasion.	Social pressure; Social norms; Group conformity; Social comparisons; Group norms; Social support; Power; Intergroup conflict; Alienation; Group identity; Modelling

Abbreviations: TDF, theoretical domains framework, Taken from [150].

Inductive thematic analysis

Inductive analysis provides thematic context within each TDF domain. The domain-specific thematic analyses are conducted by the primary researcher guided by the seminal work of Braun and Clarke [197], whereby a theme is defined as something that "captures something important about the data in relation to the research question and represents some level of patterned response or meaning within the data set". Their established method for thematic analysis includes: (1) data familiarization; (2) generating initial codes (which can be seen as pre-themes or interesting features of the data); (3) searching for themes within codes; (4) reviewing themes; (5) defining and naming themes; and (6) producing a report of the themes [197]. The inductive analysis must go beyond the description of the data – it must make compelling arguments in relation to the research question. The inductive analysis is strengthened by the involvement of the research team as "critical friends", where members of the research team review themes and provide input and suggestions for their refinement [198,199]. Each critical friend should provide their own unique expertise to the research question. It is imperative that the process used for the inductive analysis is explicitly reported and satisfies accepted criteria for qualitative research excellence [197].

Identifying intervention options and policy categories

As previously mentioned, the behavioural diagnosis resulting from deductive and inductive analyses can be linked back to the COM-B model using the BCW, allowing for easy identification of both the relevant intervention functions and policy categories to be used in intervention design [150]. The predominant TDF domains inform the researcher on the most important aspects of COM-B to be considered in intervention design. An initial matrix of COM-B components mapped against intervention functions identifies which intervention functions will be of most use for the target behaviour (**Figure 2.3**). Once intervention functions are identified, they are linked to policy categories using an additional matrix (**Figure 2.4**), allowing for the selection of the most relevant policy category to support in intervention function delivery [150].

	Intervention functions								
	Education	Persuasion	Incentivisation	Coercion	Training	Restriction	Environmental restructuring	Modelling	Enablement
Physical capability					■				■
Psychological capability	■				■				■
Physical opportunity					■	■	■		■
Social opportunity						■	■	■	■
Automatic motivation		■	■	■	■		■	■	■
Reflective motivation	■	■	■	■					

Figure 2.3 – Matrix of intervention functions linked to COM-B components.
Each COM-B component identified as relevant through TDF coding is linked to the intervention function likely to be effective in bringing about that change as indicated in blue. Adapted from [150]. Used with permission.

	Policy categories						
	Communication / marketing	Guidelines	Fiscal measures	Regulation	Legislation	Environmental/ Social planning	Service provision
Education	■	■		■	■		■
Persuasion	■	■		■	■		■
Incentivisation	■	■	■	■	■		■
Coercion	■	■	■	■	■		■
Training		■	■	■	■		■
Restriction		■		■	■		
Environmental restructuring		■	■	■	■	■	
Modelling	■						■
Enablement		■	■	■	■	■	■

Figure 2.4 – Matrix of policy categories linked to intervention functions.
Each intervention function identified as relevant is linked to the policy categories likely to be appropriate and effective in supporting each intervention function, as indicated in blue. Adapted from [150]. Used with permission.

2.2.3 Mode of Delivery analyses

Mode of Delivery (MoD) analyses reveals the preferred ways in which the intervention is delivered and received, describing both *how* the intervention will be delivered and by *whom* the intervention will be delivered. This is in addition to the invention options and policy categories identified through the BCW, which identify what to target in the intervention and not how it will be directly delivered. The delivery of behaviour change interventions (i.e., how BCTs are used to deliver the intervention) is guided by the Mode of Delivery of Behaviour Change Intervention Taxonomy version 0 (MoDTv0) [200,201]. Within transcript data, the identical process used for barrier and facilitator extraction is used to extract and form consensus on desired modes of delivery between two coders based on this taxonomy.

2.2.4 Metrics for inter-rater reliability for deductive analyses

To ensure that barrier and facilitator extraction, TDF deductive coding [164], and MoD coding [201] is consistent with accepted gold-standards of measurement, coding

reliability is assessed. Both barrier and facilitator extraction and MoD analyses should quantify the percentage agreement between coders. If acceptable levels of agreement (>70% agreement) for one-third of the data exist after double-coding, the primary researcher may continue independently extracting/coding the data without double extraction from the other coder.

Inter-rater reliability is calculated to measure the reliability of deductive coding using the TDF. Reliability is established using Cohen's Kappa [202] and prevalence-adjusted bias-adjusted Kappa (PABAK) [203]. Cohen's Kappa is more robust than precent agreement as it considers the possibility of agreement between raters (coders) occurring by chance [202]. However, Cohen's Kappa is highly dependent on prevalence and the distribution of data across categories (TDF domains). To control for this, PABAK assumes fifty percent prevalence of the category and the absence of bias [203]. Comparing the two kappas, PABAK therefore reflects the ideal situation, ignoring variation caused by prevalence. PABAK is most reliable when comparing for two raters, making it an excellent measure of reliability in TDF coding [164,204]. Inter-rater reliability is considered moderate with values between 0.41 – 0.60, substantial with values between 0.61 – 0.80, and almost perfect with values between 0.81 – 1.00 [205]. Specific to the TDF, reliability between coders is acceptable if scores of Cohen's Kappa and PABAK exceed 0.60 [164].

2.2.5 Measure of reliability for inductive analyses

Thematic analyses inherently conform to the idea that multiple truths exist with the data (a constructivist view of the data), making it methodically unsound to make use of the aforementioned measures of reliability within inductive analyses [197,206]. However, there are accepted gold-standard approaches to thematic analysis, as described above [197]. Transparency is paramount in thematic analysis presentation and description, in addition the adhering to measure of rigor in qualitative research. Thematic analyses require regular self-reflection from the primary researcher [207]. Additionally, it is important to have individuals with experience in qualitative methods, interest in intervention design, and knowledge of working with individuals with SCI acting as critical friends throughout the thematic analyses [198,199]. The use of critical friends and an integrated knowledge translation approach in consultation with knowledge users throughout the research process, enhances the rigor, sincerity, credibility, and resonance of the self-reflective inductive analysis [199].

Chapter 3

A longitudinal assessment of autonomic function during the acute phase of spinal cord injury: use of low frequency blood pressure variability as a quantitative measure of autonomic function

3.1 Abstract

High-level SCI can disrupt cardiovascular autonomic function. However, the evolution of cardiovascular autonomic function in the acute phase following injury is unknown. We evaluated the timing, severity, progression and implications of cardiovascular autonomic injury following acute SCI. We tested 63 individuals with acute traumatic SCI (aged 48±2years) at five timepoints: <2 weeks, and 1-, 3-, 6-12, and >12-months post-injury. Supine beat-to-beat SAP and RRI were recorded and low frequency variability (LF SAP and LF RRI) determined. Cross-spectral analyses were used to determine baroreflex function (low frequency) and cardiorespiratory interactions (high frequency). Known electrocardiographic markers for arrhythmia and self-reported symptoms of cardiovascular dysfunction were determined. Comparisons were made with historical data from chronic SCI and able-bodied controls. Most individuals had high-level (74%) motor/sensory incomplete (63%) lesions. All participants had decreased LF SAP at <2 weeks (2.22±0.65mmHg^2). Autonomic injury was defined as high-level SCI with LF SAP <2mmHg^2. Two distinct groups emerged by 1-month: autonomically-complete SCI with sustained low LF SAP (0.76±0.17mmHg^2) and autonomically-incomplete SCI with increased LF SAP (5.46±1.0mmHg^2, $p<0.05$). Autonomically-complete injuries did not recover over time. Cardiovascular symptoms were prevalent and worsened with time, especially in autonomically-complete lesions, and chronic SCI. Baroreflex function and cardiorespiratory interactions were impaired after SCI. Risk of arrhythmia increased immediately after SCI, remaining elevated throughout the acute phase. Acute SCI is associated with severe cardiovascular dysfunction. LF SAP provides a simple, non-invasive, translatable, quantitative assessment of autonomic function, and is most informative 1-month after injury.

3.2 Introduction

It is well appreciated that the cardiovascular autonomic dysfunction that accompanies SCI has profound effects on activities of daily living [6,43], and can manifest with life-threatening cardiovascular conditions [208]. Of particular concern for individuals living with high-level SCI (at or above the sixth thoracic level [T6]), is the inability to regulate autonomic cardiovascular control due to loss of descending control of efferent sympathetic nerves [209]. This often manifests with poor HR and blood pressure control through disruption of sympathetic outflow to the heart and key peripheral vasculature beds that mediate vascular resistance and capacitance responses [208,209]. Accordingly, these individuals are prone to episodes of AD (sudden profound hypertension triggered by sensory stimuli from below the lesion level) [59], OH (hypotension in the upright position) [12], fatigue [52,53], and cardiac arrhythmia [29,210]. However, the progression and evolution of cardiovascular autonomic dysfunction during the first year (acute phase) of SCI is not known. This makes it difficult to predict the severity and time course of the complex cardiovascular consequences of SCI, and complicates their management.

One contributing factor to this gap in the literature may be the lack of a gold-standard *quantitative* method to assess cardiovascular autonomic dysfunction following SCI. Any such tool would need to be suitable for use in individuals in the acute post-injury phase, be able to accurately quantify the severity of injury to autonomic pathways, provide meaningful information concerning the extent of autonomic dysfunction an individual is likely to experience, and be able to track changes in function over time [208]. The quantitative evaluation of beat-to-beat fluctuations in HR and blood pressure (and their interactions) using spectral and cross-spectral analysis can potentially satisfy these criteria for assessing autonomic dysfunction after SCI. These analyses permit quantitative evaluation of cardiac sympathetic and vagal control [211], sympathetic control of the vasculature [29], the sensitivity and delay of the cardiac baroreflex [129,185], and the interactions between respiratory and cardiovascular parameters [129,187]. These analyses are of particular interest because they are well established measures of cardiovascular autonomic function in the able-bodied [109,129,187], and have already been applied to both human [29] and experimental [114] SCI. This provides a useful means to apply results from bench-to-bedside, thus promoting translational discovery

science. Other benefits are the low cost, non-invasive nature, and minimal participation required [187].

Assessment of autonomic function in the acute period after SCI is particularly challenging because of the potential for discordance between motor, sensory, and autonomic injury [17,138] accompanying neurogenic shock (global loss of sympathetic outflow to the peripheral vasculature associated with profound hypotension) initially after injury [208,211,212], and the potential for spontaneous recovery of autonomic pathways due to plasticity [213,214]. We aimed to evaluate whether spectral and cross-spectral analyses of cardiovascular function would be: (i) suitable to track the progression and evolution of injury to cardiovascular autonomic pathways over the first year after injury; (ii) able to identify individuals with severe lesions to cardiovascular autonomic pathways; (iii) associated with symptoms or signs of cardiovascular dysfunction.

3.3 Methods

3.3.1 Ethical approval

This study was approved by the Department of Research Ethics at Simon Fraser University and Vancouver Coastal Health Research Institute. All aspects of this study conform to the principles outlined in the Declaration of Helsinki [215]. All participants provided written informed consent at the time of testing.

3.3.2 Participants

Eligible participants were at least 18 years of age, had recently sustained a traumatic SCI, and were a current inpatient in the Acute Spine Unit at Vancouver General Hospital. Individuals were excluded from the study if they had known cardiovascular or neurological diseases prior to sustaining their injury, cauda equina or conus lesions, diabetes mellitus, and/or were involved in other research studies with clinical interventions. Additional exclusion criteria included medical/psychiatric conditions or substance abuse disorders that were likely to affect their ability to consent to or complete the study, inability to communicate in English, and pregnancy.

3.3.3 Experimental protocol

In this longitudinal study, participants were tested at four time-points during the first year (acute phase) following SCI (**Figure 3.1**): **Visit 1**, 2-14 days post-injury; **Visit 2**, 2-4 weeks post-injury; **Visit 3**, 2-3 months post-injury; and **Visit 4**, 6-12 months post-injury; as well as a fifth visit (**Visit 5)**, 12-18 months post-injury (subacute phase) (**Figure 3.1**). During each test visit, participants were fitted with a standard three-lead ECG (lead II) and a non-invasive beat-to-beat finger blood pressure monitor (Finometer Midi, Finapres Medical Systems [FMS], Amsterdam, Netherlands). Blood pressure and ECG were recorded supine for 15-minutes (sampling rate 200Hz). Data were stored for offline analysis of beat-to-beat blood pressure and ECG signals.

Following this recording participants were asked to complete a questionnaire about their cardiovascular symptoms (including OH, AD, arrhythmia, and fatigue) [43,216].

Neurological level and severity of injury to motor and sensory pathways at each timepoint was determined using the American Spinal Injury Association impairment scale (AIS) [217]. Based on level criteria, individuals with injuries at or above T6 were considered "at risk" of cardiovascular dysfunction. Based on AIS grade, individuals with AIS A injuries were considered motor/sensory complete.

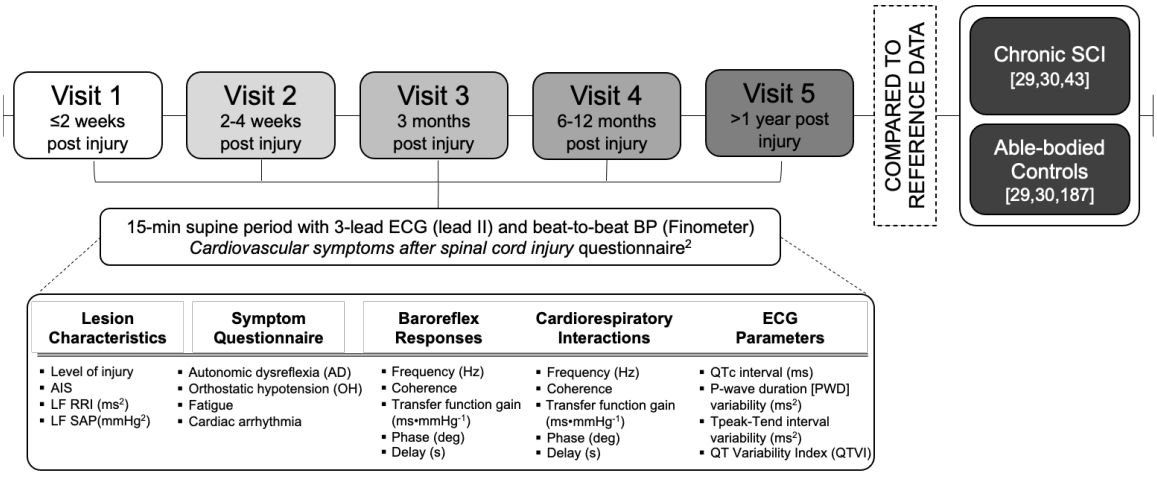

Figure 3.1 – Study protocol.

3.3.4 Data analyses

Autonomic completeness of injury

AR monovariate models were fitted to time series generated from beat-to-beat SAP and RRI to determine both blood pressure and HR variability [129,187,218]. Occasional ectopic beats were removed using linear interpolation of adjacent normal beats, and significant trends removed by subtracting the best polynomial function fitted to the data using low pass filtering [187]. Three peak frequencies were identified for each power spectrum: VLF (<0.03Hz); LF (0.5-15Hz) and HF(>0.15Hz). The central frequency, as well as both absolute and percent power at each frequency domain, were determined by computation of the residuals [188]. We focused our analyses on the key autonomic parameters of interest: LF RRI (reflecting oscillations in vagal outflow generated through the baroreflex and driven by sympathetically induced LF SAP) and LF SAP (reflecting sympathetic control of the vasculature).

Autonomic completeness of injury was inferred from LF SAP variability according to our standard approach [29]. An injury was considered autonomically-complete (severe injury to cardiovascular autonomic pathways) where LF SAP variability <2mmHg^2 and injuries were at or above T6 at Visit 2. Autonomic completeness was not determined from Visit 1 because of the high likelihood of neurogenic shock, with global, temporary, loss of sympathetic control immediately following injury that might confound estimates of injury to descending sympathetic pathways. In cases where Visit 2 data were not available, autonomic completeness was inferred from LF SAP <2mmHg^2 at the subsequent visit.

Baroreflex function and cardiorespiratory interactions

Baroreflex function was assessed by cross-spectral analysis of LF SAP and LF RRI. Frequency-related squared coherence, phase shift, and TFG between SAP and RRI signals were quantified by fitting a bivariate autoregressive model to the time series [129]. Discrete values of these variables were taken at the frequency corresponding to the maximal coherence value for the frequency range of interest, where the estimated error is minimal [129,219]. Coherence indicates the strength of the relationship between SAP and RRI covariance, with 0 indicating no relationship and 1 indicating complete interdependence; coherence $\geq$0.5 indicates statistically significant correlations between the two signals [115]. Cross spectral analyses in the LF range were taken to describe

properties of the arterial baroreflex, where spontaneous oscillations in LF SAP induce oscillations in LF RRI mediated by the baroreflex. Phase (deg) represents the time delay between input signal (LF SAP) and output response (LF RRI), and is negative where changes in LF SAP precede changes in LF RRI. Phase was converted to time delay in seconds by the following formula:

$$delay\ (s)\ =\ phase\ (deg)\ \left(\frac{frequency\ (Hz)^{-1}}{360}\right).$$

TFG (ms·mmHg^{-1}) indicates the sensitivity or magnitude of the reflex response. Cardiorespiratory interactions were calculated in exactly the same way, but with determination of central frequency, phase (time delay), coherence, and TFG at the respiratory frequency, i.e. in the HF range.

ECG markers of arrhythmia risk

ECG parameters (RRI, PWD, QT interval corrected for HR using Bazzett's method [QTc], T_{peak}-T_{end} interval [TpTe], and QTVI) were determined using customised software (LabView 2010, National Instruments) as described previously [30]. The variability for each ECG interval parameter was determined using AR spectral analyses. QTVI was determined by the following formula [30,184].

$$QTVI = log\ 10\ \frac{\left(QT_v/{QT_m}^2\right)}{\left(RR_v/{RR_m}^2\right)}$$

where v and m denote the variability and mean, respectively. Typically, QTVI is a negative number. The more positive (closer to zero) the QTVI, the greater the risk for ventricular arrhythmia.

Symptoms of OH, AD, and fatigue

Symptoms of OH, AD, and perceived arrhythmias (palpitations) were quantified as described previously [43]. A fatigue severity score was calculated using a linear visual-analog scale (0, no fatigue; 10 severe fatigue) from an average of three sample questions from the Fatigue Severity Scale [53,220].

Comparisons to historical data from individuals with chronic SCI and healthy able-bodied controls

Where applicable, data from these individuals with acute/subacute SCI were compared to existing historical data from individuals with chronic SCI [29,30,43] and healthy able-bodied controls [29,30,187]. These data were collected previously by our research group, using the same techniques and analysis, and provide perspective on the evolution of cardiovascular dysfunction over time after SCI, and in the context of able-bodied normative data.

Statistical analyses

Data processing was performed using R (Version 3.3.3) and RStudio (Version 1.1.453). Statistical analyses were performed using Sigmaplot 14 (Systat Software Inc., San Jose, CA). Data were tested for normality and parametric or non-parametric assumptions were used as appropriate. Comparisons for whole group data over time were performed using one-way ANOVA. Comparisons of outcomes measures over time-points and between sub-groups were performed using two-way ANOVA. Spearman rank correlations and linear regressions were used to assess the relationships between variables. Statistical significance was assumed where $p<0.05$. Where appropriate, data are represented as mean ± standard error, unless otherwise stated.

3.4 Results

3.4.1 Demographic and injury information

Information on participant demographics and injuries can be found in Table 2.1. We tested 63 individuals on at least one occasion (51 males) who had injuries ranging from C1-L1, and a range of injury severities based on AIS scores. Forty-seven participants (74%) were at risk for developing autonomic injuries based on level criteria (injuries at or above T6). Assessment of LF SAP at Visit 2 revealed that 40% of participants met criteria for autonomically-complete injuries i.e. some of those with high-level injuries had at least some preservation of cardiovascular autonomic function.

Table 3.1 – Participant characteristics.

Participant characteristics	
Sample size (F/M)	63 (12F/51M)
Age	48.2±2.0 years
Duration of injury by visit	
Visit 1	12±1 days
Visit 2	29±2 days
Visit 3	72±3 days
Visit 4	174±7 days
Visit 5	415±17 days
Injury characteristics	***n (%)***
Autonomically-complete	25 (40%)
Level of injury	
Cervical	36 (57%)
High-thoracic (T1-T6)	11 (17%)
Low (T6-L1)	16 (25%)
AIS Score	
A	23 (37%)
B	10 (16%)
C	12 (19%)
D	16 (25%)
Unknown	2 (3%)

Data are presented as mean±standard error or n (%) as appropriate. Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; F, female; M, male

3.4.2 Autonomic assessment

We have previously used LF SAP criteria to distinguish autonomic completeness of injury in individuals with chronic SCI [29]. However, we were interested to see whether this classification also applies in the acute phase of SCI, and whether LF RRI criteria could also be used to identify different subgroups of SCI based on the severity of impairment to autonomic parameters. We compared the evolution of LF RRI and LF SAP with time after injury for the group as a whole and subdivided according to lesion characteristics (**Figure 2.2**). There were no significant differences in either LF RRI or LF SAP over time or between subgroups when classified according to severity of injury based on AIS scores. Discrimination based on level criteria for risk of autonomic injury revealed lower LF SAP and LF RRI in those who were at risk, but a limited ability to distinguish subgroups at any given timepoint. There was a significant increase in LF SAP over time in those who were not at risk ($p=0.021$). When considering subgrouping based on autonomic completeness of injury, there was a significant main effect of group for both LF RRI ($p=0.002$) and LF

SAP (p=0.002), where they were reduced in individuals with autonomically-complete lesions. Based on post-hoc testing, the ability to discriminate between individuals with autonomically-complete and autonomically-incomplete lesions was present from Visit 2 onwards when using LF SAP criteria, but not until Visit 5 based on LF RRI criteria. When compared to reference data from individuals with chronic SCI (1.84±0.5 $mmHg^2$, n=26) [29] and healthy able-bodied controls (5.18±1.0 $mmHg^2$, n=43) [29,187], LF SAP tended to be reduced in all participants compared to able-bodied controls, regardless of injury characteristics, at Visit 1 (2.22±0.65 $mmHg^2$, n=22, p=0.064). By Visit 2, the resolution of autonomic function in participants with autonomically-incomplete lesions rendered this the first time-point from which autonomic function could be accurately discriminated. From this point onwards, LF SAP was significantly higher in those with autonomically-incomplete lesions, and normalised compared to control data. LF SAP remained reduced compared to control data at all timepoints in those with autonomically-complete SCI. These results confirm the utility of discrimination between those with severe autonomic injury and those who have autonomically-incomplete lesions using LF SAP criteria. Accordingly, all subsequent analysis will focus on discrimination between subgroups based on autonomic completeness of injury using LF SAP criteria.

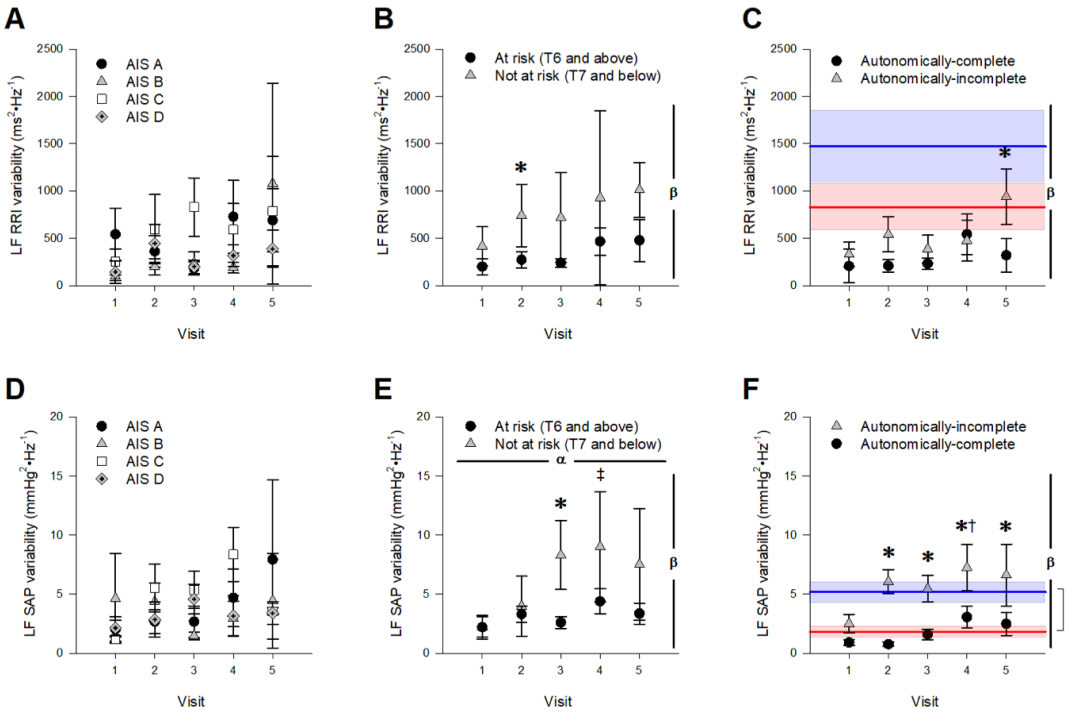

Figure 3.2 – Evolution of LF SAP and LF RRI over time after injury.
(A) There were no differences in LF RRI over time or between groups when individuals were classified according to severity of injury to motor and sensory pathways (AIS). (B) When classified according to risk for cardiovascular autonomic injury based on level criteria, LF RRI was higher in individuals not at risk ($p=0.002$). (C) When classified according to autonomic completeness of injury, LF RRI was higher in individuals with autonomically-incomplete injuries ($p=0.045$). (D) There were no differences in LF SAP over time or between groups when individuals were classified according to severity of injury to motor and sensory pathways (AIS). (E) When classified according to risk for cardiovascular autonomic injury based on level criteria, LF SAP was higher in individuals not at risk ($p=0.002$), and increased over time ($p=0.021$). (F) When classified according to autonomic completeness of injury, LF SAP was higher in individuals with autonomically-incomplete injuries ($p<0.001$). Red shading indicates reference values (mean ± SE) for LF RRI and LF SAP from individuals with chronic SCI[10] and in blue shading, from healthy able-bodied controls[10,14]. Statistical significance: ∗ denotes significant difference between groups ($p<0.05$); ‡ denotes significant difference between Visit 4 compared to Visit 1 for all participants ($p<0.05$); † denotes significant difference between Visit 4 compared to Visit 1 within the subgroup of individuals with autonomically-incomplete injuries ($p<0.05$); horizontal bars (α) denote significant main effect of visit; vertical bars (β) denote significant main effect of subgroups. Previously reported differences between individuals with chronic SCI and healthy able-bodied controls are shown with black brackets. Abbreviations: LF RRI, low frequency R-R interval; LF SAP, low frequency systolic arterial pressure; AIS, American Spinal Injury Association Impairment Scale.

3.4.3 Relationships between autonomic assessment and AIS score

As noted above, autonomic parameters could not be distinguished between subgroups based on severity of injury to motor and sensory pathways determined using the AIS score. This disconnect between injury to autonomic, motor, and sensory pathways is underscored in **Figure 3.3**. These data show representative examples of LF SAP data

in individuals with varying levels and severities of injury based on AIS score. In one example, an individual with a high-level incomplete lesion according to classification of motor and sensory pathways (C4 AIS D) is seen to have near-abolition of LF SAP at all time points - a severe autonomic injury - despite relative preservation of motor and sensory function (**Figure 3.3A**). In another example, an individual with a low-level injury, in whom autonomic pathways would not be expected to be impaired, shows blunted LF SAP at Visit 1, which is then recovered in all subsequent visits (**Figure 3.3B**). These data also show the various profiles of LF SAP at Visit 2, the time-point at which autonomic completeness is determined (**Figure 3.3C**). This example shows an individual with a low-level lesion and accordingly the expected preservation of normal LF SAP, as well as two individuals with very similar (high-level motor and sensory incomplete) lesions based on AIS criteria but very different severities of injury to autonomic pathways.

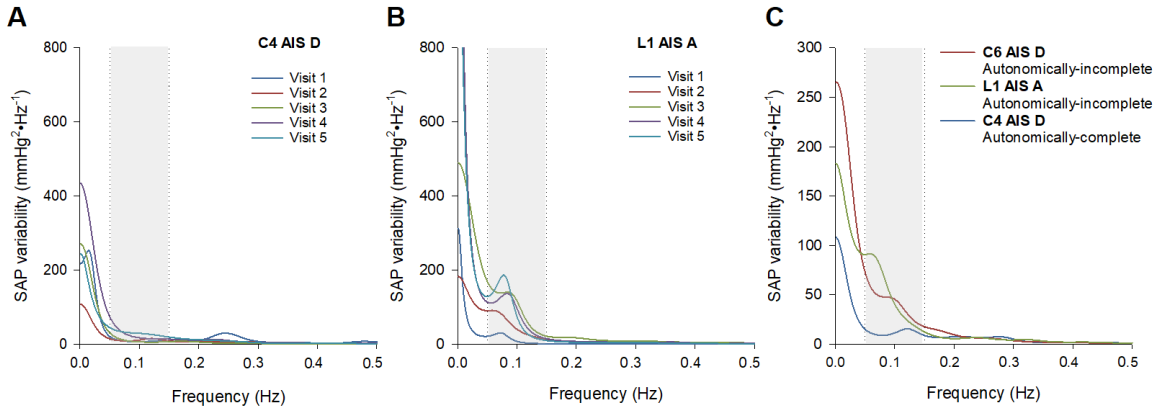

Figure 3.3 – Example power spectra showing blood pressure variability profiles.
(A) Typical systolic arterial pressure power spectra and their evolution over time in an individual with a high level (C4) AIS D autonomically-complete injury. Note that although this individual has an incomplete lesion according to classification of motor and sensory pathways (AIS D), they have near-abolition of low frequency variability at all time points, indicating an autonomically-complete lesion that does not recover over time. (B) Typical systolic arterial pressure power spectra and their evolution over time in an individual with a low level (L1) AIS A autonomically-incomplete injury. Low frequency variability was reduced at Visit 1, but recovered over subsequent visits. (C) Typical spectra for three individuals with different lesion characteristics at the time-point of determination of autonomic-completeness. The individual with the low level (L1) AIS A lesion has an autonomically-incomplete lesion, indicated by their low-level injury and robust low frequency variability. Note that two individuals with high level injuries with similar motor and sensory function had markedly different autonomic function, indicating the possibility of a disconnect between injury to motor, sensory and autonomic pathways. Grey shading highlights the low-frequency band used to assess autonomic-completeness of injury. Abbreviations: SAP, systolic arterial pressure; AIS, American Spinal Injury Association Impairment Scale.

3.4.4 Symptoms

Cardiovascular autonomic symptoms were prevalent and did not improve with time after injury; in fact, symptoms of AD, OH and fatigue became worse over time, with particularly high scores in individuals with chronic SCI (**Table 3.2**). There was a main effect of autonomic completeness of injury, whereby symptoms of arrhythmia (p=0.013) and fatigue (p=0.012) were worse in individuals with autonomically-complete than autonomically-incomplete lesions. This also tended to be the case for symptoms of AD, although this did not quite achieve statistical significance (p=0.088).

We considered whether self-reported symptoms were correlated, based on the visit most likely to represent late symptomatology (Visit 5). In individuals with autonomically-complete lesions self-reported symptoms of AD and OH were highly correlated with each other (r=0.729; p=0.0016), and symptoms of both AD and OH were correlated with fatigue (r=0.668; p=0.006 and r=0.682; p=0.005), indicating a high combined symptom burden within the first-year post-injury. Interestingly, quantification of autonomic severity of injury using LF SAP at Visit 2 (or equivalent) tended to be significantly correlated with late (Visit 5) symptoms of OH (r=-0.436; p=0.09) and was significantly correlated with late symptoms of fatigue (r=-0.857; p=0.006) in those with autonomically-complete lesions.

In addition, quantification of autonomic severity of injury using LF SAP at Visit 5 was significantly correlated with late symptomatology in those with autonomically-complete lesions: symptoms of OH (r=-0.695; p=0.017); symptoms of fatigue (r=-0.668; p=0.047); and tended to be associated with symptoms of AD (r=-0.515; p=0.09).

Table 3.2 – Symptoms of cardiovascular dysfunction.

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Chronic SCI[2]	Visit (p)	Complete-ness (p)
AD Symptom Severity Score	All	11.43±2.31 (23)	10.50±1.34 (32)	9.61±1.28 (28)	8.71±1.59 (21)	7.00±1.28 (15)	15.98±1.20	**0.002**	-
	Autonomically -complete	17.40±3.34 (5)	12.17±2.26 (12)*	9.33±1.73 (15)	8.36±1.50 (11)	9.42±1.74 (7)	-	0.197	0.088
	Autonomically -incomplete	9.78±2.21 (18)	9.50±1.66 (20)	9.92±1.78 (13)	9.10±2.02 (10)	4.88±1.10 (8)			
OH Symptom Severity Score	All	6.91±1.18 (23)	5.63±1.14 (32)	4.75±0.88 (28)	4.38±1.43 (21)	4.60±1.38 (15)	10.52±0.73^{V3,V4}	**<0.001**	-
	Autonomically -complete	7.20±1.77 (5)	6.25±1.45 (12)	5.00±1.21 (15)	5.27±1.48 (11)	6.43±1.55 (7)	-	0.648	0.220
	Autonomically -incomplete	6.83±1.21 (18)	5.25±1.26 (20)	4.46±0.88 (13)	3.40±1.18 (10)	3.00±0.86 (8)			
Fatigue Score	All	3.64±0.55 (22)	2.80±0.44 (32)	2.17±0.46 (28)	2.20±0.51 (21)	2.70±0.76 (15)	3.63±0.20	**0.027**	-
	Autonomically -complete	5.41±1.07 (5)*	3.24±0.68 (12)	2.45±0.58 (15)	2.78±0.68 (11)	3.56±0.91 (7)	-	0.091	**0.012**
	Autonomically -incomplete	3.18±0.59 (17)	2.51±0.50 (20)	1.86±0.43 (13)	1.57±0.46 (10)	1.96±0.45 (8)			
Arrhythmia Severity Score	All	0.7±0.34 (23)	0.47±0.26 (32)	0.82±0.28 (28)	0.81±0.35 (21)	0.40±0.29 (15)	0.96±0.1	0.363	-
	Autonomically -complete	1.80±0.56 (5)	0.42±0.29 (12)	1.13±0.36 (15)	1.18±0.44 (11)	0.86±0.33 (7)	-	0.646	**0.013**
	Autonomically -incomplete	0.39±0.2 (18)	0.50±0.25 (20)	0.46±0.20 (13)	0.40±0.14 (10)	0±0 (8)			

Statistical significance: * denotes significant difference between individuals with autonomically complete and incomplete SCI; ^{Vn} denotes significant difference between visit n. Data for individuals with chronic SCI are taken from[2]. Data are presented as mean±standard error (n). Abbreviations: AD, autonomic dysreflexia; OH, orthostatic hypotension; SCI, spinal cord injury.

3.4.5 Baroreflex function

For the group as a whole, LF central frequency was left-shifted (0.08±0.01 Hz, p=0.019) and coherence was low at Visit 1 (0.41±0.05, p<0.001) but these did improve over time (**Table 3.3**). TFG was low compared to individuals with chronic SCI and able-bodied controls at all time points (all p<0.001), and did not improve over time. LF phase was low initially but increased over time (p=0.004), with an associated decrease in the time delay between oscillations in SAP and RRI (p=0.005). When considering data from only those in whom coherence criteria were met, TFG was statistically smaller compared to both able-bodied controls and individuals with chronic SCI at Visit 3 (p=0.007 and p<0.001) and Visit 5 (p=0.041 and p=0.005) (**Figure 3.4A**). Phase was significantly less negative compared to individuals with chronic SCI at Visit 4 (p=0.045), with a significant main effect of time (p=0.009), but there were no significant differences in the delay over time (**Figure 3.4B**).

Given the low coherence, particularly in the early time points, we only considered subgroup analyses on data for which coherence was >0.5 (56% of all recordings). There were no significant differences between subgroups distinguished by level, AIS, or autonomic completeness at any time point.

Table 3.3 – Cross-spectral analyses of cardiovascular and respiratory parameters over time.

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Chronic SCI	Control	Visit (p)	Classification (p)	Interactions (p)
Low Frequency (0.05-0.15 Hz)											
All	Frequency (Hz)	0.08±0.01	0.08±0.01	0.10±0.01[V2]	0.10±0.01	0.10±0.01	0.09±0.01	0.10±0.003	**0.019**		
	TFG (ms•mmHg^{-1})	4.95±0.94	6.00±0.80	5.69±0.70	7.05±0.94	6.60±0.79	14.9±1.50[V1-V5]	13.30±1.70 [V1-V5]	**<0.001**		
	Coherence	0.41±0.05	0.44±0.03	0.52±0.04	0.50±0.04	0.59±0.04	0.58±0.04[V1,V2]	0.66±0.04	**<0.001**		
	Phase (deg)	-88.07±9.27	-76.26±5.98	-68.22±2.06	-57.73±5.68[V1]	-59.97±9.04	-87.27±5.80[V4]	-74.34±3.44	**0.004**		
	Delay (s)	-3.59±0.53	-3.79±0.61	-2.06±0.19[V2]	-1.94±0.31	-2.22±0.68	-3.23±0.39	-2.12±0.12	**0.005**		
	n	22	34	30	22	14	26	17			
Coherence≥0.5	Frequency (Hz)	0.08±0.01	0.10±0.01	0.11±0.01	0.10±0.01	0.10±0.01	0.09±0.01	0.10±0.01	0.566		
	TFG (ms•mmHg^{-1})	7.43±1.36	10.03±1.75	6.87±0.88	9.81±1.34	7.12±0.79	15.04±1.59[V3,V5]	14.01±1.88 [V3,V5]	**<0.001**		
	Coherence	0.68±0.06	0.68±0.03	0.67±0.03	0.57±0.03	0.65±0.03	0.66±0.02	0.69±0.03	0.982		
	Phase (deg)	-90.90±21.10	-66.03±7.50	-62.58±4.50	-55.66±5.58	-63.27±10.79	-85.24±4.93[V4]	-75.79±2.91	**0.009**		
	Delay (s)	-4.09±1.51	-2.19±0.47	-1.92±0.27	-1.68±0.26	-2.54±0.84	-2.87±0.32	-2.19±0.1	0.089		
	n	6	11	18	11	11	20	15			
Autonomically-complete (coherence≥ 0.5)	Frequency (Hz)	-	0.09±0.02	0.12±0.02	0.11±0.02	0.11±0.02	0.09±0.01	-	0.652	0.178	0.914
	TFG (ms•mmHg^{-1})	-	11.11±2.45	7.84±1.53	11.28±2.27	6.38±1.19	15.42±2.83[V3,V5]	-	**<0.001**	0.393	0.910
	Coherence	-	0.66±0.12	0.65±0.11	0.59±0.11*	0.65±0.12	0.65±0.04	-	0.973	0.103	0.649
	Phase (deg)	-	-69.94±14.12	-59.83±10.46	-55.79±10.89	-62.38±15.23	-96.12±5.76[V3,V4]	-	**0.006**	0.531	0.650
	Delay (s)	-	-2.36±0.54	-1.74±0.36	-1.68±0.37	-3.09±0.96	-3.22±0.51	-	0.236	0.441	0.844
	n	0	5	8	5	5	8	-			
Autonomically-incomplete (coherence≥ 0.5)	Frequency (Hz)	0.08±0.01	0.10±0.02	0.10±0.01	0.10±0.02	0.09±0.01	0.09±0.01	-			
	TFG (ms•mmHg^{-1})	7.43±1.23	9.13±1.53	6.10±1.02	8.58±1.41	7.74±1.27	13.98±2.08	-			
	Coherence	0.68±0.11	0.70±0.11	0.68±0.10	0.73±0.11	0.65±0.10	0.65±0.03	-			
	Phase (deg)	-90.90±15.76	-62.77±9.86	-64.78±9.79	-55.55±8.81	-64.01±9.78	-80.51±6.86	-			
	Delay (s)	-4.09±0.83	-2.04±0.38	-2.06±0.35	-1.69±0.28	-2.07±0.32	-2.74±0.46	-			
	n	6	6	10	6	6	11	-			

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Chronic SCI	Control	Visit (p)	Classification (p)	Interactions (p)
					High Frequency (0.2-0.3Hz)						
All	Frequency (Hz)	0.28±0.02	0.27±0.01	0.26±0.01	0.25±0.01	0.26±0.01	0.24±0.01^{V1}	0.26±0.01	**0.045**		
	TFG (ms•mmHg^{-1})	5.24±0.93	6.98±0.97	5.75±0.85	8.37±1.82	6.41±1.15	18.67±2.90^{V1-V5}	19.84±3.05^{V1-V5}	**<0.001**		
	Coherence	0.46±0.05	0.60±0.04	0.56±0.04	0.51±0.05	0.47±0.07	0.48±0.05	0.50±0.06	0.303		
	Phase (deg)	-13.20±8.26	-23.59±4.27	-31.25±8.21	-22.45±6.09	-6.58±6.79	-44.99±12.72	-54.25±5.36^{V1,V5}	**0.004**		
	Delay (s)	-0.14±0.08	-0.25±0.04	-0.35±0.09	-0.26±0.07	-0.07±0.08	-0.53±0.14^{V1,V5}	-0.57±0.05^{V1,V5}	**0.002**		
	n	22	34	30	22	14	26	17			
Coherence ≥0.5	Frequency (Hz)	0.29±0.01	0.27±0.01	0.26±0.01	0.25±0.01	0.27±0.01	0.23±0.01	0.26±0.02	0.258		
	TFG (ms•mmHg^{-1})	6.90±1.52	8.34±1.20	7.11±1.10	12.16±2.93	8.51±1.87	25.00±5.83^{V1-V5}	27.66±4.05^{V1-V5}	**<0.001**		
	Coherence	0.64±0.04	0.73±0.03	0.71±0.03	0.69±0.04	0.66±0.06	0.73±0.03	0.72±0.04	0.329		
	Phase (deg)	-13.80±7.15	-17.40±0.03	-23.16±4.48	-15.83±4.19	-3.89±4.70	-41.20±16.60	-53.76±6.72^{V1-V5}	**0.002**		
	Delay (s)	-0.16±0.08	-0.19±0.05	-0.26±0.05	-0.18±0.06	-0.03±0.05	-0.51±0.22	-0.56±0.07^{V5}	**0.005**		
	n	11	25	19	12	7	11	8			
Autonomically-complete (coherence≥ 0.5)	Frequency (Hz)	0.26±0.05	0.27±0.04	0.25±0.04	0.24±0.04	0.25±0.05	0.21±0.01	-	0.383	**0.010**	0.813
	TFG (ms•mmHg^{-1})	6.72±1.82	8.39±1.54	6.09±1.15	11.62±2.45	6.06±1.23	28.94±9.15^{V1-V5}	-	**<0.001**	0.811	0.950
	Coherence	0.74±0.15	0.75±0.11	0.70±0.11	0.75±0.14	0.63±0.12	0.77±0.05	-	0.659	0.169	0.536
	Phase (deg)	-11.61±2.86	-17.80±6.04	-19.29±4.11	-21.42±4.63	2.17±3.08	-32.79±30.21	-	0.114	0.483	0.900
	Delay (s)	-0.15±0.03	-0.20±0.06	-0.22±0.05	-0.26±0.06	0.04±0.03	-0.45±0.41	-	0.110	0.766	0.953
	n	3	12	10	5	3	6	-			
Autonomically-incomplete (coherence≥ 0.5)	Frequency (Hz)	0.29±0.04	0.28±0.04	0.28±0.04	0.26±0.04	0.29±0.05	0.24±0.02	-			
	TFG (ms•mmHg^{-1})	6.64±1.16	8.30±1.58	8.24±1.52	12.55±2.67	10.36±1.81	16.45±7.83	-			
	Coherence	0.61±0.09	0.71±0.10	0.72±0.11	0.65±0.10	0.69±0.11	0.67±0.04	-			
	Phase (deg)	-14.62±4.76	-17.04±3.78	-27.45±5.46	-11.83±2.85	-8.44±1.47	-60.42±5.17	-			
	Delay (s)	-0.17±0.05	-0.18±0.04	-0.30±0.06	-0.12±0.03	-0.08±0.01	-0.69±0.02	-			
	n	8	13	9	7	4	4	-			

Statistical significance: * denotes significant difference between individuals with autonomically complete and incomplete SCI; Vn denotes significant difference between visit n. Statistical significance (p values) are also presented for the main effects of visit, subgroup classification based on autonomic completeness of injury, and their interactions. Data for individuals with chronic SCI are taken from and for healthy able-bodied controls from [30] . Data a re presented as mean±standard error. Abbreviations: TFG, transfer function gain.

3.4.6 Cardiorespiratory interactions

For the group as a whole, HF central frequency was right-shifted at Visit 1 (0.28±0.02 Hz, p=0.045), particularly compared to individuals with chronic SCI, but did normalise over time. TFG was also reduced in all visits compared to individuals with chronic SCI and able-bodied controls (p<0.001) (**Table 3.3**). Phase was negative and increased compared to individuals with chronic SCI and able-bodied controls (p=0.004), corresponding to a reduced delay that did not increase over time (p=0.002). When considering data from only those in whom coherence criteria were met (56 % of all recordings), again TFG was reduced at all time-points and did not improve over time (**Figure 3.4C**). Phase was significantly more positive at all time points compared to healthy able-bodied controls, corresponding to a tendency to a smaller time delay compared to controls that reached statistical significance at Visit 5 (**Figure 3.4D**). There was a main effect for the HF central frequency to be significantly higher in those with autonomically incomplete lesions, but there were no other significant differences between sub-groups distinguished by level, AIS or autonomic completeness of injury at any time-point.

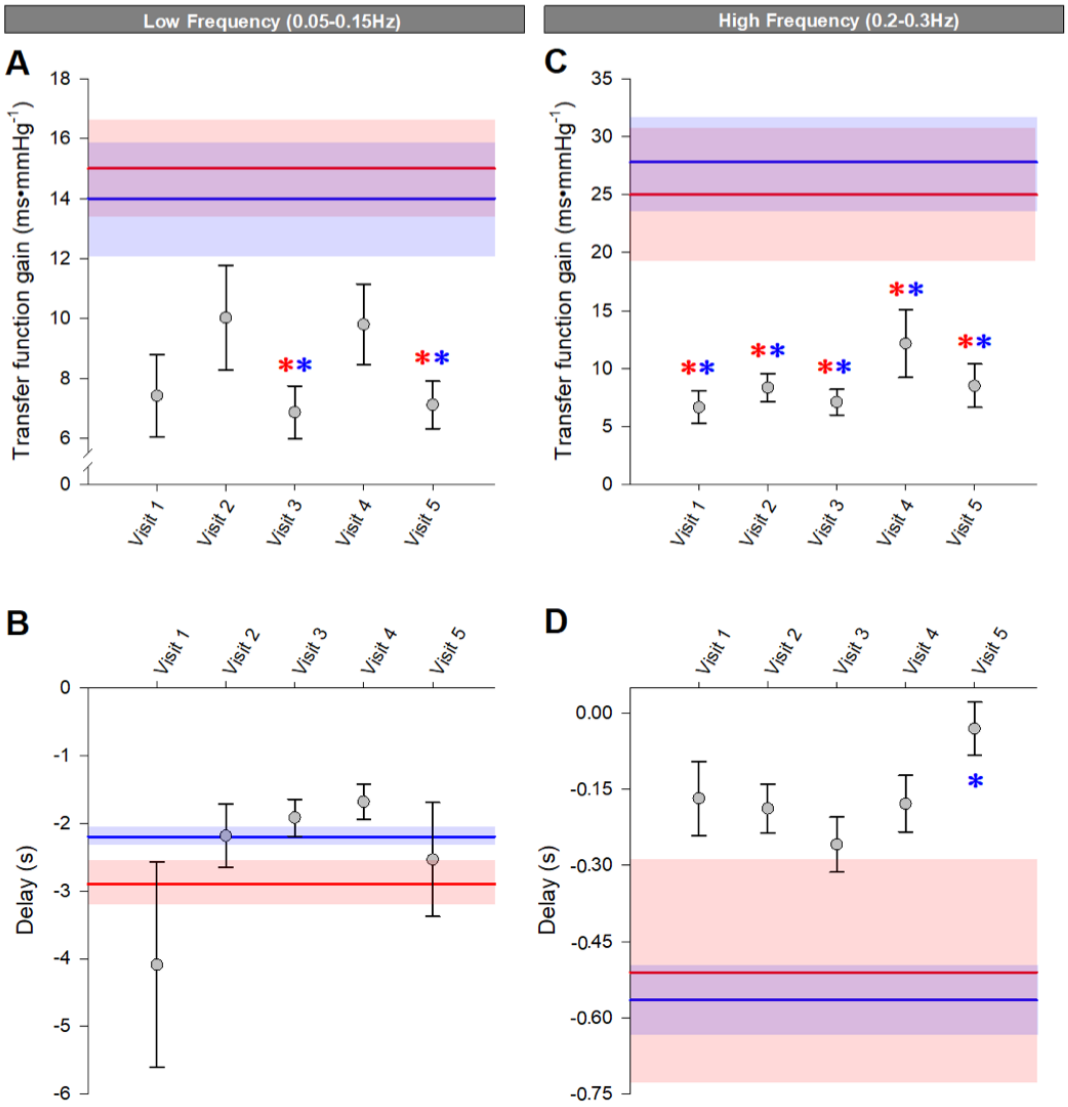

Figure 3.4 – Cardiovascular (low frequency) and respiratory (high frequency) cross-spectral parameters in individuals with coherence ≥ 0.5.

(A) LF TFG was significantly lower than in individuals with chronic SCI and health able-bodied controls at Visit 3 and Visit 5. (B) There was no significant difference in LF delay over time. (C) HF TFG was significantly lower in individuals with acute SCI (Visit 1-5) compared to individuals with chronic SCI and healthy able-bodied controls ($p<0.001$). (D) HF Delay was reduced in individuals with acute SCI compared to healthy able-bodied controls at Visit 5 (0.005). Red shading indicates reference values (mean ± SE) for chronic SCI [30], and in blue shading, from individuals with healthy able-bodied controls[10]. Statistical significance: * denotes statistical difference from chronic SCI ; * denotes statistical difference from healthy able-bodied controls[10]. Abbreviations: LF, low frequency; HF, high frequency; TFG, transfer function gain.

3.4.7 ECG analyses

Interval analyses

ECG interval parameters were compared over time (Visit 1 – Visit 5) and to reference data from individuals with chronic SCI and healthy able-bodied controls [30]. Resting RRI lengthened over time for all participants ($p<0.0001$), indicating slowing of HR. This effect was more pronounced in individuals with autonomically-incomplete injuries than those with autonomically-complete injuries ($p=0.042$), in whom HR tended to be slower initially. PWD was longer in the late acute period (Visit 3: 124±14ms; Visit 4: 129±15ms) compared to chronic SCI (102±4ms) and controls (100±4ms) (all $p<0.01$). There were no significant differences in T_{peak}-T_{end}, between subgroups categorised by either lesion level, AIS, or autonomic completeness of injury, or compared to those with chronic SCI or healthy able-bodied controls.

Additionally, when assessing total variability of RRI within the first five visits, variability was increased in those with autonomically-incomplete injuries compared to those with autonomically-complete injuries ($p=0.014$). Within those with autonomically-incomplete injuries, variability increased over the first year (Visit 1 vs Visit 4, $p=0.012$) consistent with the resolution of autonomic dysfunction. There were no significant differences in RRI variability between subgroups defined by level of injury, or AIS classification.

Markers of arrhythmia risk

Mean QTc, as well as QTVI, PWD variability, and T_{peak}-T_{end} variability for all participants were compared both over time and to reference data for individuals with chronic SCI and able-bodied controls [30] (**Figure 3.5**). Mean QTc was significantly increased at Visit 1 and Visit 3 compared to both healthy controls and individuals with chronic SCI, but did decrease over time ($p=0.0001$), becoming normalised compared to reference data. PWD variability was significantly increased over all 5 visits (all $p<0.01$), compared to both individuals with chronic SCI and healthy controls, with no significant improvement over the five visits. QTVI was significantly increased at Visit 1 and 3 compared to individuals with chronic SCI ($p=0.082$ and $p=0.006$) and at Visits 1-4 compared to healthy controls (all $p<0.001$) but did significantly decrease over time ($p<0.001$). T_{peak}-T_{end} variability was not significantly different compared to controls or

individuals with chronic SCI and did not change over time, although there was a trend, for higher T_{peak}-T_{end} variability at Visit 3 compared to able-bodied controls (p=0.075).

There were no significant differences in these markers for arrhythmia (Mean QTc, QTVI, PWD variability or T_{peak}-T_{end} variability) between subgroups classified according to lesion level, AIS, and autonomic completeness of injury over the five experimental visits (p all >0.05). We considered whether the severity of autonomic impairment, based on LF SAP at Visit 2 (or equivalent), was correlated with these markers of arrhythmia based on the visit most likely to represent late outcomes (Visit 5). There were no significant correlations between autonomic completeness of injury and markers of risk for arrhythmia either for the group as a whole, or in a subanalysis of only those with autonomically-complete lesions. Of note, in those with autonomically-complete injuries, late (Visit 5) markers of risk for ventricular arrhythmia were significantly correlated with each other (QTVI was correlated with mean QTc r=0.745, p=0.007; T_{peak}-T_{end} variability was correlated with mean QTc r=0.587, p=0.042, and QTVI and T_{peak}-T_{end} variability tended to be correlated r=0.527, p=0.09).

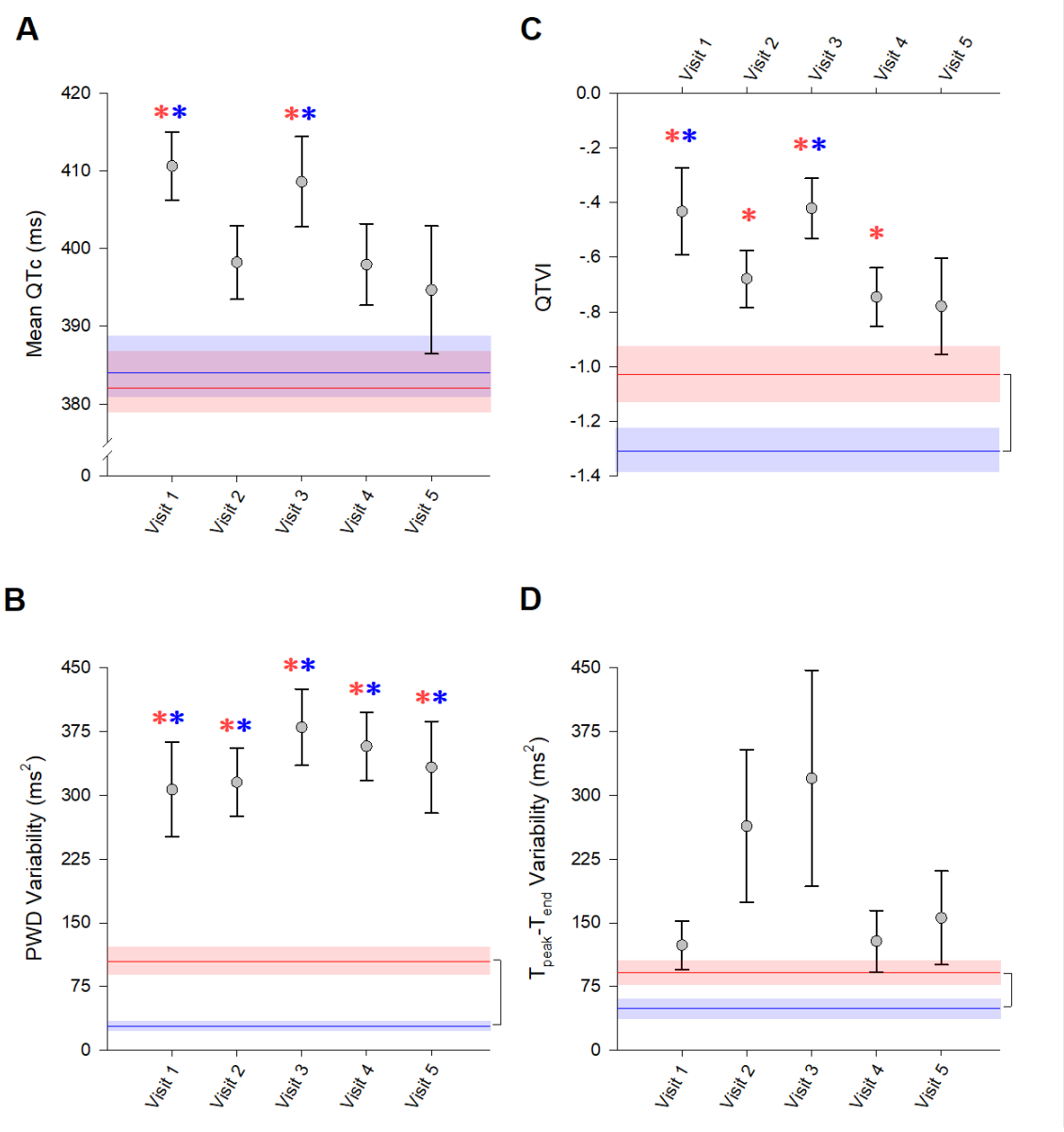

Figure 3.5 – Evolution of electrocardiographic predictors of cardiac arrhythmia over time after injury.

(A) Mean QTc (ms) was initially increased compared to reference data from individuals with chronic SCI and able-bodied controls (Visit 1 and Visit 3) but normalised over time (p=0.0001). (B) PWD was increased throughout the acute stage (Visits 1-5) compared to individuals with chronic SCI and healthy able-bodied controls (p<0.0001). (C) QTVI was increased initially compared to both individuals with chronic SCI and healthy able-bodied controls and decreased over time (p<0.001). (D) There were no significant trends in T_{peak}-T_{end} variability over time and no significant differences compared to those with chronic SCI or healthy able-bodied controls. Red shading indicates reference values (mean ± SE) for chronic SCI[29] , and in blue shading, from individuals with healthy able-bodied controls[29]. Statistical significance: * denotes statistical difference from chronic SCI[29]; * denotes statistical difference from healthy able-bodied controls[29]. Previously reported differences between individuals with chronic SCI and healthy able-bodied controls are shown with black brackets. Abbreviations: QTc, corrected QT interval; PWD, P-wave duration; QTVI, QT variability index; T_{peak}-T_{end}, T_{peak}-T_{end} interval.

3.5 Discussion

This is the first study to assess the timing, severity, progression and implications of cardiovascular autonomic injury in the acute phase after SCI. We have demonstrated that LF SAP is a feasible and applicable method for the quantitative assessment and classification of severity of cardiovascular autonomic (sympathetic) injury in the acute care setting. As predicted, LF SAP (as a direct measure of peripheral sympathetic activity) was a more discriminate tool than LF RRI (which incorporates sympathetic and vagal influences on the heart), AIS injury severity (which assesses motor and sensory function), and level of injury (which does not discriminate injured pathways) for the assessment of autonomic function post-injury. Not only was this technique able to discriminate individuals with autonomically-complete and autonomically-incomplete lesions within the first month post-injury, it was also able to identify significant differences in the severity of symptoms of cardiovascular dysfunction between those with different severities of lesions to cardiovascular autonomic pathways. In general, the symptom burden was high and did not improve over time - in fact symptoms of AD, OH, and fatigue worsened over time. Symptoms of arrhythmia, fatigue, and AD were higher in individuals with blunted LF SAP, and thus autonomically-complete lesions. These data highlight the need for aggressive management of cardiovascular dysfunction in individuals with SCI, particularly those with autonomically-complete lesions, and in light of the profound impact of cardiovascular dysfunction on quality of life for individuals with SCI [6,43]. Furthermore, these symptom profiles challenge prior dogma that OH improves over time [24], as well as previous notions that AD is rare in the first weeks after SCI [221,222].

We have once again demonstrated that there is a disconnect between the severity of injury to cardiovascular autonomic pathways and severity of injury to motor and sensory pathways as determined by AIS scores. While this has been reported many times by our research group [29,43,190] and others [17,138], there are still numerous reports in which AIS A injuries are considered to be “severe” and accompanied by profound injury to cardiovascular autonomic pathways [29]; this assumption should continue to be challenged as it may not always be the case. Obviously, individuals with lesions below T7 are at low risk for cardiovascular autonomic concerns, and should be reassured [223]. Individuals with injuries above this level, even those with motor and sensory incomplete lesions, can also have profound autonomic impairment, thus rationalizing the use of LF

SAP to identify risk of cardiovascular dysfunction after SCI. Recently, ASIA and ISCoS released the first guidelines for scoring autonomic function following SCI [138]. Although this is a major improvement to the pre-existing impairment scale (which previously assessed motor and sensory function alone) this new addition fails to accurately *quantify* autonomic function following SCI. Although we have shown a connection between quantitative and qualitative markers of autonomic dysfunction, we, like the Autonomic Standards Committee responsible for the creation of the ISAFSCI [138], recognize that there is no current clinical standard with which to accurately quantify the degree of autonomic dysfunction after injury. We believe the addition of LF SAP to the assessment of autonomic function post-injury provides a robust quantitative tool, allowing clinicians and researchers to accurately describe autonomic impairments post-injury. In addition, use of LF SAP represents an ideal tool to assess changes in autonomic function in clinical trials, with the additional benefit that it can be used in pre-clinical research [114], facilitating translation of results from bench-to-bedside and back.

While we advocate for the use of LF SAP to assess autonomic function after SCI, there are some caveats to this approach. We found that it was not possible to discriminate between individuals with autonomically-complete and autonomically-incomplete lesions until Visit 2 (approximately one-month post-injury). Prior to this time point there was global suppression of sympathetic function irrespective of later autonomic severity of injury in all participants. We suspect that this reflects the numerous autonomic insults occurring during this time, including the presence of neurogenic shock, other accompanying trauma, blood loss, surgery, medication use, deconditioning, etc. However, after the first few weeks we were able to document the emergence of two distinct groups - one with the resolution of LF SAP (autonomically-incomplete) and one where LF SAP remains absent or blunted (autonomically-complete).

We were keen to determine whether LF RRI would also provide a useful tool for discrimination of cardiovascular autonomic function after SCI. Although we did detect a reduction in LF RRI in those with autonomically-complete injuries, the ability to discriminate between groups was weaker, and did not emerge until later time points after injury. This presumably reflects that LF RRI is not a direct measure of sympathetic function, and also incorporates vagal (parasympathetic) influences on HR [224,225], which would not be expected to be affected by SCI [226]. This highlights the need for a

pure assessment of sympathetic function when considering autonomic completeness of injury after SCI.

Irrespective of autonomic injury, it is likely that all participants displayed marked cardiovascular deconditioning consistent with their traumatic spinal injuries [211]. Indeed, the high levels of fatigue, impaired baroreflex sensitivity, and blunted LF SAP and LF RRI are hallmark features of deconditioning [29,211,225]. However, many of these markers of deconditioning were more severely impaired in participants with autonomically-complete injuries, presumably because their additional autonomic dysfunction further exacerbates the deconditioning process in addition to directly contributing to these abnormalities. Of note, we observed particularly high levels of fatigue in those with autonomically-complete lesions. This is concerning because chronic fatigue is known to negatively impact participation in rehabilitation and quality of life after SCI [43,52,53]. In community-dwelling SCI, high levels of fatigue have been linked to polypharmacy [51] and this may be one factor that contributes to the high levels of fatigue we observed [43].

Our cross spectral analyses revealed profound impairments in baroreflex function in the acute phase after SCI, with low coherence between changes in blood pressure and HR, reduced baroreflex sensitivity and a tendency to longer reflex delay. There are many factors that might play a role in impaired baroreflex function in the acute phase after SCI, including blunted BPV, which would reduce the input stimulus to the baroreflex [29,227], the inability to activate baroreflex-mediated sympathetic modification of HR in those with high-level autonomically-complete lesions [104], cardiovascular deconditioning [55,211,225], and medication use [228]. The higher baroreflex sensitivity in those with chronic SCI suggests that baroreflex function does improve with time after injury, presumably due to reductions in deconditioning and reliance on intact cardiac vagal modulation [225]. We did not see a greater degree of impairment in baroreflex function in participants with autonomically-complete injuries, which may be attributed to the predominance of vagal influences on cardiac baroreflex during supine rest [225]. Of interest, baroreflex sensitivity decreases in individuals with cervical SCI when sitting [29].

When considering cardiorespiratory interactions, we found profound reductions in response gain along with a shortened time delay between respiratory-associated changes in blood pressure and HR. We also observed a higher central frequency of these respiratory oscillations that normalised over time and likely reflects the tendency to rapid,

shallow breathing after SCI secondary to paralysis of the accessory muscles of breathing and the presence of neurogenic shock [229]. There are two main theories as to the mechanisms underlying these cardiorespiratory interactions: (i) respiratory-induced changes in intrathoracic pressure in the HF range introduce baroreflex-mediated, predominantly vagal, modifications in HR [230]; (ii) respiration-induced changes in intrathoracic pressure generate HF oscillations in blood pressure, and with similar timing, generate oscillations in HR (respiratory sinus arrhythmia) perhaps mediated by vagal activation via the Hering-Breur reflex [131]. A baroreflex-mediated mechanism requires a sufficiently long latency for a reflex response to occur [231]; the short response delay (-70ms to -35ms) and profound impairments in baroreflex function observed in individuals with acute SCI favours the latter explanation. In individuals with chronic SCI and able-bodied controls the response delay is increased (-530ms and -570ms) and baroreflex function improved, and this might suggest greater reliance on a baroreflex-mediated mechanism. There is one previous study that examined cardiorespiratory interactions in the sub-acute period after SCI and they also found low cardiorespiratory sensitivity with a similar phase in their cohort of individuals with SCI [113]. However, there were some discrepancies between our data and the earlier report, which reported greater interdependence of cardiorespiratory interactions (higher coherence) in individuals with SCI compared to controls as well as longer response time delays in individuals with subacute SCI (-241ms) and a *feedforward* pattern of HR into pressure in able-bodied controls (+443ms) [113]. The reasons for these discrepancies are unclear, but may reflect that in the present study participants were breathing spontaneously, and in the earlier study participants were asked to pace their breathing to a metronome, which was noted to be poorly tolerated in those with SCI [113]. Indeed, previous reports have documented that fixed breathing in healthy controls produces inconsistencies in the phase shift, without impacting the gain [232]. Interestingly, manipulation of breathing rates with mechanical ventilation also produces positive phase shifts [233]. Given the impact of SCI on respiratory function, difficulties for participants with SCI in adhering to metronome breathing protocols, and documented effect of altering breathing patterns on these cardiorespiratory interactions, we advocate that these analyses be conducted with spontaneous breathing where possible.

This study is also the first to assess ECG parameters and their evolution with time during the first year after SCI. A key finding of these analyses is the immediate impact SCI

has on proarrhythmic cardiac activity. We showed blunted HR variability in individuals with acute SCI, which is known to carry an adverse cardiovascular risk profile [234]. We also showed adverse changes in numerous ECG-based markers of risk for both atrial and ventricular arrhythmia. Our data supports our previous findings that markers of arrhythmia are increased following SCI [30,184,190]. However, what was not appreciated in previously reported studies is the timing and magnitude of these changes in cardiac electrical function over the first year of injury: these proarrhythmic changes occur almost immediately after sustaining a SCI and persist in individuals with chronic SCI when compared to able-bodied controls, even in the face of some improvements when comparing those with acute and chronic SCI. These data are consistent with the detrimental impact of neurogenic shock, cardiovascular deconditioning, and loss of the ability to regulate cardiac sympathetic outflow on cardiac electrical function [12,29,208,212].

We did not show relationships between markers of arrhythmia risk and autonomic completeness of injury in the acute phase, even though greater impairments in electrocardiographic parameters have been reported in those with autonomically-complete lesions in the chronic phase after SCI [30]. This may reflect the numerous additional challenges to cardiac function, such as medication use, surgery, other trauma etc. in the acute phase of SCI, which obscure the relationship with autonomic function at this early time point and/or that electrical remodelling secondary to impaired autonomic function takes time to develop. It is also important to appreciate that these recordings were taken during supine rest, and thus participants were not under sympathetic challenge. We have previously shown that individuals with severe autonomic injuries have a greater propensity to develop cardiac arrhythmias during increased sympathetic activation (i.e., during bouts of AD) compared to at rest [190]. Interestingly, we found that symptoms of arrhythmia were more pronounced in those with autonomic injury, and might reflect a greater propensity to induce arrhythmia in these individuals with provoking stimuli. One key aspect to note is that given the clearly abnormal ECG findings during resting conditions in this cohort of individuals with acute SCI, it is likely that the risk of developing cardiac arrhythmia during provoking autonomic stimuli such as during AD is actually underestimated. Certainly, the increased risk for developing cardiac arrhythmias seen in all participants in the acute phase after SCI underscores the need for periodic ECG monitoring, and careful attention to reports of palpitations.

3.6 Limitations

There were several limitations to this study. The primary challenge was that, as with many longitudinal studies, there was a loss to follow-up over the course of the five experimental visits. This might increase the statistical likelihood of failing to detect differences between groups or time points. Despite this, we show robust statistical significance across all measures. We did not assess the effect of medication administered during acute care on our recordings, apart from those considerations taken on testing days. It has recently been shown that polypharmacy contributes to high levels of fatigue [51], and use of baclofen, commonly prescribed after SCI, is associated with marked neurological (motor/sensory) recovery [228]; the effects of baclofen on recovery of autonomic function are unknown. We did not power this study to examine interaction effects with medication use, but do consider that our results reflect the clinical reality of acute care after SCI, where polypharmacy is inherently common and might affect autonomic function. We also recognise that the connections we have made to data from individuals with chronic SCI are based on historical data from our research group [29,30,187], and would be further strengthened with a continuation of this longitudinal study into the chronic phase. At the present time these data are not available, and the challenges with loss to follow-up render them difficult to obtain. The benefit to these historical comparisons are the ability to place these data in context with the longer term outcomes after SCI, and with data from healthy able-bodied controls, using identical data collection and analysis approaches.

3.7 Conclusion

We showed that spectral and cross-spectral analyses of cardiovascular function can be used to track the progression and evolution of injury to cardiovascular autonomic pathways after SCI. Severity of injury to autonomic pathways can be discerned by 1-month post-injury and autonomically-complete lesions are associated with a high cardiovascular symptom burden. Acute SCI is also marked by severe deconditioning, persistent baroreflex and cardiorespiratory dysfunction, and abnormal ECG characteristics, regardless of stratification according to AIS scores, risk for cardiovascular injury based on level criteria, and autonomic injury. We propose the use of LF SAP as a simple, effective translatable tool for the measurement of cardiovascular autonomic

function after SCI. Given these results, consideration of cardiovascular dysfunction after acute SCI should be prioritised when considering the most appropriate rehabilitation and management approaches for individuals with SCI.

Chapter 4

Clinical recommendations for use of lidocaine lubricant during bowel care after spinal cord injury prolong care routines and worsen autonomic dysreflexia: results from a randomised clinical trial

4.1 Abstract

SCI impacts autonomic function and bowel management. Bowel care is a potential trigger for AD (paroxysmal hypertension elicited by sensory stimuli below the level of lesion). AD can be life threatening so strategies to minimise AD are prioritised after SCI. Lidocaine lubricant is recommended during bowel care with the rationale to minimise the sensory stimulus, reducing AD. We aimed to assess whether lidocaine lubricant (Xylocaine 2%) ameliorates AD during at-home bowel care compared to standard lubricant (placebo). Participants (n=13; age 44.0±3.3years) with high-level SCI (C3-T4) performed their normal at-home bowel care on two days, each time using a different lubricant, with continuous non-invasive cardiovascular monitoring. Injury to spinal autonomic (sympathetic) nerves was determined from low-frequency systolic arterial pressure (LF SAP) variability. Participants displayed reduced autonomic function (LF SAP 3.02±0.84mmHg^2), suggesting impaired autonomic control. Bowel care duration was increased with lidocaine (79.1±10.0minutes) compared to placebo (57.7±6.3minutes; p=0.018). All participants experienced AD on both days, but maximum SAP was higher with lidocaine (214.3±10.5mmHg) than placebo (196.7±10.0mmHg; p=0.046). Overall, SAP was higher for longer with lidocaine (6.5x10^5±0.9x10^{5}mmHg•beat) than placebo (4.4x10^5±0.6x10^{5}mmHg•beat; p=0.018) indicating a higher burden of AD. HR and rhythm disturbances were increased during AD, particularly with lidocaine use. At-home bowel care was a potent trigger for AD. Our findings contradict recommendations for lidocaine use during bowel care, suggesting anaesthetic lubricants impair reflex bowel emptying, resulting in longer care routines with an increased burden of AD.

4.2 Introduction

In addition to the well-known loss of motor and sensory function following traumatic SCI, autonomic function is also severely impacted [4,19,55]. This loss of autonomic function occurs independent of motor and sensory disturbances, and impacts a range of physiological processes. In particular, autonomic dysfunction adversely impacts cardiovascular control and bowel function for individuals living with SCI, with the former complicating the latter [68]. We recently reported that bowel care concerns profoundly impact quality of life for community-dwelling individuals living with SCI, who identified bowel management as a key modifiable factor with the potential to improve their quality of life [43].

Bowel impairments after SCI are primarily related to the impact of injury on GI function, as the coordination of GI motility is dependent on central motor and autonomic control, as well as intrinsic regulation by the enteric nervous system [41]. This NBD is highly dependent on the level of injury. Accordingly, NBD is classified as UMN dysfunction or LMN dysfunction, depending on whether the injury level is above or below the conus medullaris (L1), respectively [41]. UMN lesions maintain reflex activity in the sacral segments of the cord, resulting in loss of voluntary bowel control, with preservation of reflexive defecation. This often results in a spastic sphincter, with constipation and fecal retention that require intervention to trigger defecation [42] - a hyperreflexive bowel. LMN lesions also result in loss of voluntary control of the bowel, but are accompanied by loss of sacral reflexive control with a lax external sphincter, resulting in a high frequency of fecal incontinence - an areflexive bowel.

Individuals with high lesion levels (at or above T6) also commonly experience injury to the autonomic sympathetic nerves responsible for HR and blood pressure control. This profound cardiovascular impairment is a key concern for individuals living with SCI and is linked to high cardiovascular morbidity and mortality following SCI [6,37]. In individuals with high lesion levels, bowel care routines can exacerbate cardiovascular dysfunction by eliciting a condition known as AD [235]. AD is characterized by paroxysmal hypertension in response to sensory stimuli (noxious or non-noxious) below the level of injury [18] that elicit a sympathetic reflex, resulting in widespread vasoconstriction of the splanchnic vascular bed and other vessels below the level of injury. This leads to a dangerous increase in blood pressure, which typically also presents with a marked

baroreflex-mediated reduction in HR [18–20,58], and is sustained until the sensory stimulus is removed. Typical causes include a distended bladder or bowel, bladder and bowel care routines, pressure sores, and infections [18,58]. AD can present clinically with symptoms including profound headache, facial flushing, sweating above the level of injury, blurred vision, increased spasticity and nausea [18,58]. The high sympathetic discharge associated with AD is also proarrhythmogenic, and many individuals report palpitations during AD [30]. However, AD can also present asymptomatically, which is challenging because in the absence of symptoms individuals may not take action to remove the triggering stimulus and resolve the episode [21,65]. This is important because AD has been linked to cognitive impairments, cerebral hemorrhage, stroke, myocardial infarction and arrhythmia, and death [17,22,23,37].

Bowel care *practices* [57] (treatment plans designed to minimize or eliminate the occurrence of unplanned or difficult evacuations) are diverse and complex, with individuals often needing a multifactorial approach to bowel management. Bowel care *routines* [57] (the process of assisted defecation) often require chemical (suppository) and/or mechanical (digital stimulation, manual evacuation, and/or abdominal massage) interventions to elicit reflexive defecation. These methods often employ the use of a lubricant to minimise the potential for damage to the rectal mucosa. We have shown that cardiovascular complications associated with bowel care negatively impact quality of life and are associated with high levels of isolation [43]. Accordingly, AD management should be a target for bowel care intervention [6,43].

One proposed method for reducing AD severity during bowel care is administration of an anesthetic lubricant to the rectum, with the goal of mitigating the afferent stimulus, and so blunting the AD response to bowel care [58,67]. The local anaesthetic lidocaine (a sodium channel blocker) has been recommended for the reduction of AD severity during bowel care, and is often advocated in clinical bowel care guidelines [18,21,58,67]. However, current clinical recommendations for its use are dated [67] and the evidence regarding the use of lidocaine during bowel care procedures is conflicting [70,236,237]. We aimed to determine whether the use of a topical anesthetic lubricant (2% lidocaine) ameliorates cardiovascular complications compared to a placebo lubricant during at-home bowel care. Additional aims include evaluation of the impact of lidocaine on time to complete bowel care, and self-reported symptoms of AD during care.

4.3 Methods

4.3.1 Ethical Approval

This study was approved by the Department of Research Ethics at Simon Fraser University and conforms to the principles outlined in the Declaration of Helsinki [215]. Participants provided written informed consent and the trial was registered (Clinical.Trials.gov #NCT01567605).

4.3.2 Participants

Participants were recruited using a multi-method approach. Print advertisements were circulated through our community partners, SCI-BC by way of their quarterly publication, *The Spin*, and online advertisements were posted through our institutional website (www.icord.org).

Eligible participants were individuals aged >18 years of age who had been living with a traumatic SCI for at least one year, with an established bowel care routine, and a prior history of AD (with lesion level T6 or higher). Individuals were excluded from the study if they had a medical/psychiatric condition or substance abuse disorder that was likely to affect their ability to complete the study, used a ventilator, had a colostomy, or did not perform regular bowel care for any reason. Additional exclusion criteria included any skin breakdown in the areas receiving pressure during the bowel program, inability to communicate in English, use of medicines containing lidocaine, allergy to lidocaine, and pregnancy.

4.3.3 Experimental Procedure

We conducted a registered double-blind placebo-controlled crossover clinical trial where participants were randomised to a series of two treatments: lidocaine lubricant (Xylocaine 2%) and standard lubricant (KY Jelly; placebo) on two consecutive at-home visits (**Figure 4.1**). The sequence of conditions was determined by random draw, using a complete randomised design, by a researcher external to the research team; seven participants were randomised to the lidocaine arm of the study first, and six to the placebo arm of the study first. Testing took place between August 2016 and October 2018.

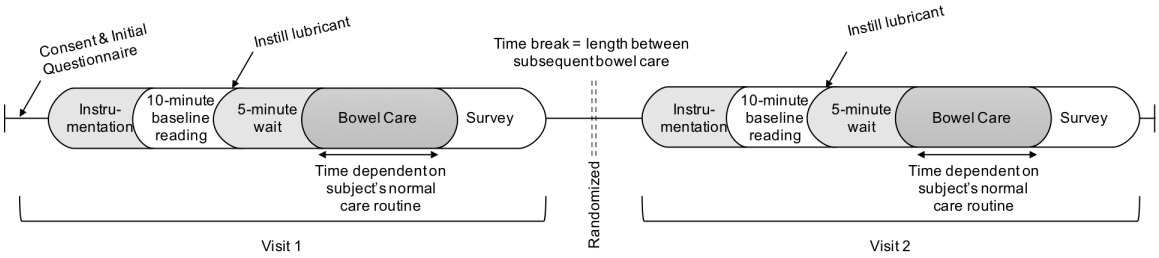

Figure 4.1 – Protocol schematic.
This double-blind placebo-controlled crossover clinical trial took take place over two consecutive visits. Each participant was randomly assigned to a sequence of two treatments: lidocaine lubricant (Xylocaine 2%) and standard lubricant (KY Jelly; placebo). Participants performed their normal bowel care during two in-home visits, each time with the lubricant assigned for that test day, with continuous non-invasive beat-to-beat cardiovascular monitoring (Finapres Medical Systems (FMS), Amsterdam, Netherlands). An initial 10-minute baseline reading was performed in the position in which participants conducted their bowel care. Participants were then asked to instill 5mL of the lubricant using a specialized device (Cleanstream XL Lubricant Launcher, CleanStream) 5-minutes prior to beginning their care routine. Prior to the first visit, participants were asked to complete a questionnaire about their bowel management and general bowel continence. At the end of each visit, participants completed a second questionnaire specific to their bowel care that day.

Prior to the first visit, participants completed a questionnaire about their bowel management and general bowel continence [43]. On each visit, participants were fitted with a standard three-lead ECG (lead II) and a non-invasive beat-to-beat finger blood pressure monitor (Finometer Midi, Finapres Medical Systems [FMS], Amsterdam, Netherlands). After a 10-minute baseline recording (sampling rate 200Hz), participants inserted 5mL of lubricant into the rectum using a specialised device (Lube Launcher XL, CleanStream, Huntington Beach, USA) to ensure that a minimum amount of lubricant was administered. Following insertion of the lubricant, participants waited 5-min before starting bowel care (to allow for mucosal absorption of lidocaine, which has a typical onset of action of 3-5 minutes). Participants were then provided with an additional 15mL of lubricant and asked to perform their bowel care routine as usual, replacing their normal lubricant with the lubricant provided for that day. The maximum recommended dosage of lidocaine is 600mg/12 hour. The dosage provided (20ml of 2% lidocaine) is equivalent to 400mg. The 20ml volume was determined based on discussion with bowel care providers and individuals with SCI concerning their typical lubricant needs. This dosing strategy is in line with other similar studies. Given the typical half-life of lidocaine (1.5-2 hours) we are confident there was optimal dosing throughout the duration of bowel care.

Five minutes after insertion of the test lubricant, a timer was started and the participant commenced their usual care routine. Bowel care routines were not

standardised because the primary interest was to investigate the real-world feasibility and impact of this clinical recommendation in a community setting with usual participant care routines. When the participant signalled the end of their care routine (defined as the time when bowel evacuation was completed, prior to cleaning), the timer was stopped, and the bowel care duration noted. The cardiovascular monitoring equipment was then removed. Participants then completed a questionnaire specific to their bowel care on that day, reporting the method of bowel care employed as well as the severity of cardiovascular symptoms experienced [43]. Self-reported symptoms of AD were determined as described previously [43]. Two participants chose not to complete the post-bowel care questionnaire.

4.3.4 Autonomic dysfunction

Severity of autonomic dysfunction was determined through spectral analyses of LF SAP. LF SAP oscillations (~0.1Hz) reflect sympathetic control of the vasculature, and thus indicate the presence or absence of autonomic cardiovascular control following SCI [29]. Participants with LF SAP lower than 3.75mmHg^2 were determined to have autonomically-complete injuries.

4.3.5 Cardiac rate and rhythm analyses

ECG data were visually inspected offline after completion of the study. The number of beats that met criteria for bradycardia (<60bpm) and tachycardia (>100bpm) was determined during baseline and bowel care, and expressed as a percentage of the total number of beats in the corresponding phase. In addition, each beat was classified as either sinus rhythm, or not, and any arrhythmia or conduction abnormalities noted.

4.3.6 Data analyses

Beat-to-beat SAP and diastolic (DAP) arterial pressures were extracted throughout the testing period. MAP was calculated as DAP + 1/3 x (SAP-DAP). HR was determined from the RRI of the ECG. SV and Q were determined using Modelflow [179,181], and TPR calculated as MAP / Q. Data were collected at a sampling frequency of 200 Hz and averaged over 5 successive beats. All parameters were extracted for the entire duration of baseline and bowel care, as well as for only the first 25 minutes of bowel care. Maximal responses were also determined during bowel care regardless of the time at which they

occurred ($Parameter_{max}$). AD was defined as an increase in SAP_{max} of at least 20mmHg [138] compared to baseline. The overall burden of AD was determined from the area under the SAP curve (the product of SAP and heart beat).

4.3.7 Statistical analyses

Data processing was performed using R (Version 3.3.3) and RStudio (Version 1.1.453). Statistical analyses were performed using Sigmaplot 14 (Systat Software Inc., San Jose, CA). Data were tested for normality and parametric or non-parametric assumptions were used as appropriate. Comparisons of cardiovascular outcomes and symptoms between conditions (lidocaine and placebo) and test phases (baseline and during bowel care) were performed using two-way repeated measures ANOVA. Spearman rank correlations and linear regressions were used to assess relationships between variables. Fisher's exact test was used to evaluate differences in proportions of responses between test conditions. Student t tests were used to compare responses between placebo and lidocaine conditions (e.g. time to complete bowel care). Statistical significance was assumed at $p<0.05$. Where appropriate, data are represented as mean ± standard error, unless otherwise stated. Researchers, participants, care providers, and those analysing the data were blinded to the test condition. Researchers were unblinded just prior to statistical analyses.

4.4 Results

4.4.1 Demographic and Injury Characteristics

Demographic and injury information can be found in Table 4.1. All participants had high level lesions placing them at risk for cardiovascular complications and AD; therefore, all had UMN NBD with hyperreflexive bowels. All participants had experienced prior documented AD with low resting LF SAP, consistent with severe injury to descending autonomic (sympathetic) pathways.

Table 4.1 – Participant demographic and injury information.

Demographic and injury information	
Sample size (n)	13 (9M/4F)
Age (years)	44.0±3.3
Time post-injury (years)	13.9±2.4
Injury level	C3-T4
Injury severity	AIS A-C
LF SAP ($mmHg^2$)	3.02±0.84
# of days between testing	2.5±0.5

Where applicable, data are expressed as mean ± standard error. Abbreviations: LF SAP, low frequency power of systolic arterial pressure.

4.4.2 General bowel practices

Participant care routines were conducted in a supine side-lying position (n=6; 46%), or seated on a commode or toilet (n=7; 54%). Of those who commenced their care routine in a side-lying position (for suppository insertion), 5 individuals then transferred to a commode or toilet in preparation for and during the passage of stool. Bowel care procedures employed included: rectal suppository (n=12; 92%); digital stimulation (n=8; 62%); and manual removal of stool (n=1; 8%), either alone or in combination. Bowel care was performed independently (n=2; 15%), or with the partial (n=4; 31%) or total (n=7; 54%) assistance of a care aide or family member. Bowel care was typically conducted once per day (n=3; 23%), every other day (n=9; 69%), and every third day (n=1; 8%). Each individual employed the same care routine (their usual care) in the same position for both testing days. The mean between visit duration for the two test conditions was 2.5±0.5 days. One participant was unable to pass stool on the lidocaine test day.

A representative example tracing showing the responses and timing of bowel care in one individual is shown in **Figure 4.2**. AD was triggered by numerous aspects of bowel care, including insertion of lubricant, insertion of suppository, rectal checks, passage of stool and cleaning.

The time taken to complete bowel care was significantly longer on the lidocaine than the placebo test day (**Figure 4.3A**).

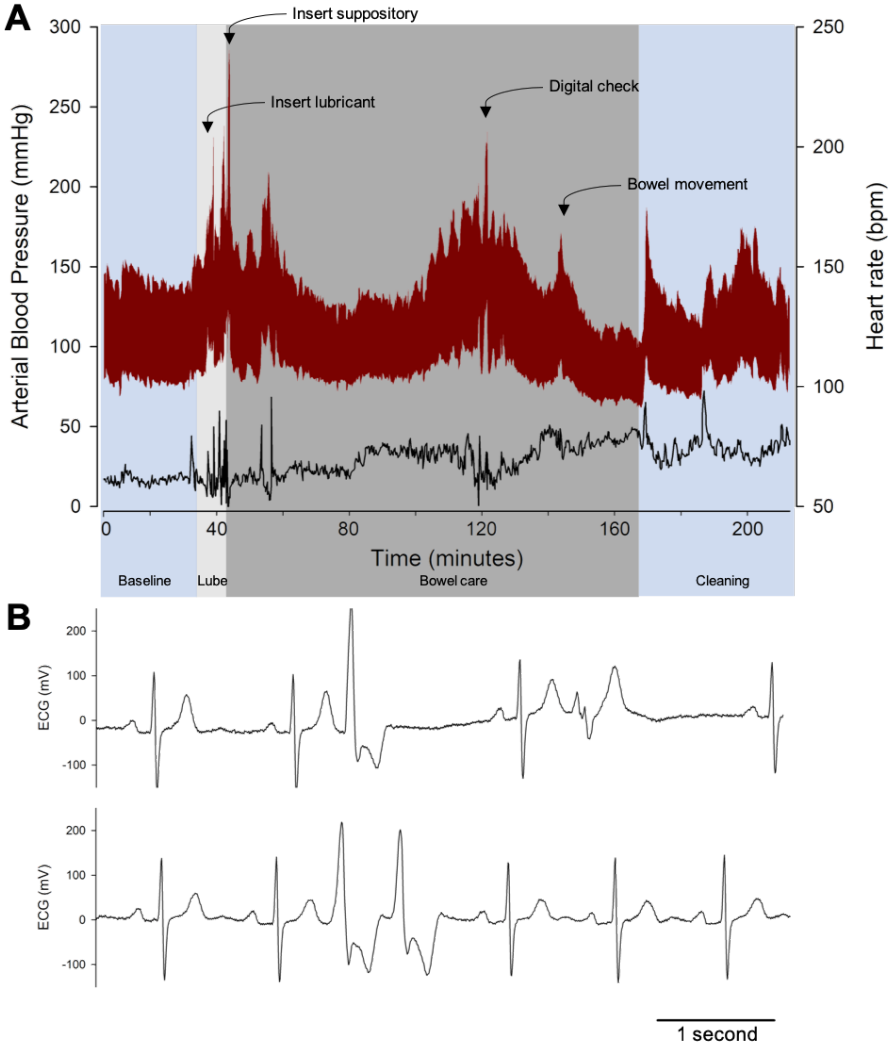

Figure 4.2 – Representative example tracing showing arterial blood pressure, heart rate, and ECG responses to bowel care.

(A) Beat-to-beat blood pressure and heart rate recording from an individual with a C4 AIS A injury collected on the lidocaine test day. Resting blood pressure (red) was slightly elevated, perhaps reflecting mild colorectal distension induced autonomic dysreflexia (AD) prior to beginning care. Episodic severe AD was provoked by bowel care procedures including insertion of lubricant and suppository, as well as rectal checks and the passage of stool. Note, cleaning also induced a severe AD response. Concurrent heart rate changes (black) during AD episodes reflect presence arrhythmia or abnormal heart rate control during this severe sympathetic stimulus. Interestingly, AD often triggered paradoxical tachycardia despite providing a strong stimulation for baroreflex mediated bradycardia. The grey shaded region indicates the duration of bowel care. (B) Representative example ECG traces of cardiac abnormalities in an individual with a C5 AIS A injury, (top; multifocal ventricular ectopics occurring in bigeminy, bottom; couplet of ventricular ectopics) provoked during episodes of AD induced by bowel care, collected on the lidocaine test day. Abbreviations: ECG, electrocardiogram.

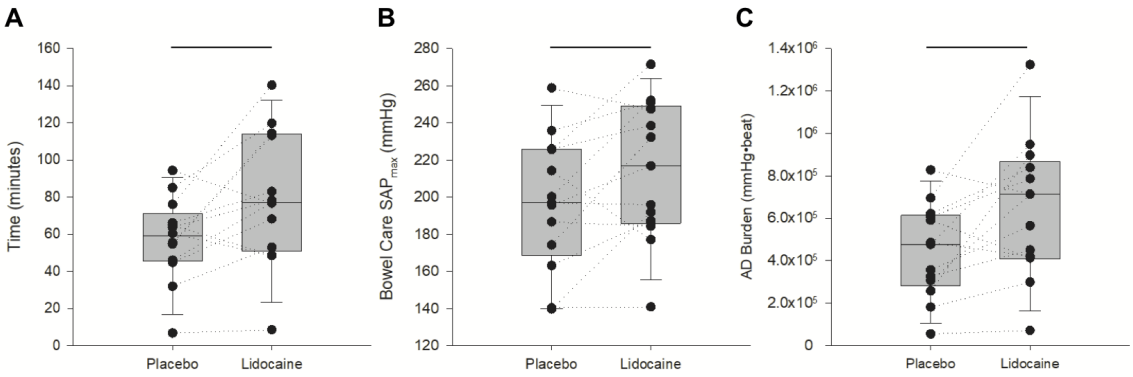

Figure 4.3 – Lidocaine use was associated with adverse bowel care outcomes.
(A) Lidocaine prolonged the time to complete bowel care when compared to the placebo condition (p=0.018). (B) Lidocaine use was associated with more severe autonomic dysreflexia (AD), with a higher maximum systolic arterial blood pressure (SAP_{max}) during bowel care in the lidocaine than placebo condition (p=0.046). (C) Lidocaine use increased the burden of AD compared to placebo (p=0.018), defined as the area under the systolic arterial pressure curve during bowel care (the product of systolic arterial pressure and heart beat). Abbreviations: AD, autonomic dysreflexia; SAP, systolic arterial pressure.

4.4.3 Cardiovascular responses to bowel care

Baseline cardiovascular parameters were not significantly different between lidocaine and placebo test days (**Table 4.2)**. Cardiovascular responses during bowel care are shown in **Table 4.2**. All participants had an increase in SAP greater than 20mmHg on each test day, confirming the presence of AD in both placebo and lidocaine conditions. The magnitude of the blood pressure rise was negatively correlated with the baseline blood pressure (r=-0.406; p=0.04). Compared to baseline, the ΔSAP_{max} during placebo was +80±8.7mmHg and during lidocaine was +90.5±13.4mmHg (p=0.386); only three individuals had a smaller (reduced by ≥10mmHg) ΔSAP_{max} with lidocaine than with placebo. SAP_{max} during bowel care was significantly higher with lidocaine than placebo (**Figure 4.3B**). The overall burden of AD on the cardiovascular system (the area under the SAP curve during bowel care) was significantly greater with lidocaine than placebo (**Figure 4.3C**). There was a significant correlation between SAP_{max} during bowel care and the overall burden of AD (**Figure 4.4**). On both test days, participants also experienced profound bradycardia with large and significant increases in SV_{max}, Q_{max} and TPR_{max} during bowel care compared to baseline, and compared to the mean values during the whole period of bowel care (**Table 4.2**). SV_{max} was smaller on the lidocaine than the placebo test day (p=0.005).

We considered the possibility that the lidocaine was effective at reducing the severity of AD, but only during its presumed maximum efficacy, within the first 25 minutes after insertion of the lubricant. Accordingly, we compared the SAP_{max} (lidocaine: 172.9±8.4 mmHg; placebo: 182.8±10.3 mmHg; p=0.313) and AD burden, expressed as the area under the SAP curve (lidocaine: $1.8x10^5$±0.1 $x10^5$ mmHg; placebo: 1.8 $x10^5$±0.2 $x10^5$ mmHg; p=0.9), between the two conditions over the initial 25 minutes of bowel care. Again we found no significant benefit of lidocaine use for the amelioration of AD.

Table 4.2 – Responses to bowel care in placebo and lidocaine conditions

	Placebo	Lidocaine	Between group differences
Time to complete bowel care (mins)	57.7±6.3	79.1±10.0§	21.5±7.8 [6.2 – 36.7]
Baseline			
RRI (ms)	892±42	896±48	4.4±20.2 [-35.2 – 44.0]
SAP (mmHg)	116.7±5.0	123.8±7.2	7.1±5.2 [-3.0 – 17.3]
SV (mL)	79.3±5.6	81.5±6.9	2.1±6.7 [-11.0 – 15.3]
Q (L/min)	5.42±0.3	5.4±0.4	0.1±0.4 [-0.7 – 0.9]
TPR (mmHg • min/L)	18.0±1.4	18.3±1.8	0.3±2.1 [-3.8 – 4.3]
Bowel care			
RRI_{mean} (ms)	908±47	910±50	1.7±19.0 [-35.5 – 39.0]
SAP_{mean} (mmHg)	126.7±7.5	135.7±6.7	9.0±5.3 [-1.4 – 19.4]
SV_{mean} (mL)	77.2±7.2	70.6±7.2	-6.6±3.5 [-13.4 – 0.2]
Q_{mean} (L/min)	5.24±0.4	4.79±0.4	-0.5±0.2 [-0.9 – 0.0]
TPR_{mean} (mmHg • min/L)	21.4±1.7	26.3±3.4	4.9±2.7 [-0.4 – 10.1]
RRI_{max} (ms)	2038±359†‡	1808±182†‡	-230±410 [-1033 – 574]
SAP_{max} (mmHg)	196.7±10.0†‡	214.3±10.5†‡§	17.6±7.9 [2.1 – 33.1]
SV_{max} (mL)	147.5±12.3†‡	120.8±8.9†‡§	-41.7±19.1 [-79.2 - -4.3]†
Q_{max} (L/min)	11.18±1.4†‡	9.36±0.76†‡	22.9±42.2 [-59.8 – 105.7]
TPR_{max} (mmHg • min/L)	111.1±20.9†‡	94.63±13.1†‡	-46.2±39.2 [-123.0 – 30.7]
AuC (mmHg • beats)	$4.4x10^5$±$0.6x10^5$	$6.5x10^5$±$0.9x10^5$§	$2.0x10^5$±$0.7x10^5$ [$0.6x10^5$ – $3.5x10^5$]
ΔSAP_{max} (mmHg)	+80±8.7	+90.5±13.4	10.5±11.7 [-12.4 – 33.4]

Data are expressed as mean ± standard error. Differences between conditions (lidocaine – placebo) are expressed as mean ± standard error [confidence interval]. Abbreviations: RRI, RR interval; SAP, systolic arterial pressure; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance. Statistical significance denoted by: † significantly different from baseline; ‡ significantly different from bowel care mean; § significantly different from placebo condition.

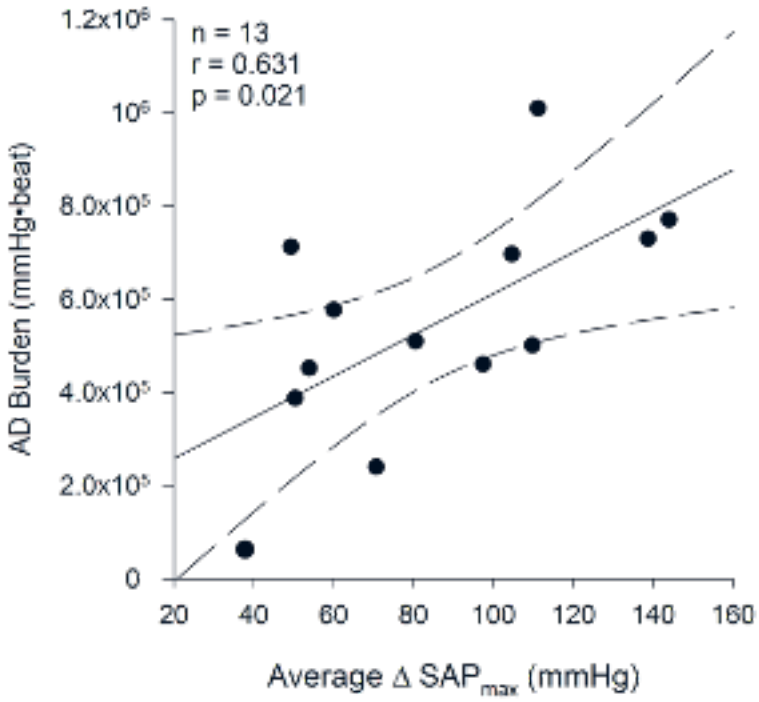

Figure 4.4 – Association between maximum systolic arterial pressure response to bowel care and the overall burden of autonomic dysreflexia.

Larger systolic arterial pressure responses, expressed as the maximum change from baseline (ΔSAP_{max}) were associated with a greater burden of autonomic dysreflexia (defined as the area under the systolic arterial pressure curve during bowel care, the product of systolic arterial pressure and heartbeat). Responses were averaged for each participant for the lidocaine and placebo conditions. Abbreviations: AD, autonomic dysreflexia; SAP, systolic arterial pressure.

4.4.4 ECG responses to bowel care

Rate changes during sinus rhythm

The incidence of abnormal HR was higher during bowel care compared to baseline for bradycardia (p=0.036) and tended to be higher for tachycardia (p=0.07) independent of the placebo or lidocaine condition (**Figure 4.5**). There were no significant differences between placebo and lidocaine conditions in the incidence of episodes of bradycardia or tachycardia at baseline or during bowel care.

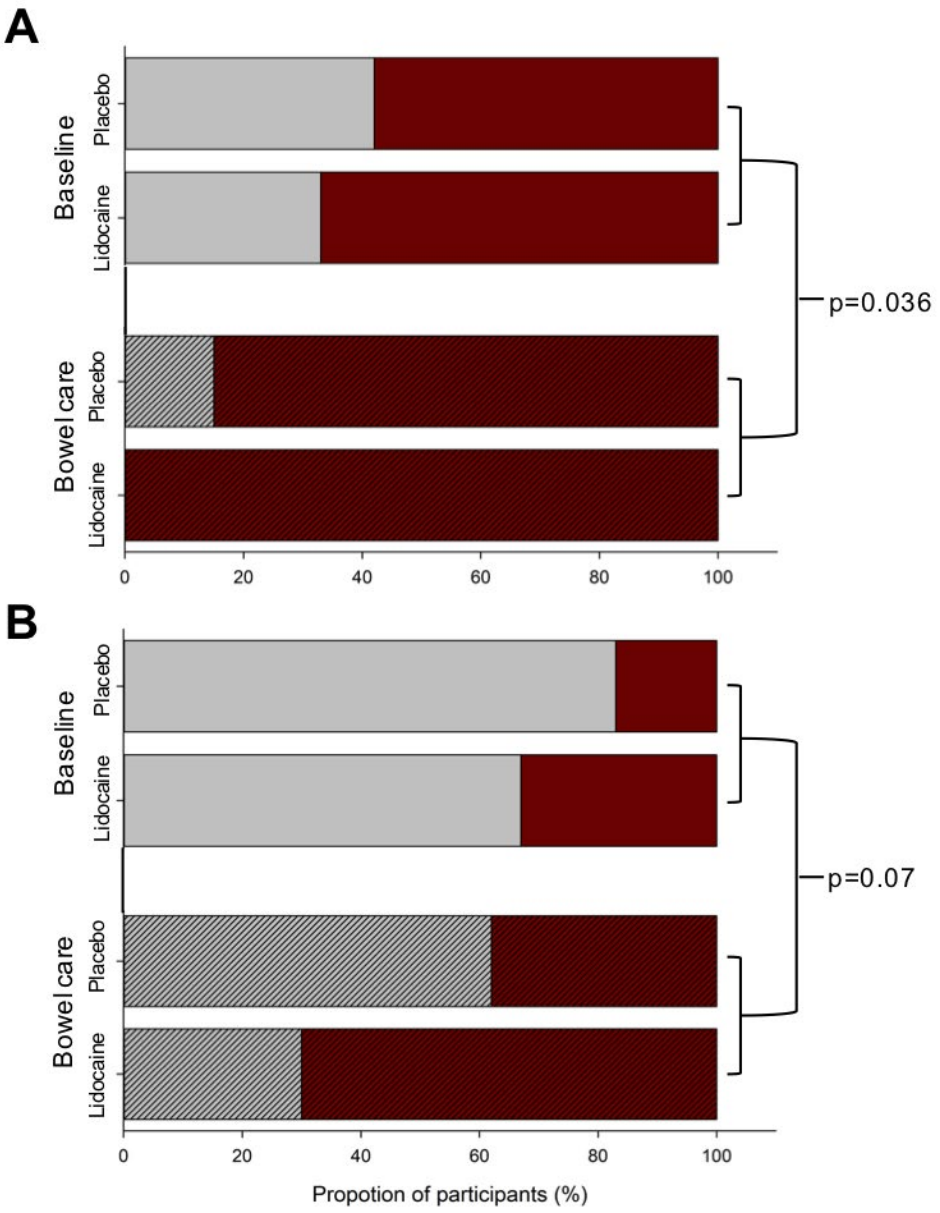

Figure 4.5 – Proportion of abnormal heart rates at baseline and during bowel care. Incidence of bradycardia (A; <60 beats per minute) and tachycardia (B; >100 beats per minute) during at baseline and bowel care in both placebo and lidocaine conditions. Grey boxes indicate the absence of abnormal beats while red boxes indicate the presence of abnormal beats. There was a significant main of test phase, whereby a higher proportion of individuals experienced episodes of bradycardia (p=0.036) and tachycardia (p=0.07) during bowel care compared to baseline for the group. There were no significant differences between placebo and lidocaine conditions in the incidence of episodes of bradycardia or tachycardia, either at baseline or during bowel care.

Rhythm and conduction abnormalities

Cardiac arrhythmia were common during bowel care (**Figure 4.2**). Considering all causes of arrhythmia independent of location of origin in the cardiac conducting system, there were more events during bowel care compared to baseline in the lidocaine condition (p=0.057), but not in the placebo condition (p=0.293). The number of all-cause arrhythmic events during bowel care was greater in lidocaine than placebo (p=0.011). In the lidocaine condition, but not during placebo, there were significantly more arrhythmic events originating from the sinus node, atria and ventricles, but not the atrioventricular node, during bowel care compared to baseline. During bowel care (**Figure 4.6**) there tended to be more events occurring in the sinus node (p=0.052), atria (p=0.084) and ventricles (p=0.051) in the lidocaine than placebo condition.

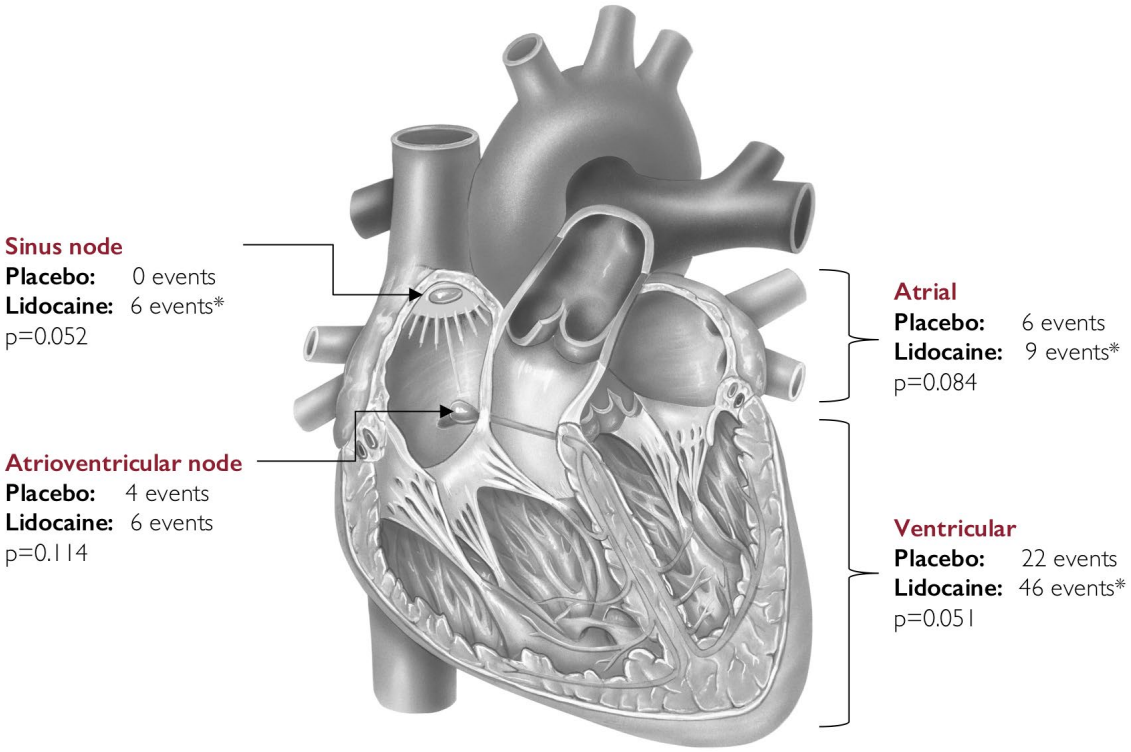

Figure 4.6 – Cardiac arrhythmia during bowel care.
Cardiac arrhythmia were observed originating from multiple locations within the cardiac conducting system. Events observed included: ectopic beats occurring in isolation; ectopic beats occurring in bigeminy; couplets of ventricular ectopic beats; sinus pauses with atrial or junctional escape beats; intermittent second degree atrioventriuclar block (type I); and intermittent bundle branch blocks. Considering all causes of arrhythmia, there were significantly more events during bowel care compared to baseline in the lidocaine condition (p=0.057), but not in placebo (p=0.293). The number of all-cause events during bowel care was greater in lidocaine than placebo (p=0.011). The number of events during bowel care according to their location of origin in the heart are shown, with p values indicating significance of the differences between placebo and lidocaine conditions. *denotes significant difference from baseline.

4.4.5 Participant perspectives

Symptoms typical of AD were reported by 100% of individuals during the lidocaine condition and 90% of individuals during the placebo condition – 80% of individuals thought they had experienced AD on the lidocaine and 90% on the placebo test day. The mean AD symptom score was the same in the lidocaine (7.6±1.5) and placebo conditions (7.0±2.0, p=0.8). The AD symptom score was not significantly correlated with the severity of AD observed when quantified as either SAP_{max} (r=0.254, p=0.27) or the AD burden (r=0.191, p=0.4).

Symptoms of palpitations were reported by 3/11 (27%) individuals during the lidocaine condition and 2/11 (18%) individuals during the placebo condition. When considering whether they normally experienced symptoms of palpitations during their bowel care 5/13 (38%) of participants felt that they did (2 rarely; 1 weekly; 2 daily).

Participants were asked about their perceptions of their bowel care on each test day. They reported that it was worse on the lidocaine day compared to the placebo test day, commonly reporting that initiation of bowel movements was prolonged with lidocaine, with time to empty being longer and more difficult compared to their normal care.

4.5 Discussion

This is the first study to continuously monitor cardiovascular responses during at-home bowel care in individuals with SCI. We showed that, despite the heterogeneity of both SCI and care routines, it is possible to make reliable and accurate cardiovascular assessments during personal care routines.

Our main findings were contrary to our hypothesis – we demonstrated that use of lidocaine lubricant actually worsened the severity of AD during at-home bowel care. This was associated with an increased time to complete care using lidocaine. This may reflect an inadvertent effect of afferent blockade on reflexive bowel emptying – necessitating longer bowel care routines with greater stimuli required to trigger emptying and so exacerbating AD. For example, digital stimulation techniques and use of suppositories rely on intact nociceptive and proprioceptive spinal reflexes. It may be that lidocaine use impairs these reflexes and prolongs the duration of bowel care.

We also found that episodes of AD induced by bowel care provoked abnormal HR responses and cardiac arrhythmia, with rate and rhythm disturbances exacerbated during the lidocaine condition, when the AD was more severe and more prolonged. The increased risk of arrhythmia during AD has been noted previously [25,27,30,31] particularly in individuals with high level autonomically-complete lesions [30]. Interestingly, the incidence of reported symptoms of palpitations during typical bowel care in the present study (38%) was similar to a previous survey of 287 individuals with SCI (32%) [43]. These data highlight the relationships between AD, HR and rhythm abnormalities, and symptoms of palpitations in individuals with SCI and their strong association with bowel care. The greater susceptibility to HR and rhythm disorders during bowel care in the lidocaine condition may reflect the more severe AD in that condition triggering cardiac abnormalities, and/or a direct effect of circulating lidocaine on cardiac sodium channels.

In terms of the participant perception of the treatment, lidocaine use did not improve symptoms of AD or palpitations, and participant questionnaires revealed that they perceived their care routines to have taken longer and bowel emptying to have been more difficult to complete in the lidocaine condition.

These data are important because currently lidocaine lubrication is recommended during bowel care based on the rationale that it would, in theory, ameliorate AD [67,238]. Based on our preliminary data these recommendations are not correct, and novel therapies to blunt AD without exacerbation of the time taken to undertake bowel care are imperative. Use of lidocaine lubrication during routine bowel care should not be recommended.

Our data suggest that lidocaine use should not be recommended during routine at-home bowel care for the amelioration of AD, and we believe this is important information for the clinical and stakeholder community. However, the inability to use lidocaine to ameliorate AD during bowel care raises the question: what is the best solution to mitigate AD induced by routine at-home bowel care? Procedures that shorten the bowel care duration might minimise the overall burden of AD, but may not improve the maximum blood pressure or symptoms provoked by bowel care. Hypotensive pharmaceutical agents might blunt blood pressure spikes during AD, but would have a long lasting effect that would place individuals at risk for syncopal events and OH once the period of AD is over. There are initial case reports showing promising responses to epidural electrical

stimulation to acutely modulate bowel function in motor-complete SCI, decreasing the time to complete bowel care [239,240]. Reports are conflicting, however, as to whether this stimulation improves bowel dysfunction according to clinical outcomes [239,240]. These initial findings underscore the need to replicate these results in larger scale placebo-controlled double-blind crossover clinical trials.

One notable observation was the burden bowel care places on individuals with SCI – all participants experienced severe AD, even in the placebo condition, with SAP_{max} of approximately 200mmHg. Associated palpitations, abnormal HR, cardiac rhythm disturbances, and symptoms of AD were prevalent. The duration of bowel care was long, almost one-hour on average, even without considering cleaning, dressing, and transfers. These data underscore the negative impact of bowel care on quality of life for individuals with SCI [43–45]. Despite high levels of dissatisfaction with bowel care, the majority of individuals with SCI are not actively modifying and optimising their care routines [43]. This may reflect a perceived lack of options for improvement in bowel care, with a lack of evidence-based clinical guidelines, and many clinical recommendations (such as the use of lidocaine lubricant to ameliorate AD) that, despite being based on sound rationale, do not work as intended. Further research into effective strategies to improve bowel care and associated cardiovascular complications should be prioritised.

This study did not assess the impact of anesthetic administration during anorectal procedures. However, previous research demonstrated that topical rectal lidocaine did not blunt the AD response to anorectal procedures [237]. There is evidence that intersphincteric anal block with 1% lidocaine injection can blunt AD responses during anorectal procedures [236]. Our findings may not apply to intersphincteric anal block during anorectal procedures, where efficient bowel emptying is not the target.

The current treatment algorithm for the emergency management of acute hypertensive crises during AD recommends use of lidocaine lubricant while performing bowel checks and manual removal of any stool present that may be triggering or contributing to the episode [67]. Although we did not examine the impact of lidocaine lubricant on bowel procedures performed as part of the acute management of AD, our data call into question the efficacy of this approach. Based on our results it is possible that use of anaesthetic lubricant while assessing bowel triggers for acute episodes of AD would impair the removal of stool, and increase the incidence of HR and rhythm disturbances,

without blunting the blood pressure rise. More research is needed to confirm the best approach for the management of acute hypertensive crises in individuals with SCI that have a bowel trigger.

It should be noted that baseline readings were taken just prior to the initiation of bowel care. As bowel care was performed according to each participant's normal bowel care schedule, we expect that their bowel was distended during this baseline reading, and that this might have induced mild AD at baseline. Despite this, all participants had blood pressure rises upon initiation of bowel care that far exceeded the clinical definitions of AD [138]. Indeed, the rise in SAP_{max} may have underestimated the true magnitude of the blood pressure rise during AD in cases where the baseline SAP was already elevated as a consequence of the presence of faecal material distending the rectum prior to starting bowel care. Interestingly, the SAP_{max} response during at-home bowel care far exceeded that of a previous study examining cardiovascular responses to a standardised in-hospital bowel routine performed by nursing staff [70]. In the earlier study blood pressure was taken intermittently rather than beat-to-beat, so it is probable that the maximum blood pressure rise was not captured. It is also noteworthy that this previous study reported some benefit from use of lidocaine during the procedure in terms of the SAP_{max} (lidocaine +33.2±14.6 mmHg; placebo +50.2±19.5 mmHg, $p<0.001$) [70]. Our data suggest this does not extend to at-home care, and may not reflect the true severity of AD due to the intermittent blood pressure recordings. Another consideration is that the time to complete bowel care or presence of arrhythmia was not reported in the previous study – even if a modest reduction in SAP were obtained during in-hospital bowel care, if this came at the cost of extended bowel care duration or increased arrhythmia, the potential for benefit from lidocaine use may be outweighed.

We designed this study to evaluate the impact of lidocaine on cardiovascular responses to usual bowel care, rather than a standardized bowel protocol. By focusing on usual care, we were able to ascertain whether lidocaine use is a feasible option for ameliorating AD in community dwelling individuals –the reality of bowel care for most people living with SCI. We recognise that the incidence/severity of AD is related to the method of bowel management [68,241]. In our study not all individuals used the same management approach; however, participants did employ the same management strategy on both test days so it is unlikely that variations in the bowel care approach influenced the

outcomes of our study. We consider that the use of real-world bowel care enhances the applicability of our findings to the SCI community.

We limited our study to individuals with high-level SCI who were known to have AD and had a consistent bowel care routine. While this means that our results may not extend to all individuals with SCI, they are likely to extend to the target user group - those with lesions placing them at risk for AD who know that they have experienced it and/or are troubled by symptoms of AD. Interestingly, while our participants were predominantly able to identify the presence of AD, their symptom scores were quite low, and did not reflect the severity of the blood pressure rise. Asymptomatic, or silent AD [21,65,241], has been documented during other potent triggers for AD, underscoring the disconnect between symptoms of AD and the severity of the blood pressure rise.

While not the purpose of the study, it is possible that these data provide additional information as to the nature of the triggering stimulus for AD. Given that local anesthesia was ineffective at reducing AD during bowel care, this could indicate that deep visceral stimuli, such as peristaltic contractions initiated during the bowel routine, are capable of triggering AD. This mechanistic insight could aid the development of bowel routines and/or treatments that minimize triggers for AD.

4.6 Limitations

We had a relatively small sample size for this study, and of course this has the potential to impact statistical power. We performed our sample size calculation for the primary outcome measure (the change in SAP_{max} during bowel care) and this was adequately powered. We conducted interim analyses once our target sample size for our primary outcome measure was reached, and given the clear and statistically robust demonstration of a detrimental effect of the lidocaine on bowel care, AD and the incidence of abnormal HR and arrhythmia, we chose not to continue our recruitment beyond that initial target.

In order to conclude that the lidocaine was ineffective, we must be certain that the dosage and timing were appropriate. We are confident that we had optimal dosing based on the known effective dosage, time of onset of action, and half-life of mucosal lidocaine. We also examined our data over the first 25 minutes of bowel care in case the impact of

the lidocaine administration was beginning to wane in some of the individuals with particularly long care routines – our results were unchanged. Lidocaine was not beneficial.

4.7 Conclusions

Enhancement of bowel care and improvement of associated cardiovascular complications has been highlighted as a priority by individuals with SCI. Routine at-home bowel care is a significant trigger for AD and associated with HR and rhythm abnormalities in individuals with high level SCI. Use of lidocaine lubricant with the rationale of blocking the afferent trigger for AD is not effective: it prolongs bowel care, worsens AD and increases the incidence of cardiac abnormalities. Lidocaine lubricants **should not be recommended** for routine bowel care in individuals with SCI.

Chapter 5

Barriers and facilitators to changing bowel care practices after spinal cord injury: a theoretical domains framework approach[1]

5.1 Abstract

Changes to autonomic processes such as bladder, bowel, and sexual function have been prioritized over improvements in movement and sensation by individuals with spinal cord injury (SCI). Individuals with SCI rely on bowel care programs (lifestyle management) and routines (methods employed) to empty their bowels. Bowel care is associated with high levels of dissatisfaction and decreased quality of life. Bowel care is also a potent trigger for cardiovascular complications in high-level SCI. Despite dissatisfaction, 71% of individuals report using the same bowel care routine for at least the past five years. This suggests a disconnect between dissatisfaction with bowel care and ability to make changes to bowel care routines. We aimed to investigate the barriers and facilitators to making change to a bowel care routine in individuals with SCI. Our approach was guided by the Behaviour Change Wheel and used the Theoretical Domains Framework (TDF) to understand these barriers and facilitators. Semi-structured interviews were conducted with individuals living with SCI (n=13, mean age 48.6±13.1 years) and transcribed verbatim (interview duration 31.9±7.1 minutes). Barriers and facilitators were extracted. Barriers and facilitators were deductively coded using TDF domains and inductively analyzed for themes within each domain. Changing bowel care after SCI was heavily influenced by four TDF domains: environmental context and resources; beliefs about consequences; social influences; and knowledge (61%). All intervention functions and policy categories were considered as viable intervention options. Human (61%) and digital modes (33%) of delivery were identified as preferred methods for intervention delivery. These findings suggest that modifying bowel care is a multi-factorial behaviour. These findings will assist in the systematic development of future interventions aimed at making changes to bowel care.

[1] Roles in this manuscript are defined by author initials: VL, Vera-Ellen Lucci; RM, Rhyann McKay; HG, Heather Gainforth; VC, Victoria Claydon.

5.2 Introduction

Over 2.5 million individuals are living with the devastating consequences of an SCI [242]. In addition to loss of movement and sensation, SCI is also associated with impaired autonomic control including, but not limited to, cardiovascular dysregulation, and bladder, bowel, and sexual dysfunctions [243]. Bowel care problems after SCI are multifactorial, but most commonly relate to NBD resulting from lack of central nervous system control [68]. Accordingly, SCI individuals often experience impairments in quality of life related to fecal incontinence and fecal urgency, constipation, hemorrhoids and abdominal distention [42,43,68]. As with all autonomic dysfunctions following SCI, problems with bowel control stem from the disruption of spinal sympathetic pathways (the “fight and flight” control mechanisms that, in general, increase activity in the internal organs). Parasympathetic (the “rest and digest” control mechanisms that tend to decrease activity in the internal organs) and motor pathways in the sacral circuitry are also disrupted, notably the pudendal nerve, which controls the external anal sphincter [73]. Bowel care after SCI is complex and also reflects a wide variety of cognitive, affective, social, and environmental barriers [6,42,43]. Such a multifaceted problem begs a multidisciplinary solution involving transdisciplinary and translational research that aims to enable people with SCI adopt appropriate bowel care routines.

An international survey of 287 individuals with SCI recently conducted by our research group revealed that people with SCI identified bowel care as a key modifiable factor for improving their quality of life [43]. From this survey, bowel management was reported to be a problem for 78% of respondents: it interfered with personal relationships (60%), and prevented staying (62%), and working (41%), away from home. Bowel management was frequently rated as one of the worst effects of living with SCI. Despite the clear concerns raised by the majority of survey respondents about their bowel care, most (71%) respondents had not made any changes to their bowel routine for at least 5 years. These data highlight knowledge translation gaps in dissemination of evidence-based bowel management strategies, and raise questions about current guidelines for bowel management and where individuals with SCI and their caregivers obtain information about this topic.

In order to develop interventions to support people with SCI, it is imperative to elucidate the barriers and facilitators underscoring changes to bowel care. To achieve this

aim, this study makes use of the TDF [164], an integrative framework to apply theoretical approaches to design interventions aimed at behavior change. The TDF is an evidence-based, validated, integrative framework with 14 domains produced from the synthesis of over 80 constructs across 33 psychological theories, that is used to broadly understand the influences of behaviour [163,164]. These 14 domains of the TDF include knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory, attention, and decision processes; environmental context and resources, social influences, emotion, and behavioural regulation.

To date, the TDF has been used in many populations [150,161,164,194,244]. Recent work has shown the usability of the TDF to understand the influences on participation in daily activities and social roles after spinal cord injury [194,195]. The theoretical basis of the TDF and its previous application in SCI populations makes it the ideal tool to evaluate issues regarding changing bowel care after SCI.

The TDF is an expansion of the COM-B model [150], an evidence-based model which states that three key elements (capability, opportunity, and motivation) influence behaviour. The COM-B model can be linked to intervention functions, policy categories, and intervention options (with associated BCTs and modes of delivery) using the BCW [150,162]. In combination with the BCW, the TDF provides a comprehensive method for designing interventions [150]. Such comprehensive approaches, though needed, are not often seen in behaviour change research.

By conducting semi-structured interviews with individuals with SCI we will identify the barriers and facilitators to making changes to optimize bowel care for individuals with SCI. An assessment of these barriers and facilitators will permit the generation of a framework for change for affected individuals. In addition to the systematic co-development of recommendations for interventions, this process will also identify preferred formats for disseminating bowel care guidelines among our target audience.

5.3 Methods

This study was approved by the Department of Research Ethics at Simon Fraser University and conforms to the principles outlined in the Declaration of Helsinki [215]. All

participants provided written informed consent at the time of screening and verbal informed consent at the time of interview.

5.3.1 Integrated knowledge translation

Conforming to the principles of integrated knowledge translation [144,167] (Chapter 1) and based on the geographical location of the study, Spinal Cord Injury British Columbia (SCI-BC) was identified as a research user and engaged throughout the research process. For more than 60 years, SCI-BC has been helping individuals with SCI living in British Columbia to adapt, adjust and thrive, and is British Columbia's preeminent organization for peer support and information about living well with an SCI. SCI-BC has a long-standing history of partnering with academic researchers, with a provincial membership of >2,500 individuals. They regularly communicate with more than 4,000 people, including individuals with SCI, family members and caregivers, health professionals, and other community and provincial stakeholders. This partnership was particularly key when developing the interview guide, piloting interview questions, and ensuring results resonated with the SCI community. Regular meetings were held with SCI-BC during project conception, and study design, as well as during intervention development and refinement. This partnership strengthened considerations regarding study design, interview questions, and developed interventions.

5.3.2 Recruitment and participants

Participants were recruited for this study through our partnership with SCI-BC. Members of SCI-BC who had agreed to receive email information about up-coming research studies were contacted by email from the SCI-BC administration office. This email included study information, eligibility criteria, and a link to complete a short online screening survey. This study was also promoted on the research participation section of the ICORD website.

Once invited by email, participants were able to access an online questionnaire where they had an opportunity to review the consent form. Those who agreed to participate completed a short survey to determine eligibility and provide contact information. Individuals were eligible to participate if they were able to effectively communicate in English, were at least 18 years of age, and were living with an SCI in

British Columbia, Canada. We employed maximum variation sampling [245] to ensure representation across the SCI community within British Columbia [246], assessing for the following parameters: age, gender, level and completeness of injury, and place of residence (i.e. urban vs. rural). Participants were selected for interview ensuring representation from the above parameters, in line with the population demographics of British Columbia [246]. Those who completed the survey and met the maximum variation sampling and eligibility criteria were contacted by telephone and a convenient date and time for the interview was scheduled.

5.3.3 Interviews

Guided by the TDF, a semi-structured interview guide was developed (Appendix B). This interview guide underwent revision by all team members. After pilot testing with a member of SCI-BC, the interview guide was further refined. The questions developed in this guide allowed participants to indicate any barriers or facilitators to changing bowel care they have experienced or feel they may experience. By identifying probing questions within each TDF domain (and therefore, each component of COM-B), we were able to gain a further understanding of each barrier and facilitator. At the end of each interview participants were also asked to describe their ideal bowel care intervention, to allow elucidation of the preferred mode of delivery for future interventions.

Using the interview guide, eligible participants were contacted, and individual phone interviews were scheduled. All interviews were conducted by the same researcher (VL). These interviews were recorded, and then transcribed verbatim and anonymised (NVivo, Version 12). The TDF was then used to categorize the barriers and facilitators to changing bowel care practices in addition to exploring emergent themes within each TDF domain. The TDF recommends at least 10 interviews, with an additional three interviews that were then appraised for the presence of new themes. If new themes emerge, 3 additional interviews are conducted until no new themes immerge (for a minimum of 13 interviews) [164].

5.3.4 Data Analysis

To fully understand the behaviour (step one of intervention design, Chapter 1), a two-phase abductive data analysis approach was taken, wherein barriers and facilitators

to changing bowel care were extracted and analysed both deductively using the TDF and inductively for themes within each TDF domain. A schematic of the study protocol can be found in **Figure 5.1**.

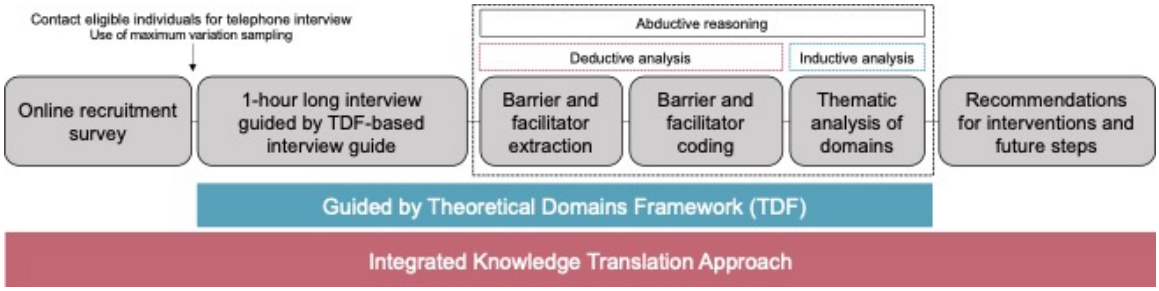

Figure 5.1 – Study protocol.

Barrier and facilitator extraction and deductive analyses

Barrier and facilitator extraction was performed independently for all interviews by two members of the research team (VL, RM), double extracting each interview. Changing bowel care was defined as any action taken to change either bowel routines (acts taken to empty bowels) or bowel programs (lifestyle actions to optimise bowel emptying). Factors that promoted changing bowel care were coded as facilitators, while factors impeding changing bowel care were coded as barriers. Extracted barriers and facilitators for each interview were then independently coded by two coders into the 14 TDF domains. Each interview was double coded, and agreement between coders recorded using Cohen's Kappa [202] and prevalence-adjusted bias-adjusted Kappa (PABAK) [203]. Any disagreement between coders was resolved through discussion. In the event that a consensus was not met, an expert coder was consulted (HG). The manual for barrier and facilitator extraction and coding can be found in Appendix B.

Inductive analysis

To gain a deeper understanding of the barriers and facilitators identified in the deductive analysis, an inductive thematic analysis was conducted within the prevalent TDF domains. The inductive analysis is strengthened by the involvement of the research team as "critical friends", where members of the research team (RM, HG, VC) review themes and provide input and suggestions for their refinement [198,199]. Each critical friend provided their own unique expertise to the research question.

5.3.5 Intervention and implementation options

Intervention options

The process of identifying intervention options was guided by the BCW [150]. To determine the source of behaviour, the prominent TDF domains were linked to their associated COM-B components. Using a series of previously developed matrices, the COM-B sources of behaviour were mapped to intervention functions, then these intervention functions were linked to the policy categories most likely to support the intervention function. The matrices used for this analysis can be found in Chapter 2.

Implementation options

Preferred modes of delivery identified by participants were extracted and independently coded by each coder using the Modes of Delivery Taxonomy version 0 [200,201] for all interviews.

5.4 Results

5.4.1 Participant demographics

Thirteen (n=13) semi-structured interviews were conducted over the phone by the first author, as guided by the TDF (see Interview Guide, Appendix B). Participant demographics can be found in Table 5.1. On average, participants had a diverse range of SCI levels (C4-L1) and serveries (AIS A – D) with interview duration averaging 31.9±7.1 minutes. Mean age at time of interview was 48.6±13.1 years and average duration since injury was 21.6±12.5 years. A majority of participants were male (n=8) and lived in urban settings (n=8).

Table 5.1 – Participant demographics.

Demographic and injury information	
Sample size (F/M)	13 (8/5)
Age	48.6±13.1 years
Duration of injury	21.6±12.5 years
Injury level	C4 – L1
Injury severity	AIS A – D
Duration of interview	31.9±7.1 minutes
Geographical region (urban/rural)	8/5

Where applicable, data are expressed as mean±SD. Abbreviations: AIS, American Spinal Injury Association impairment scale

5.4.2 Deductive analysis

The two independent coders double extracted a total of 409 barriers/facilitators from all 13 interviews, comprising 200 barriers and 209 facilitators. All barriers and facilitators were coded into at least one TDF domain, with some items coded into multiple TDF domains. This resulted in a total of 426 observations (205 barriers, 221 facilitators). For all barrier and facilitator coded the average inter-coder agreement was outstanding (Cohen's Kappa 0.76±0.04, PABAK 0.94±0.01). Numbers and proportions of barriers and facilitators identified across all 14 TDF domains can be found in Table 2.

Among barriers, the most commonly coded domain was beliefs about consequence (BCon), followed by environmental context and resources (ECR). Together these domains accounted for 48% (n=100) of all reported barriers. Other commonly coded domains for barriers included Reinforcement (12%, n=25), Knowledge (11%, n=22), and Intentions (9%, n=18). Among facilitators, the most commonly coded domain was ECR, accounting for 24% (n=54) of all facilitators, followed by Goals (19%, n=41). Across both barriers and facilitators, ECR, BCon, and Social Influences accounted for 55% of all coded barriers and facilitators (ECR, 23%, n=100; BCon, 21%, n=88; Social Influences, 11%, n=48). A visual representation of all coded barriers and facilitators can be found in **Figure 5.2**, while a representation of TDF domains by either barriers or facilitators can be found in **Figure 5.3**.

Table 5.2 – Barriers and facilitators to changing bowel care by TDF domain.

TDF Domain	Barriers			Facilitators			Overall		
	%	N occurrences	N interviews	%	N occurrences	N interviews	%	N occurrences	N interviews
Environmental context and resources	22	46	12	24	54	11	23	100	13
Beliefs about consequences	26	54	13	15	34	12	21	88	13
Social influence	7	14	5	15	34	13	11	48	13
Goals	0	0	0	19	41	13	10	41	13
Reinforcement	12	25	10	7	15	8	9	40	11
Intentions	9	18	7	9	19	9	9	37	11
Knowledge	11	22	8	1	3	3	6	25	8
Memory, attention, and decisions processes	5	10	3	1	3	4	3	13	7
Optimism	5	8	4	2	5	2	3	13	5
Beliefs about capabilities	1	1	1	3	7	5	2	8	6
Emotions	3	7	4	0	0	0	2	7	4
Behavioural regulation	0	0	0	1.5	3	3	0.5	3	3
Skills	0	0	0	1.5	3	2	0.5	3	2
Social/Professional roles and identity	0	0	0	0	0	0	0	0	0

Abbreviations: TDF, Theoretical domains framework

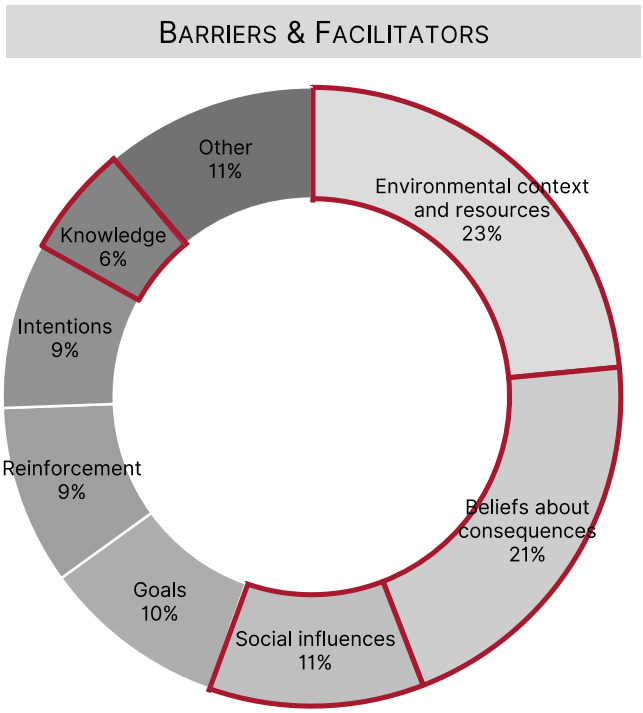

Figure 5.2 – Proportion of total barriers and facilitators by TDF domain across all interviews.

Domains outlined in red reflect those included in the inductive analysis. Abbreviations: TDF, Theoretical domains framework.

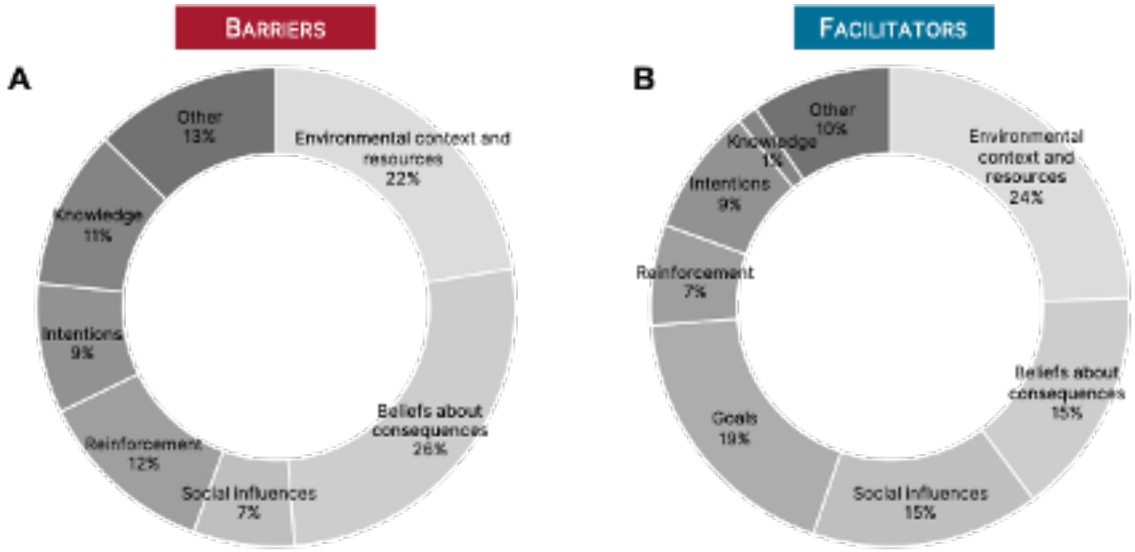

Figure 5.3 – Barriers and facilitators by TDF domain across all interviews.

(A) Proportion of barriers by TDF domains. (B) Proportion of facilitators by TDF domains. Abbreviations: TDF, Theoretical domains framework

5.4.3 Inductive analysis

A thematic analysis was conducted within the three most prominent domains (i.e., ECR, BCon, and SI) and Knowledge. These four domains were considered for inductive analysis based on the severity of their implications and their significance in interviews, as determined by the first author. Three members of the research team acted as critical friends (RM, HG, VC), aiding the primary researcher in the refinement of themes. Below, each domain is presented and described, including a description of themes within each domain, and implications for care. Dominant domains and associated themes can be found in **Figure 5.4**.

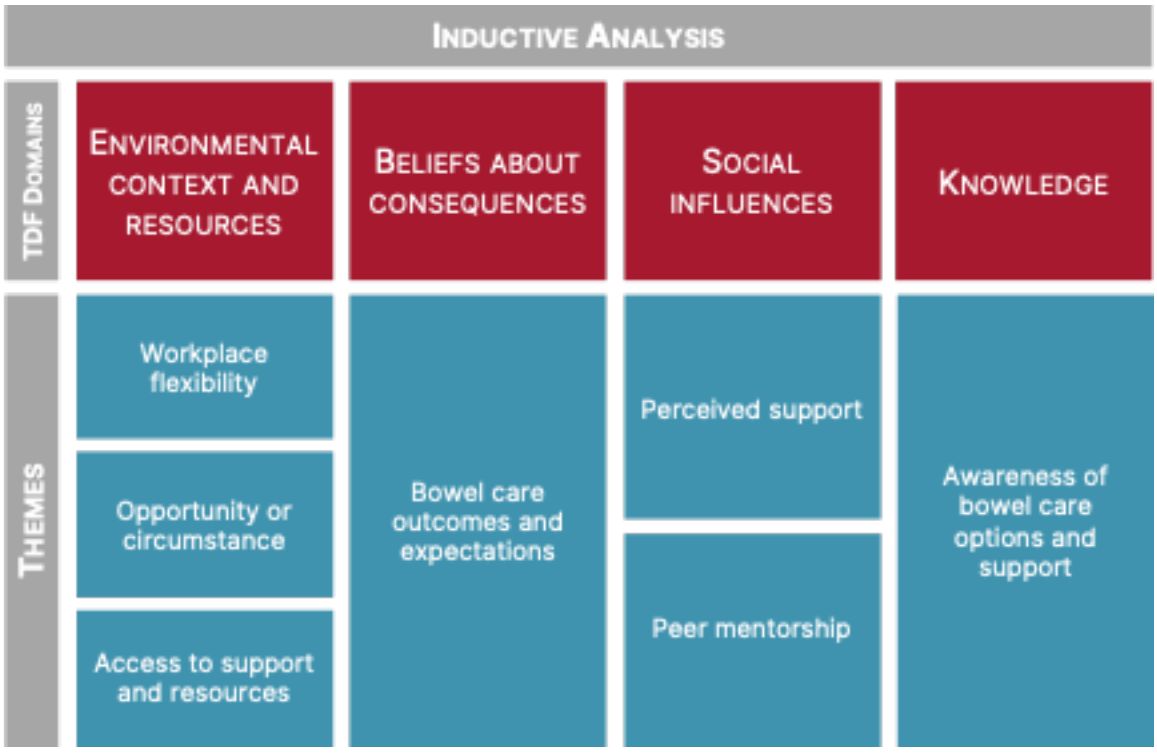

Figure 5.4 – TDF domains and associated themes related to changing bowel care practices after SCI.

Note: Red boxes represent domains and blue boxes below represent domain-specific themes. Abbreviations: TDF, Theoretical domains framework.

Environmental context and resources

ECR describes any circumstance of a person's situation or environment that discourages or encourages the development of skill and ability, independence, social competence, and adaptive behaviour aimed at changing bowel care. In the interviews, ECR accounted for 23% (n=100) of all coded barriers and facilitators (22% barrier, 24%

facilitators). ECR was identified as the most prominent domain and discussed in every interview. Participants described how flexibility in their workplace influences their decisions to change their bowel care. In addition, one's opportunity to change and access to resources were also heavily influential in the context of changing bowel care.

Workplace flexibility

Workplace flexibly was identified as a theme in facilitating changes to bowel care within the ECR domain. Participants noted that when they were engaged in a supportive and/or flexible work environment, they felt that they could better make changes to their bowel care routines when desired or necessary. One participant described how the flexibility to work from home allowed them to make changes to their bowel care routine that they may not otherwise have considered:

> *"I think that also coincides with the fact that 10 years ago, I started working... out of my home instead of my office, so it's just easier for me to jump on the toilet if I have to, you know what I mean"*

Opportunity or circumstance

In addition to workplace flexibility, one's individual opportunity or circumstance was shown to influence how individuals approach changes to bowel care. This is particularly important given the reality that approaches to bowel care must change over time to align with physiological changes in bowels throughout the ageing process or in response to other lifestyle or physiologic factors. The recognition of circumstances related to ageing were active facilitators in making changes to bowel care. Conversely, some circumstances discussed included tolerance of a suboptimal bowel care routine, stating that change would only occur if the routine worsened. Other contextual considerations to changing bowel care included learning about the impact of SCI on individual physiological processes and how best to modify bowel care to the direct needs of the individual. One participant described it as:

> *"And it took so long [to empty my bowels] that it was a nightmare and I thought that that was going to be my life. And I [eventually] realized that I needed to [learn] how [my body] responded to laxatives"*

Additionally, opportunity to change bowel care came from changes in other care routines (notably, changes in bladder care) that permitted participants to focus on prioritising changes to bowel care. When discussed, there was an obvious presence of hierarchical changes to care routines with bladder management conveyed as the less cumbersome routine to change, with more known options and advice from health care professionals:

> *"I think I'm in a good spot in terms of if I wanted to change because, like, I found something that really, really helps me manage my bladder."*

Throughout the interviews we did not identify any sex difference in bowel care practices with the exception of the bladder care. Bladder care was an important consideration for 60% (n=3) women when considering changes to bowel care. This speaks to the interplay between various physiological processes, and the heavy burden of care that stems from their management.

Access to support and resources

Another theme within the ECR domain was access to support and resources. Support (either physical or emotional) was discussed in relation to family members, caregivers, and health care professionals, community, and SCI peers. A lack of perceived support was often cited as a barrier to change, especially when discussed in the context of physical supports. Lack of support (i.e., ideas for bowel care optimisation, changes to bowel care strategies) from health care professionals decreased participants belief in proficiency among health care professionals in relation to bowel care needs. This can be seen through the following quotes:

> *"I haven't met anybody that's been able to offer...information about topics that I bring up with them"*

> *"And the thing is that the family doctor, they don't know much about spinal cord injuries, or neurogenic bladder and bowel. They really only know when something is a disaster, that it needs to be fixed. They're not like thinking about prevention, or optimizing, you know"*

"Um... unfortunately, locally, um... I certainly know a lot more than a physiatrist or a doctor, GP…I'm not saying that we're the doctors, but I know more about bowel than my doctors do."

Additionally, access to specialists was also discussed geographically with individuals in rural settings lacking this support over those in urban settings. Physical barriers to changing bowel care were also present and included both financial and time restraints. Costs associated with changing bowel care routines but not covered by extended healthcare were repeated barriers to exploring different bowel care practices. Examples of the impact of both financial and time constraints can be seen through the following quotes:

"It would depend on the cost totally…"

"It's time consuming and I was busy, still am busy, but it was more for convenient [to do my bowel care this way]"

"I mean I would have to have some time off work, or I'd have to make a change over the holidays time or something I suppose, but then it would mess up my holidays."

Beliefs about consequences

In the interviews, beliefs about consequences accounted for 21% (n=88) of all coded barriers and facilitators (26% barrier, 15% facilitators) and relates to the acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation.

Bowel care outcomes and expectations

The predominant theme within the beliefs about consequence domain surrounds bowel care outcomes and expectations. This includes both participants' beliefs about changing bowel care (what change can or what cannot do for the participant) and the impact that changing bowel care has on several aspects of life. Fear and apprehension about changing bowel care were widely discussed. One participant described it as:

"I think fear of accidents would be the biggest…yeah, the biggest challenge for anyone who's considering changes."

Though affectual, these fears were discussed as what was believed to happen if one's bowel care routine was altered.

Additionally, participants often discussed aspects of care that would change as a consequence of changing bowel care, including independence, dependence on care-aids or family care providers, as highlighted in one interview:

> *"I'm independent in every other way, so to not be able to do [aspect of bowel care] would be… eh… it would be an inconvenience to have someone come in to do that or help with that"*

This focus on bowel care outcomes and expectations was a consistent theme throughout transcripts, with every participant discussing beliefs about consequences at some point, with all participants describing it as a barrier and 12 participants discussing it in terms of facilitating changes to bowel care.

Social influences

Across all interviews, the social influences domain accounted for 11% (n=48) of all coded barriers and facilitators (7% of all barriers and 15% of all facilitators), highlighting those interpersonal processes that can influence individuals to change their thoughts, feelings, or behaviours. All interviews discussed social influences as a facilitator, with five interviews also discussing social influences as a barrier to changing bowel care. In addition to the unique influence of peer mentorship, perceived support external to SCI peers was identified as a large theme within social influences when considering changes to bowel care.

Perceived support

With the awareness that certain interpersonal relationships could influence changing bowel care, participants often regarded the level of perceived support from these resources as a barrier or facilitator to changing bowel care. This appraisal on the level of support comes directly from interactions within the interpersonal relationship and acts as a form of either direct or indirect persuasion. It is important to note that, in this context, the domain of social influence differs very subtly from ECR. ECR addresses the resources and/or supports that are or are not available to a person, whereas social influence highlights how the known resources and/or supports function. Other's perceptions,

reactions, and judgement of bowel care acted as a persuasion to change bowel care practices. For example, one participant noted the implication that travelling with friends has on bowel care:

> *"I went [away] with some friends, guy friends, and I didn't want them wiping my bum, you know, one thing to help a buddy get into a shower chair naked or with a towel over my lap, and another thing altogether to stick a finger in [my] bum and wipe [my] ass."*

In addition to social influences in the context of a peer or friendship groups, participants also identified the level of support they receive from health care professionals as a factor influencing making changes to their bowel care. These responses varied, with some participants identifying health care professionals as essential components of bowel care change, whereas others did not regard health care professional as helpful when exploring this behaviour. These two competing ideas are outlined well with the following:

> *"My doctor has not been very helpful [in regard to changing bowel care]"*

In contrast to another participant outlining the deep reverence they have for their health care provider when considering changes to bowel care routines:

> *"I think [changing my bowel care from that my doctor prescribed] would be highly disrespectful and maybe even irresponsible, because, you know it may end up going against you. You know, it may not work out to not take the advice that I've been given when I'm lucky enough to have access to that kind of care."*

Another major source of perceived support came from family members, regardless of whether family members were also family care providers. Some individuals spoke about how they felt supported to change their bowel care:

> *"I mean, my family would support me [changing my bowel care], obviously"*

While others expressed how they did not feel supported by their family, which proved to be a barrier to changing bowel care practices:

"But [my partner] did not want to know anything about number two and me, ever"

Peer mentorship

In addition to perceived support, support from peers was regarded as highly influential to making bowel care changes. Peer mentorship has repeatedly been shown to have a unique influence on individuals after SCI. Peer mentorship provided relatability regarding bowel care practices while concurrently modelling different approaches to care. It was often mentioned that, when gathered either formally or informally, conversations among individuals with SCI and their peers ultimately turn to the topic of bowel care, giving rise to a common group identity. This empathy, understanding, and collectivism was described as:

"I have all the peer groups. And so, you know, just relying on the experience of some of the older peers that, you know, are in their 70's or 80's [and] might have gone through stuff, and I mean, like, every peer coffee at some point has had a discussion on bowels."

Knowledge

Knowledge accounted for 6% of all coded barriers and facilitators (n=25) and was coded in eight interviews as a barrier, as well as being discussed in three interviews as a facilitator. The principles of thematic analysis emphasize the significance of a theme over the prevalence. Knowledge is the one domain that if unaddressed poses a larger barrier to engaging in other issues surrounding changes to bowel care If one is not aware of the available options, they do not know how to change, and therefore cannot change. Knowledge is an important component to changing bowel care and emerged as the singular theme within the knowledge domain.

Awareness of bowel care options and support

It was apparent that changes to bowel care were not always explored because of a lack of awareness surrounding bowel care options, implementing changes to bowel care, and support. This includes not only the level of understanding of the physiological disruptions to bowel function resulting from SCI, but also the knowledge of bowel care options and the resources to access those options:

"I can't say that because I'm sure somebody has one somewhere, I just don't know what it is yet" [CONTEXT: do you believe that there is an ideal working routine?]

Conversely, awareness of bowel care options empowered changes to bowel care, highlighting the importance of the knowledge domain:

"I feel like I have the tools and the knowledge I need to change it up if circumstances require it"

5.4.4 Identifying Intervention Options

When linked back to the COM-B model using the BCW, the TDF domains considered for inductive analysis (BCon, ECR, social influences, knowledge) correspond to the behavioural sources of reflective motivation, both physical and social opportunity, and psychological capability. These domains were identified as the factors that need to be addressed in order for bowel care practices to change. Using the matrix that links COM-B components to intervention functions, all intervention functions could be used to promote bowel care behaviour change. However, Enablement, Education, and Training were the three most prominent intervention functions. Invention functions were then plotted against policy categories using an additional matrix tool. This revealed that any policy categories could be considered relevant when developing interventions.

5.4.5 Identifying Implementation Options

Mode of Delivery Analysis

A total of 18 modes of delivery were double extracted by two independent coders (VL RM) from all 13 transcripts. Using the Mode of Delivery Taxonomy version 0 (MoDtv0) [200,201], extracted modes of delivery were coded into mode of delivery categories. Inter-coder agreement of mode of delivery coding was "almost perfect" (Kappa = 0.85±0.2; PABAK = 0.90±0.05). Human (61%), digital (33%), and print material (6%) were identified as potential modes of delivery. It was unclear as to how human interaction was to be used as a mode of delivery with 82% (n=9) of human modes of delivery coded as "unclear".

However, digital and print material included email (n=2), websites (n=3), instant message (n=1), and leaflet (n=1).

5.5 Discussion

These findings provide a theoretical understanding of the barriers and facilitators to changing bowel care practices after SCI. Our analyses reveal that interventions focused on bowel care change should aim to target one's reflective motivation, psychological capability, and both social and physical opportunity. As such, these interventions will require a multifaceted approach, for which we have identified applicable intervention functions and policy categories, and have revealed preferred methods for intervention delivery.

These findings align with previous work conducted into the assessment of bowel care and quality of life following SCI [6,42,43,45]. However, to our knowledge, this is the first study to assess the barriers and facilitators to changing bowel care behaviour after SCI, and these are the first intervention recommendations to be co-developed for this issue. Additionally, this study demonstrates the utility of the BCW and TDF for co-developing interventions into changing bowel care practices after SCI.

5.5.1 Understanding the behaviour

The identification of ECR, BCon, Social influences, and Knowledge as the most relevant TDF domains has clear implications for the future development of theory-based behaviour change interventions. In a way, identification of the importance of environmental and social factors is not novel in SCI research. However, it is important to note that many behaviour change intervention functions solely address one's motivation to change [162]. This approach would fail to address the environmental, social, and knowledge-based factors that also influence behaviour. This study suggests that individuals need personalised care that addresses access to knowledge and resources. However, based on their beliefs about consequences, individuals may or may not be motivated to change bowel care practices. Future interventions should explore theories that leverage all COM-B components identified in this work to enable bowel care changes aimed at increasing satisfaction and quality of life.

Environmental context and resources

Themes emerging from ECR explored the role of employment after SCI, access to care aids, and one's opportunity or circumstance to change bowel care. As ECR relates to one's physical opportunity, this domain provides information on how one is physically able to interact with their environment, and access available resources to change their bowel care [150]. Previous research assessing service needs after SCI showed that access to healthcare services was unmet within this population [247]. Additionally, a lack of financial support and time to change bowel care was a common theme within these interviews. This finding is unsurprising given the personal economic implications after SCI [3], the prevalence of fixed incomes in disabled communities [247], and the impact of fixed community care hours on care routines [143].

Complimentary to access to financial resources, these data also revealed the importance of workplace flexibility when considering changes to bowel care practices. Given that changes to employment often occur after SCI [248], it would be interesting to assess the interaction of care routines and workplace flexibility in future studies. Certainly, these findings are a definitive call for increased consideration in the workplace to allow individuals with SCI to attend to care needs.

One's circumstance or opportunity to change bowel care was also a common theme within the ECR domain. A surprising finding was the interplay between bladder and bowel care in the context of changing bowel care. Properly managed bladder function was shown to facilitate changes to bowel care, specifically in women. This might reflect that the methods used for bladder drainage that differ between men and women, with increased need for transfer and intermittent catherization in women. However, it was clear there was a hierarchical consideration to changing care routines, with changes to bladder care taking priority over changes to bowel care. This finding complements previous research that showed that individuals with SCI will adopt fluid restriction to help with troublesome bladder care, even if it negatively impacts other aspects of quality of life or managing bowel care routines [43]. The impact of fluid restriction on bowel care again displays the interconnectedness of these two care practices. The interplay of autonomic dysfunction (bladder, bowel, sex) is well appreciated in autonomic research [6,243,249]. However, this study highlights the importance of understanding care routines in context with each other, and underscores the need for holistic care.

Beliefs about consequences

Outcomes and expectations about changing bowel care practices were central to BCon. BCon addresses how one's reflective motivation [150], or appraisal of the negative or positive consequences to changing bowel care influence the behaviour. Negative outcomes commonly discussed were the fear of bowel accidents and/or the uncertainty of the outcomes when changing care. It is well appreciated that fecal incontinence is common, and a key area of concern after SCI [42,43,48,250]. Despite a variety of bowel care, lesion levels, and injury severity. practices, concerns about continence were common among all participants, as evident in our themes.

Other investigations have revealed the impact that bowel care has on quality of life [6,42,43,45]. Given its impact on quality of life, it is perhaps not surprising that changing bowel care would also be considered to have an impact on quality of life, with considerations regarding the perceived consequences heavily influencing the desire to make changes to bowel care. However, changing bowel care is not the only aspect of SCI that is associated with concerns about negative consequences. Other urogenital considerations have also been shown to be associated with perceived negative outcomes [251]. Again, this finding underscores the interplay present between different autonomic dysfunctions after SCI and highlights the need for their comprehensive management.

Social influences

It was not surprising these interviews discussed the unique power of peer mentorship as a prominent facilitator to changing bowel care practices because SCI peer mentorship has been shown previously to increase self-efficacy when assessing health care outcomes [252,253]. Peer mentorship is also important to consider given the role it can play in increasing bowel care knowledge. Peer mentoring have been shown to be useful when facilitating adjustment after SCI [254,255]. Peer mentorship has been described as providing increased credibility, over that of non-peer relationships [256]. The particularly unique perspective that peer mentorship provides should be explored when developing interventions aimed at changing bowel care.

The influence of healthcare providers, family members, and family support providers on making changes to bowel care was evident. These interpersonal dynamics have been increasingly shown to be a major influence on behaviour change after SCI

[193,257,258]. This finding is consistent with research that has shown the role that familial support plays in rehabilitation and care, and relationship quality has also been shown to be related to levels of perceived social support [258]. Additionally, having a live-in partner has been shown to increase mobility and economic sufficiency, showing the multiple roles that family support has after SCI [255]. The perception of health care provider credibility was also shown to influence bowel care behaviours. This perception is an interesting consideration for the dissemination of bowel care strategies and underscores the need for health care providers to be informed about current best-practices, while prioritising bowel care in their interactions.

Knowledge

Knowledge was discussed in relation to both knowledge of the physical changes to bowel and gastrointestinal function as a consequence of SCI and knowledge of the resources or supports available to aid bowel management, addressing how informed one is about options to change behaviour [150]. Perhaps not surprisingly, it has been shown that clinical practice guidelines have poor adherence among health care professionals administering bowel care procedures unless they are targeted by a specific intervention [259]. As individuals with SCI commonly learn bowel care approaches during their in-patient rehabilitation, it is imperative that health care providers adhere to proper bowel care guidelines. This importance of education and training in care routines during rehabilitation is underscored by a recent study that showed that less than 50% of SCI patients had good knowledge about bladder management and pressure ulcers after discharge from an inpatient rehabilitation centre [260].

The role of knowledge in the context of care routines of course reflects in part whether clinical care guidelines reflect current best practice, and this is not always the case, with a significant lag between research discovery and adoption into clinical standards. For example, current bowel care guidelines incorporate advice concerning the use of local anaesthetics for the management of cardiovascular complications of bowel care [261] that directly contradicts recent data [190]. This finding highlights the need for increased evidence-based bowel management strategies and regular updates to clinical care guidelines. As knowledge creation is a key component to the knowledge-to-action framework of knowledge translation [166], it is important that knowledge tools are constantly evaluated so that their application can be appraised.

Interestingly, knowledge was identified as an important factor influencing the ability to make changes to bowel care, while the skills domain was not a prominent consideration in the interviews. This finding suggests the accessing information about bowel care change, not implementing changes, represents the greater barrier to change.

It is important to note that we first selected prominent TDF domains for inclusion in our inductive analyses. However, the inclusion of the knowledge domain was a decision made by the primary researcher based on the behavioural diagnosis that emerged from the deductive coding. These themes emerged as important, modifiable, addressable concerns as identified by the primary author [262]. However, it is important to recognise that the inclusion of the knowledge domain in the inductive component of these analyses may be different upon reanalysis by another evaluator. This approach is well-recognised and appropriate in thematic, inductive analyses, where is possible that a reanalysis of the work would produce different findings with nonoverlapping components [197]. However, the results of both the deductive and inductive analyses have been overseen by team members acting as critical friends in the research process. These findings also resonated with our community partners and were identified as actionable, addressable concerns. These steps enhanced the rigor, sincerity, credibility, and resonance of the self-reflective inductive analysis [199]

5.5.2 Intervention and implementation options

To date, there is an abundance of literature surrounding bowel management strategies and community-level assessments of bowel programs. This body of work provides us with an understanding of how bowel care is currently being conducted in the community. Bowel care is a key concern for individuals with SCI [6,43,44]; however, the lack of research examining interventions aimed at improving care is troubling. To date, there are few case studies investigating the use of functional electrical stimulation to improve bowel care [263,264] and autonomic dysfunction following SCI, in addition to investigations using exoskeletons to improve bowel function [265]. Additionally, guidelines for at-home community care are dated and provide conflicting evidence [57,74,190]. There are no theory-based interventions to our knowledge. This paucity in the literature provides a unique opportunity to address prominent bowel care concerns using frameworks that will allow for the evaluation of intervention.

This study made use of the TDF to both categorise and understand barriers and facilitators to bowel care change. The use of this framework provides organisation to understand this behaviour. By embedding the factors that influence bowel care behaviour change within the TDF, researchers can develop interventions that target the most relevant influences on behaviour. However, the TDF is a framework is not a theory and therefore, does not provide rationale as to how constructs are linked and influenced by each other. Thus, when this behavioural diagnosis is used to inform intervention design, that intervention must be grounded in behaviour change theories. The BCW provides a systematic approach to identify and link constructs influencing behaviour to intervention strategies. Identifying a behaviour change theory that aligns with the constructs identified in this research may be a useful addition to guide intervention development and evaluation.

5.5.3 Future directions

In this study the TDF was used to understand the barriers and facilitators underpinning behaviour change in the context of bowel care and enable the co-development of intervention recommendations. With the recommendations from this study, interventions into changing bowel care practices can now be co-developed between researchers and community organisations with the ultimate aim of improving bowel care satisfaction. To do this, next steps include the translation of these recommendations into concrete, actionable tools. The recommendations created will be evaluated using feasibility criteria (i.e., APEASE criteria to determine if the recommendations are **a**ffordable, **p**ractical, **e**ffective, **a**cceptable, **s**afe, and **e**quitable) [150]. It is important these future steps continue to use an integrated knowledge translation approach. Consultation and co-development with community organisations will create relevant and informed decisions. Guiding principles for integrated knowledge translation to conduct and disseminate SCI research have recently been released [144]. These rigorously co-developed principles should be used to support meaningful SCI partnerships, in turn improving the relevancy and impact of this research.

Further barrier and facilitator assessments

This work also revealed the unique impacts of caregivers and health care providers on changing bowel care practices. Interestingly, work into the role of caregivers after SCI

shows that caregivers often face the same barriers as individuals with SCI. As such, it is crucial that the role of caregivers on bowel care practices and their barriers and facilitators to changing bowel care also be assessed. In addition to caregivers and support providers, this study also underscored the importance of health care providers when considering changes to bowel care practices. Accordingly, there is an additional need to assess the barriers and facilitators to changing bowel care practices among health care professionals. It will be important to assess providers from a variety of health care settings, ranging from specialised outpatient bowel care programs and rural-community dwelling GPs. It is clear that changing bowel care is multi-faceted, lends well to the complexity of the human condition, and the heterogeneity of SCI. Future investigation into bowel care practices needs to address a myriad of concerns, especially those outlined by our findings.

5.6 Strengths and limitations

While this study made excellent use of maximum variation sampling, our scope was specific to individuals living with SCI in British Columbia, Canada. In spite of this limitation, we saw common themes emerge between participants regardless of lesion level, injury severity, and geographical location. Given that British Columbia is a large, diverse province, we believe that our findings are applicable to other individuals living with SCI in Canada. However, regional differences in care access and available resources across provinces should be considered. Given our partnership with SCI-BC, these results are directly relevant to the British Columbian context, where interventions can be co-developed and implemented through this partnership. Our partnership with SCI-BC, the co-development of the interview guide, and recommendations for intervention displayed the importance of an integrated knowledge translation approach. This approach increased the feasibility and relevancy of this work. Additionally, this work employed the use of validated behaviour change strategies [163]. The systematic use of behaviour change theory to develop behavioural interventions may increase their efficacy and reproducibility [162].

In addition to satisfaction, bowel care complications have also been shown to adversely impact quality of life. Most notably, the cardiovascular dysfunction that occurs concurrently with bowel care and management seen in high-level SCI has a profoundly negative impact on quality of life [43]. The nature of this study did not permit investigation of cardiovascular autonomic dysfunction. However, future investigations of the

relationships between bowel care and cardiovascular problems should be considered in the context of making changes to bowel care routines.

Additionally, the proportion of women in this study exceeded that of the SCI demographic which may suggest that women have more continence concerns or more willingness to discuss continence concerns. Additionally, recruitment material suggested that the interview could be conducted by someone with a female name which could have impacted willingness to disclose.

5.7 Conclusions

It is apparent that bowel care is an area of dissatisfaction among individuals living with SCI. We have shown there are numerous factors that influence changing bowel care practices, especially those influencing environment, resources, beliefs about consequences, social influences, and knowledge. These data will allow for further iteration of the knowledge translation products, development of bowel care resources, and assist in the co-development of bowel care interventions that will provide a deeper understanding of the mechanisms that influence the uptake of new knowledge within the many facets of the SCI community.

Chapter 6

Markers of susceptibility to cardiac arrhythmia in experimental SCI and the impact of sympathetic stimulation and exercise training

6.1 Abstract

Injury to descending bulbo-spinal autonomic (sympathetic) pathways is common in individuals with high-level SCI and is associated with abnormal control of blood pressure and HR. In individuals with high-level SCI, sympathetic stimulation (such as those seen during periods of AD; paroxysmal hypertension provoked by sensory stimuli below the injury) is proarrhythmogenic. Exercise training is a key component of SCI rehabilitation and management of CVD risk, but it is unclear whether exercise training influences susceptibility to cardiac arrhythmia. We aimed to evaluate: (i) whether susceptibility to arrhythmia increases in a rodent-model of SCI; (ii) the impact of the sympathomimetic drug dobutamine (DOB) on arrhythmia risk; (iii) whether exercise training ameliorates arrhythmia risk. Twenty-one Wistar rats were divided into 3 subgroups: T2 contusive SCI non-exercisers (T2, n=7), T2 contusive-SCI exercisers (30min/day 5day/week) completing passive hindlimb cycling training (PHLC, n=7), and T10 contusive SCI (T10, n=7). Known electrocardiographic (ECG) arrhythmia markers and heart rate variability (HRV) parameters were evaluated before (PRE), 1-week (POST) and 5-weeks post-SCI (TERM) at baseline and during DOB infusion (30μg/kg/min). At baseline, markers of arrhythmia risk were increased after injury in both T2 and T10 animals. DOB decreased R-R interval ($p<0.001$), and increased markers of risk for ventricular arrhythmia, particularly in high-level (T2) animals ($p<0.05$). Exercise training blunted the exacerbation of markers of arrhythmia in the presence of DOB. Susceptibility to cardiac arrhythmia is increased in experimental SCI and DOB further increases susceptibility to arrhythmia in high-level SCI. Exercise training did not improve markers of arrhythmia at rest but did ameliorate markers of arrhythmia risk during sympathetic stimulation.

6.2 Introduction

CVD is the leading cause of morbidity and mortality globally [266]. After SCI, the onset of CVD occurs earlier, and progresses at a faster rate [10,37], leading to decreased life expectancy for individuals with SCI [267]. The development of cardiac arrhythmias is a hallmark feature of CVD [27]. However, cardiac arrhythmia can also occur in isolation after SCI due to the profound cardiac dysfunction that accompanies high-level injuries [31]. After SCI, disruption to the spinal pathways that regulate sympathetic outflow to the heart results in parasympathetic predominance, which has been linked to bradycardia, asystole, and cardiac arrhythmias [26]. Accordingly, bradyarrhythmias are well documented in the acute stages of SCI [27–29]. However, arrhythmias (both bradyarrhythmia and tachyarrhythmia) have also been observed during episodes of AD (sudden and profound reflex hypertension due to sympathetic activation in response to sensory stimuli below the level of injury) [25,30]. AD occurs in individuals with high-level SCI at or above the 6th thoracic level (T6), where injury to descending spinal sympathetic pathways impairs the ability to regulate vascular resistance and arterial blood pressure [59]. The extreme hypertension that occurs during AD, coupled with the dysregulation of the descending spinal pathways that regulate cardiac sympathetic outflow following high-level SCI, leads to an increase in the spatial dispersion of ventricular repolarization and further increases susceptibility to cardiac arrhythmia [26].

The increased risk of cardiac arrhythmia both in the chronic phase of SCI as well as in the presence of AD has been hypothesized to be the result of cardiac sympathovagal imbalance, leading to remodeling of cardiac tissue [29,30]. Classically, the sympathetic and parasympathetic control of the heart are understood to have a reciprocal relationship. However, instances of co-activation have been shown in able-bodied individuals during the provocation of protective (peripheral chemoreceptor, startle, noxious, ocular, defensive) but not during regulatory (baroreceptor) reflexes [268]. A well-documented example of autonomic co-activation can be seen during cold water immersion, which elicits a both a dive reflex (associated with vagal activation and bradycardia) and a cold shock response (associated with sympathetic activation and tachycardia). This results in simultaneous and conflicting positive and negative chronotropic influences on the heart, and appears to be highly proarrhythmogenic [269,270]. This co-activation has been coined “autonomic conflict” [269] and is also seen during AD, where the high sympathetic drive

triggers baroreflex-mediated increases in cardiac parasympathetic activity. While the presence of cardiac arrhythmia is well documented during AD, it is not yet known if autonomic conflict is a leading cause of such events.

Dobutamine (DOB) is a sympathomimetic (predominantly a β1-adrenergic agonist) agent that enhances cardiac sympathetic activity. Accordingly, DOB may provide a useful tool to investigate the role of sympathetic activation in the context of risk for cardiac arrhythmias, providing novel insight into the high reported susceptibility to cardiac arrhythmia during episodes of AD.

Additionally, exercise training is known to have cardio-protective effects and is a proven treatment and prevention option against CVD [38,242]. With the advent of new exercise guidelines for the SCI population [242], it is essential to examine whether exercise training modulates the negative cardiac consequences of SCI. While global cardiac responses to exercise have been studied [271], it is unclear how exercise influences susceptibility to cardiac arrhythmia.

Therefore, in this study we aimed to: (i) examine the effects of high-level (T2; at risk for AD) and low-level (T10; not at risk for AD) SCI on electrocardiographic parameters; (ii) examine the impact of DOB on electrocardiographic parameters in these animals; (iii) examine whether exercise training initiated after injury affects these responses.

6.3 Methods

6.3.1 Ethics approval

All procedures were conducted in accordance with the Canadian Council for Animal Care, with ethical approval from the University of British Columbia.

Experiments were conducted in 21 male Wistar rats (250 – 300g, Harlan Laboratories), divided into 3 groups: a low-level contusive SCI (T10, n=7) without exercise, a high-level contusive SCI (T2, n=7) without exercise, and a passive hindlimb cycling group (PHLC, n=7) with high-level contusive SCI both at the T2 spinal level (**Figure 6.1**).

6.3.2 Surgery

Prophylactic antibiotic treatment with enrofloxacin (Baytril; 10 mg/kg, subcutaneous [s.c.], AVP) was administered for 3 days prior to SCI surgery. On the day of surgery, rats were anesthetized with isoflurane (5% at induction chamber and maintenance with 2.5%, 1.5-2 L/min oxygen flow). Buprenorphine (0.02 mg/kg, s.c.), enrofloxacin (10 mg/kg, s.c.) and warmed lactated Ringer's (5 mL, s.c.) were administered prior to surgery. After being shaved and cleaned, the skin, fascia, and muscle layers superficial to the C7-T3 vertebrae were incised along the dorsal midline. The spinal cord was exposed via the removal of the T2 lamina. A 400-kDa contusion with a 5-s dwell time was made at T2 using an Infinite Horizon impactor (Precision Systems and Instrumentation, LLC, Fairfax Station, VA). T10 animals had the same procedure as described above except injury was performed at the T10 spinal level. Muscle and skin layers were closed with 4-0 myocryl and 5-0 prolene sutures, respectively. Animals recovered in a temperature-controlled environment (33°C, Animal Intensive Care Unit, HotSpot for Birds, Los Angeles, CA). Rats were weighed and monitored daily for the duration of the study. For three days post-surgery, the rats were administered enrofloxacin (10 mg kg^{-1}, s.c.), buprenorphine (0.02 mg kg^{-1}, s.c.), and lactated Ringer's solution. Bladders were manually expressed three to four times each day until spontaneous voiding could be achieved independently (~10 days). These care protocols have been described in detail elsewhere [271].

6.3.3 Exercise intervention

PHLC training began 8 days post-surgery and continued for 25 days. PHLC rats completed 30-minute ergometer cycling sessions 5 days per week (frequency 0.5 Hz). A leather sling with two holes for their hind limbs was used to briefly suspend the rats while their hind paws were secured to the ergometer pedals with gauze and Parafilm. This exercise protocol has been described in detail elsewhere [271].

6.3.4 Electrocardiographic assessments and dobutamine challenge testing

ECG assessments (lead II) were obtained by an individual blinded to the experimental groups pre- (PRE), 1-week (POST) and 5-weeks (TERM) post-surgery.

Rodents were anesthetized with isoflurane (as noted above), maintained at a surgical depth of anesthetic, and placed in a supine position while their thorax was shaved. Body temperature was maintained at 37-38°C while HR was monitored with a three-lead ECG using LabChart 8 Software (ADInstruments, Colorado Springs, CO USA). Following the acquisition of baseline (i.e. 0µg; BL) reading, the tail was cleaned, and the tail vein was cannulated with a 27-gauge butterfly needle. Dobutamine (Dobutamine, I.V., Hospira; DOB) was intravenously infused in a step-wise manner with progressively increasing doses (5, 10, 20 and then 30µg/kg/min) using an automated perfusion pump (Harvard apparatus; Southnatick, MA, USA). The 5µg/kg/min dose was administered for five min to reach a peak response (a plateau in the HR) and each consecutive dosage was infused for four minutes to obtain a peak HR response to the drug. After completion of the final dosage, animals were removed, and their recovery was monitored in a temperature-controlled environment. This protocol is described in detail elsewhere [271]. At completion of the experiment animals were euthanized by overdose with isoflurane (5% isoflurane with 2L min^{-1} oxygen) and underwent a thoracotomy.

A schematic of the protocol can be seen in **Figure 6.1**.

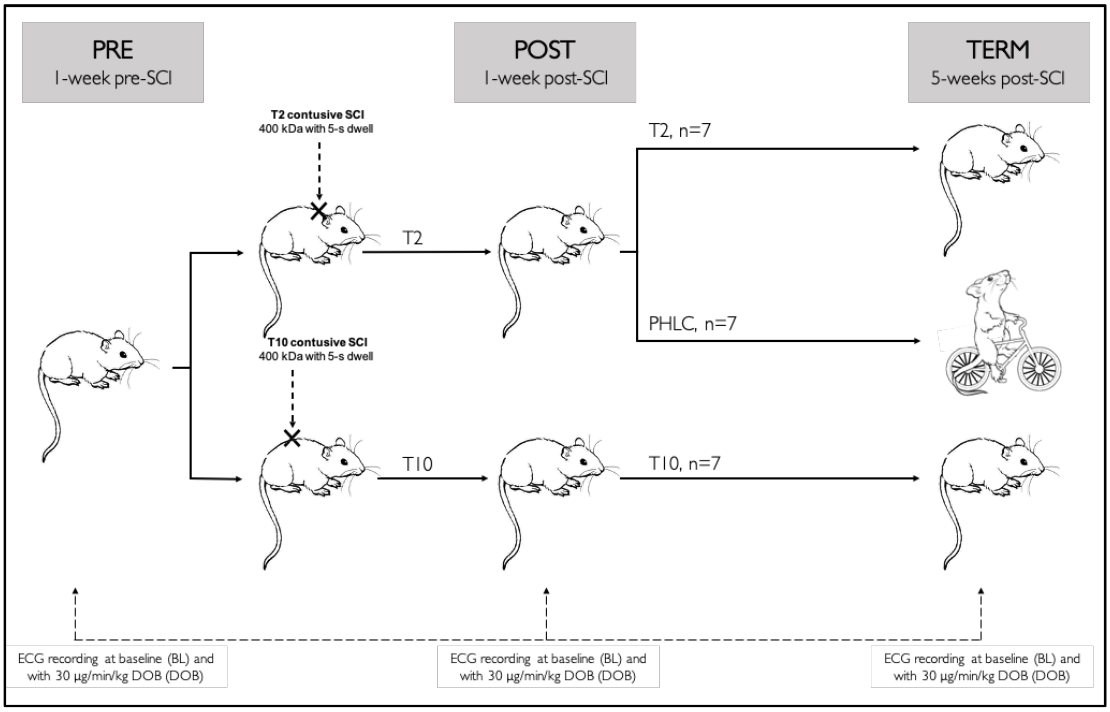

Figure 6.1 – Protocol schematic.
Abbreviations: PHLC, passive hindlimb cycling; DOB, dobutamine; ECG, electrocardiogram.

6.3.5 Outcome measures

Monovariate AR spectral analyses of cardiac intervals were performed to evaluate autonomic cardiovascular control of LF (sympathovagal), HF (vagal), and VLF (cardiovascular mortality) HRV as described previously [29,114]. VLF (< 0.1 Hz), LF (0.4–1.2 Hz), and HF (1.2–3.0 Hz) peaks were identified for each spectrum, and the power and central frequency at each peak were calculated by computation of the residuals [188]. LF-to-HF ratio was used to assess sympathovagal balance [29]. Indices of atrial (increased PWD mean and variability [PWD_{var}]) and ventricular (increased T_{peak}-T_{end} interval mean [TpTe] and variability [$TpTe_{var}$], markers of transmural dispersion of repolarisation; and increased heart rate corrected QT interval mean [QTc] and variability [QTc_{var}], markers of overall duration of repolarization) arrhythmia risk were determined from ECG [30] at baseline and during peak DOB (30µg/kg/min) using customized software (LabView).

6.3.6 Statistical analyses

Data processing was performed using R (Version 3.3.3) and RStudio (Version 1.1.453). Statistical analyses were performed using Sigmaplot 14 (Systat Software Inc., San Jose, CA). Data were tested for normality and parametric or non-parametric assumptions were used as appropriate. Comparisons for whole group data (baseline, DOB, or ΔDOB conditions) over time were performed using one-way ANOVA. Comparisons between outcome measures over time (PRE, POST, TERM), and/or between subgroups (T2, T10, PHLC), and/or the impact of condition (BL, DOB) were performed using 2-way ANOVA. Comparisons between outcome measures over time (PRE, POST, TERM), between subgroups (T2, T10, PHLC), and within conditions (BL, DOB) were performed using 3-way ANOVA.

6.4 Results

6.4.1 Baseline ECG parameters and HRV

The baseline ECG parameters can be seen in Table 6.1. There was a significant main effect of injury on RRI, where it was shorter in T10 animals (164.60±4.19ms) than in both T2 (187.41±3.88ms, $p=0.004$) and PHLC (198.93±6.18ms, $p<0.001$), reflecting bradycardia with high-level injuries. There was a main effect of group ($p<0.001$) on RRI,

which was significantly longer in PHLC compared to both T10 ($p<0.001$) and T2 ($p=0.043$) animals, and in T2 compared to T10 ($p<0.001$). There was also a significant main effect of time-point ($p=0.002$), where RRI was increased at both POST and TERM compared to PRE ($p=0.031$; $p=0.002$).

Table 6.1 – Baseline ECG Parameters.

Mean±SE (n)	PRE	POST	TERM	Group	Time	Interaction
Mean RRI (ms)						
T2	187.40±7.50 (7)^{PHLC}	182.34±5.38 (7)	193.34±7.66 (6)	**<0.001**^{PHLCvT10,PHLCvT2,T10vT2}	**0.002**^{PREvPOST,PREvTERM}	**<0.001**
PHLC	165.52±3.92 (7)^{POST,TERM}	209.15±4.82 (7)$^{T2,\ T10}$	222.13±7.04 (7)$^{T2,\ T10}$			
T10	165.13±8.01 (7)	166.69±8.06 (7)	161.55±6.18 (6)			
Mean PWD (ms)						
T2	14.51±0.31 (7)	13.49±0.73 (7)	15.08±0.89 (6)	0.908	**0.004**^{PREvTERM,POSTvTERM}	0.602
PHLC	14.85±0.78 (7)^{TERM}	18.34±1.26 (6)	21.84±3.25 (6)			
T10	12.49±0.65 (7)	13.95±0.65 (7)	13.58±0.46 (5)			
Mean TpTe (ms)						
T2	14.51±0.31 (7)	13.49±0.73 (7)	15.08±0.89 (6)	*0.056*	0.255	0.162
PHLC	14.85±0.39 (7)	13.65±0.73 (7)	14.91±0.35 (7)			
T10	12.49±0.65 (7)^{T2,PHLC}	13.95±0.65 (7)	13.58±0.46 (5)			
Mean QTc (ms)						
T2	97.02±2.94 (7)	95.79±3.17 (7)	99.36±3.29 (6)	**<0.001** ^{PHLCvT10,PHLCvT2}	0.756	**0.018**
PHLC	93.52±1.68 (7)	87.05±2.98 (7)^{T2,T10}	86.69±1.89 (7) ^{T2,T10}			
T10	90.71±2.65 (7) ^{POST,TERM}	100.30±2.64 (7)	100.22±2.45 (5)			

Data are presented as mean±standard error (n). Statistical significance: $^{PRE,\ POST,\ TERM}$ denotes significant difference between timepoints; $^{T2,\ PHLC,\ T10}$, denotes significant difference between subgroups. Statistical significance (p values) are also presented for the main effect of subgroup, timepoint, and their interactions. Abbreviations: PRE, 1-week pre-SCI; POST, 1-week post-SCI; TERM, 5-weeks post-SCI; PHLC, passive hindlimb cycling; RRI, R-R interval; PWD, P-wave duration; TpTe, Tpeak-Tend interval; QTc, corrected QT interval.

At PRE, RRI was significantly longer in T2 compared to PHLC ($p=0.043$) and tended to be longer in T2 compared to T10 ($p=0.058$). At PRE, mean RRI was shorter in PHLC than POST ($p<0.001$) and TERM ($p<0.001$). At both POST and TERM, mean RRI was longer in PHLC compared to T2 ($p=0.011$; $p=0.004$) and T10 ($p<0.001$; $p<0.001$). PWD increased over time ($p=0.004$), with PWD increased at TERM compared to PRE ($p=0.004$) and POST ($p=0.018$). Mean PWD was particularly increased at TERM compared to PRE in the PHLC animals ($p=0.01$). TpTe tended to be different between groups when considered as a main effect ($p=0.056$), although this did not quite achieve statistical significance; there was a decreased TpTe in T10 at PRE compared to T2 ($p=0.037$) and PHLC ($p=0.02$).

There was a main effect of group for QTc ($p<0.001$), which was significantly longer in both T2 ($p=0.001$) and T10 ($p=0.001$) compared to PHLC. At both POST and TERM, mean QTc was significantly longer in T2 ($p=0.04$; $p=0.005$) and T10 ($p=0.002$; $p=0.004$) compared to PHLC. In T10, QTc increased at POST ($p=0.038$) and at TERM ($p=0.046$) compared to PRE.

Measures of HRV can be seen in Table 6.2. The central frequencies of the VLF, LF, and HF ranges were not different between the three groups, and did not change over time. There was a significant main effect of both subgroup and timepoint for VLF HRV, but post-hoc testing failed to identify any significant differences. LF HRV was not significantly affected by either time or subgroup. HF power increased at TERM in the PHLC animals compared to PRE ($p=0.016$) and POST ($p=0.038$), with associated increases in total power at TERM compared to both PRE ($p=0.002$) and POST ($p=0.021$) in PHLC. In PHLC the LF-to-HF ratio decreased at POST ($p=0.016$) and TERM ($p=0.018$) compared to PRE. The LF-to-HF ratio was also increased at pre in PHLC compared to T10 ($p=0.009$).

Table 6.2 – Heart rate variability over time

Mean±SE (n)	PRE	POST	TERM	Group	Time	Interaction
Baseline						
Total power (ms^2)						
T2	3.57±0.91 (7)	3.11±0.48 (7)	4.06±0.65 (7)	0.914	*0.055*	0.102
PHLC	1.94±0.13 (7)	3.02±0.67 (7)	6.08±0.90 (7)^{PRE,POST}			
T10	3.51±0.56 (7)	4.27±1.49 (7)	3.83±0.84 (6)			
Very Low Frequency (ms^2)						
T2	1.03±0.45 (7)	0.77±0.23 (7)	2.03±0.92 (7)	**0.039**	**0.049**	0.405
PHLC	0.07±0.00 (7)	0.44±0.12 (7)	1.28±0.41 (7)			
T10	0.68±0.26 (7)	0.26±0.06 (6)	0.48±0.12 (6)^{T2}			
Low Frequency (ms^2)						
T2	1.31±0.36 (7)	0.85±0.52 (7)	1.67±0.32 (7)	0.558	0.198	0.193
PHLC	1.00±0.34 (7)	0.95±0.35 (7)	2.17±0.65 (7)			
T10	0.55±0.21 (7)	1.58±0.60 (6)	0.88±0.35 (6)			
High Frequency (ms^2)						
T2	0.80±0.16 (7)	0.80±0.18 (7)	0.99±0.34 (7)	0.417	*0.055*	0.171
PHLC	0.72±0.31 (7)	0.91±0.25 (7)	1.85±0.38 (7)^{PRE,POST}			
T10	1.4345±0.34 (7)	0.65±0.12 (6)	1.21±0.29 (6)			
LF/HF						
T2	1.64±0.35 (7)	1.30±0.66 (7)	2.12±0.34 (7)	0.544	0.456	**0.022**
PHLC	3.50±1.17 (7)^{POST,TERM}	1.20±0.34 (7)	1.11±0.23 (7)			
T10	0.91±0.47 (7)^{PHLC}	2.18±0.73 (7)	1.08±0.45 (6)			

Data are presented as mean±standard error (n). Statistical significance: $^{T2, PHLC, T10}$ denotes significant difference between subgroups; $^{PRE, TERM}$ denotes significant difference between timepoints. Statistical significance (p values) are also presented for the main effect of subgroup, timepoint, and their interactions. Abbreviations: PRE, 1-week pre-SCI; POST, 1-week post-SCI; TERM, 5-weeks post-SCI; PHLC, passive hindlimb cycling; LF/HF, ratio of low frequency to high frequency power.

The evolution of parameters of ECG variability at baseline can be seen in **Figure 6.2A-C**. All three markers of arrhythmia risk (PWD_{var}, $TpTe_{var}$ and QTc_{var}) had a main effect of time (p all <0.001). Baseline PWD_{var} increased over time by TERM in T2 compared to PRE (p=0.043), PHLC compared to POST (p=0.024) and PRE (p=0.016), and T10 compared to POST (p=0.023) and PRE (p=0.027). Baseline $TpTe_{var}$ increased over time by TERM in T2 compared to POST (p=0.004) and PRE (p=0.002), PHLC compared to POST (p=0.002) and PRE (p=0.003), and T10 compared to POST (p=0.048) and PRE (p=0.0025). Baseline QTc_{var} was significantly increased in T10 compared to PHLC at TERM (p=0.030), baseline QTc_{var} increased over time by TERM in T2 compared to POST (p=0.06), and T10 compared to POST (p=0.017) and PRE (p<0.001).

6.4.2 Effects of DOB infusion on ECG parameters

As DOB is a sympathomimetic agent, we first assessed its impact on RRI and markers of sympathetic activity. Compared to BL, DOB decreased RRI (p<0.001) and increased LF-to-HF ratio (p=0.004) with an overall reduction in total power (p<0.001). This response was not different between subgroups. DOB did not affect PWD at any time point, and there were no differences in the PWD during DOB between groups. However, during DOB mean TpTe was increased (p=0.003), and the magnitude of increased TpTe was larger at POST (p=0.006) and TERM (p=0.009) compared to PRE. In addition, the increase in TpTe with DOB was larger in both T2 (p<0.001) and PHLC (p<0.001) compared to T10. Mean QTc was also increased with DOB (p=0.001), with larger increases in mean QTc in PHLC (p=0.005) and T2 (p=0.002) compared to T10. In addition, mean QTc during DOB tended to increase over time (p=0.052).

When considered as the change from baseline, mean TpTe responses to DOB infusion were larger at POST than PRE (p=0.004), and PHLC animals had larger increases in TpTe with DOB than both T10 (p=0.012) and T2 (p=0.038) animals. There was also a main effect of subgroup on QTc response to DOB (p<0.001), with T10 animals having smaller increases in QTc with DOB than PHLC (p<0.001) and T2 (p=0.032) animals.

Figure 6.2D-F shows absolute ECG variability parameters overtime and between groups with DOB infusion. There was a significant main effect of time (p=0.042) and subgroup (p=0.05) with DOB on PWD_{var}, where PWD_{var} during DOB lower in PRE in T2

animals compared to POST (p=0.038) and TERM (p=0.006). At TERM, PWD_{var} was significantly increased in T2 animals compared to PHLC (p=0.043). With DOB, there was also a significant main effect of time (p<0.001) and subgroup (p=0.007) on $TpTe_{var}$. $TpTe_{var}$ during DOB increased over time by TERM in PHLC compared to PRE (p=0.017), and in T2 compared to both POST (p=0.008) and PRE (p<0.001). At TERM, $TpTe_{var}$ was significantly increased in T2 animals compared to T10 (p=0.016). There was also a significant main effect of time (p<0.001) on QTc_{var} with DOB. With DOB, QTc_{var} increased over time by TERM in T2 compared to POST (p=0.018) and PRE (p<0.001).

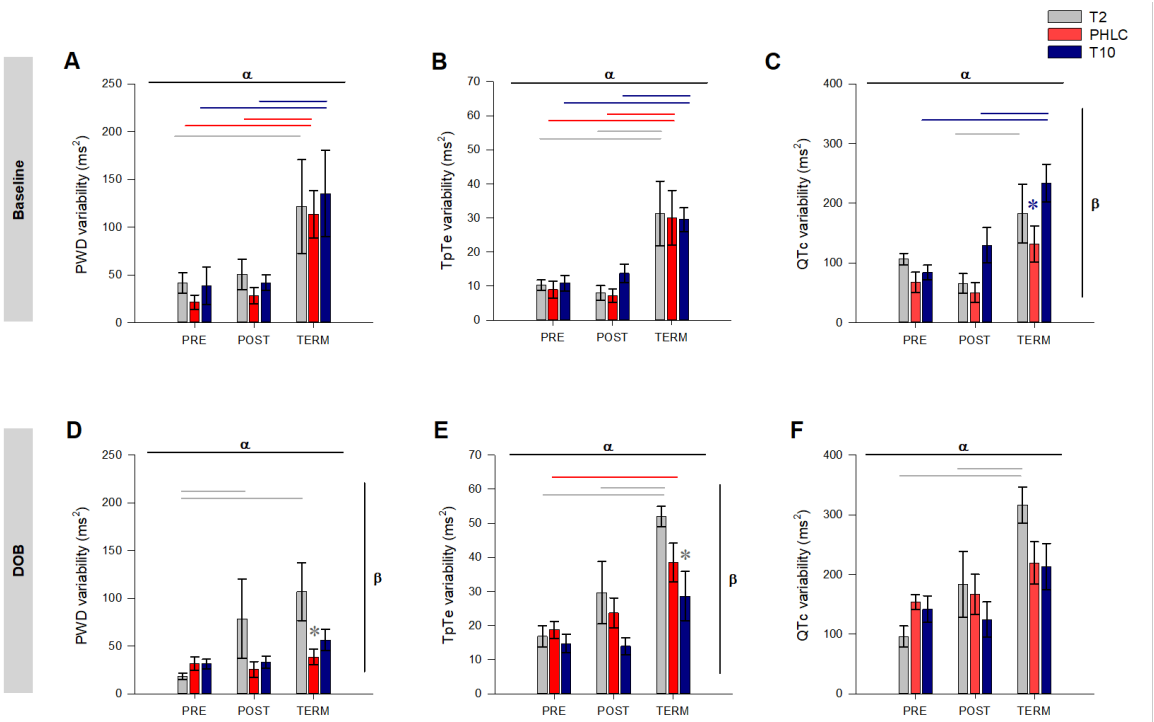

Figure 6.2 – The evolution of ECG variability parameters overtime at baseline and with DOB.

(A) Baseline PWD variability was significantly higher at TERM compared to PRE in all three groups, and was greater at TERM than POST in T2 and PHLC. (B) Baseline TpTe variability was increased at TERM compared to PRE and POST in all three groups. (C) Baseline QTc variability was increased in T2 and T10 compared to POST and was greater in T10 at TERM than at PRE. QTc variability did not increase at TERM in PHLC and was significantly lower than T10. (D) With DOB, PWD variability was greater at TERM than PRE and POST in T2 animals only, and was higher at TERM in T2 compared to PHLC. (E) With DOB, TpTe variability was increased at TERM compared to both PRE and POST in T2 animals, and was higher at TERM than PRE in PHLC. Responses at TERM were larger in T2 animals than T10. (F) With DOB, QTc variability was increased over time by TERM in T2 compared to POST and PRE. Statistical significance: * (grey) denotes statistical difference from T2 subgroup; * (dark blue) denotes statistical difference from T10 subgroup; horizontal bars (α) denote significant main effect of timepoint ($p<0.05$); vertical bars (β) denote significant main effect of subgroups ($p<0.05$); grey horizontal bars denote significance within T2 overtime ($p<0.05$); red horizontal bars denote significance within PHLC overtime ($p<0.05$); blue horizontal bars denote significance within T10 overtime ($p<0.05$). Abbreviations: PRE, 1-week pre-SCI; POST, 1-week post-SCI; TERM, 5-weeks post-SCI; PHLC, passive hindlimb cycling; PWD, P-wave duration; TpTe, T_{peak}-T_{end} interval; QTc, corrected QT interval; DOB, dobutamine.

6.5 Discussion

This is the first study to assess the development and progression of cardiac arrhythmia risk in a rodent model of contusive SCI. We showed that ECG markers of arrhythmia are negatively impacted by experimental SCI, and further exacerbated by DOB infusion. We also showed that exercise training using PHLC did not improve baseline

cardiac electrophysiological parameters, although adverse responses to DOB were blunted with PHLC.

6.5.1 SCI adversely impacted markers of atrial and ventricular arrhythmia risk

As expected, a longer RRI was observed in animals with high-level SCI, which can be attributed to vagal predominance in the face of autonomic injury [29,211]. This was associated with increases in markers of risk for both atrial (PWD_{var}) and ventricular ($TpTe_{var}$ and QTc_{var}) arrhythmia. These data suggest pathological electrical remodelling after SCI [272], and are consistent with previously reported data by our group [30].

6.5.2 DOB further exacerbated the adverse effects of SCI on ECG parameters

DOB is a sympathomimetic agent [273], and as such had predictable effects on HR, decreasing RRI while increasing markers of sympathetic activation. This tachycardic response was associated with increases in the relative duration of ventricular repolarisation (QTc and TpTe), an observation that has been seen after DOB infusion in individuals with coronary artery disease [273]. DOB also further increased the risk for both atrial and ventricular arrhythmia, with further increases in mean PWD, TpTe and mean QTc, as well as the variability of PWD, TpTe and QTc, particularly in the T2 animals. These data support observations made previously that sympathetic stimulation after high-level SCI tends to be proarrhythmogenic [27,29–31,190], with numerous reports of cardiac arrhythmia and/or palpitations occurring during the high cardiac sympathetic activity that is associated with episodes of AD [31,43,190].

Interestingly, the vulnerability to sympathetic stimulation in rodents with contusive SCI using this injury model has also been shown to be associated with adverse changes in left ventricular function, with blunted responses to DOB based on echocardiographic markers of cardiac dysfunction at 1-week after injury, but a hyperresponsive response 5-weeks after SCI [274]. We observed changes to ECG parameters with DOB as early as 1-week post injury, suggesting that cardiac electrical remodelling occurs prior to structural remodelling.

6.5.3 Heart rate variability analyses

In PHLC we saw significant increases in HF HRV and total power at TERM associated with a decreased LF-to-HF ratio that, along with the concurrent bradycardia in these animals, are all compatible with the known effects of exercise on HRV and vagal tone [266], providing supporting evidence that a training effect was indeed achieved in these animals.

Interestingly, we did not see the reduction in LF HRV (efferent baroreflex sympathovagal influences on HR) or VLF HRV (a marker of all-cause cardiovascular mortality) in the animals with high-level SCI that might be expected based on their injury to sympathetic pathways, and this is in contrast to previous reports in rats [114] and individuals [29,189] with SCI. This might reflect several differences in methodology in the present study. For example, previous work in rodent models of SCI was conducted in conscious, freely moving animals [114] or awake individuals with SCI [29,189]. In the present study data were collected in anesthetised animals, and as such, cardiovascular variability was blunted. This is compatible with previous reports on the effects of anesthesia on HRV in rodents [275] and might render it impossible to detect further reductions in LF HRV following injury due to a “floor” effect. Another difference is that the previous reports employed complete transection injuries [114]. It may be that the contusion injury model in the present study produces a more variable or less complete injury to spinal sympathetic pathways. It is also possible that any decrement in sympathetic regulation of HR in these animals in the LF range is compensated by vagal modulation [211], and so there is no net change in LF HRV.

HF HRV reflects cardiac vagal regulation associated with respiration [109], and was not affected in the present study, presumably because the cardiac vagus nerves do not pass through the spinal cord and thus are not affected by the injury paradigm employed.

DOB increased the LF-to-HF ratio, associated with decreased total HRV and decreased RRI and this which is compatible with the known sympathomimetic actions of DOB.

Analyses of HRV provide useful information on cardiac autonomic regulation, and appear to provide responsive markers of the vagolytic effects of exercise training, and the

actions of sympathomimetic agents. However, in the context of autonomic markers of the severity of injury to autonomic pathways after SCI, the concurrent influences of both vagal and sympathetic components of the autonomic nervous system complicate the analysis of HRV as a marker of autonomic severity of injury. BPV, particularly in the LF range, provides a more robust marker of injury to spinal autonomic (sympathetic) pathways after SCI [29,114,276].

6.5.4 Passive exercise training does not improve detrimental ECG changes at baseline in high-level SCI

Based on the significantly longer RRI after PHLC training, it is likely that a training effect was achieved. In humans, reductions in HR observed after exercise training can be attributed to increased parasympathetic drive and changes to intrinsic HR control as a result of exercise-induced cardiac remodelling [266]. Animals performing exercise training also exhibited increases in PWD. However, unlike in the T2 animals that did not exercise, the animals performing exercise training had decreases in QTc at TERM. Unsurprisingly, due to the nature of these high-level injuries, we saw increases in atrial and ventricular variability parameters by TERM in the T2 injured animals that did not complete exercise training as well as the PHLC animals, again reflecting an increased risk for atrial and ventricular arrhythmia.

Previously, our group has shown that these markers of atrial and ventricular arrhythmia risk increase over time in humans during both the acute phase and into chronic SCI [30,189]. Our results in the T2 animals are consistent with this, showing the translatability of our model. These detrimental changes in markers for arrhythmia risk were also seen in the T2 animals that performed PHLC, suggesting that overall PHLC did not ameliorate arrhythmia risk at baseline (although there was some improvement in QTc_{var} at TERM in the baseline condition that could reflect a modest reduction in risk).

The extent of cardiac remodelling that occurs with exercise training is dependent, in part, on the modality of exercise training. PHLC training has been reported to increase cardiac filling and improve SV [271]. It may well be at PHLC alone is of an insufficient intensity to completely ameliorate arrhythmia risk that occurs with high-level injury. It is possible that a combination therapy with active-arm and passive-leg exercise training, which has been shown to improve cardiovascular function in humans with SCI [277], may

be a better approach to improve cardiac electrical remodelling. As new exercise guidelines for individuals with SCI suggest consistent aerobic activity to combat the development of CVD [38,242], it will also be important to assess changes to ECG parameters using this approach.

6.5.5 Passive exercise training had a protective effect on responses to DOB in animals with T2 SCI

As noted previously, DOB worsened the adverse cardiac electrical changes that occurred after T2, but not T10, SCI. In PHLC animals the HR increase with DOB was greater, perhaps because of the lower resting HR, and therefore increased cardiac reserve. Despite the higher HR rise with DOB, the animals in the exercise intervention arm of the study had smaller increases in markers of the duration of ventricular repolarisation with DOB after injury.

6.6 Limitations

There were several limitations to this study. We used a contusive injury model instead of the more traditionally used complete transection model. Whilst this model is thought to more clearly recapitulate the clinical reality of SCI, and has been previously validated [276], the variability of the injury to descending spinal pathways is higher [189], which may reduce our ability to detect between group differences. Despite this inherent physiological variability, we show increased risk of arrhythmia development in high-level injured animals, consistent with previously reported changes in individuals with SCI [30,189,190]. In fact, it may be that the present data underestimate the severity of cardiac electrical remodeling with more severe injury models.

We did not quantify the severity of injury to cardiac sympathetic pathways. One quantitative way to assess the loss of autonomic function after SCI would be through the use of LF SAP analyses [187]. Recently, our group has shown this to be a leading assessment tool for the quantification of injury to cardiovascular autonomic pathways following SCI, effective in both the acute and chronic phase of injury [189,271]. These analyses are preferred over HRV assessments as LF SAP is a purer measure of sympathetic function, unlike its counterpart in HR variability analyses, which includes a component related to cardiac vagal tone that is unaffected by SCI. In the future, animal

models should employ measures of LF SAP to determine the degree of autonomic impairment after experimentally-induced SCI.

It is important to note that the induction of sympathetic challenge (through the use of DOB) in a controlled environment, though a useful proxy for recreating the cardiac challenge seen during AD, does not account for the paroxysmal nature of AD. In addition, unlike with sympathetic challenge with DOB, AD is often accompanied by autonomic conflict, with baroreflex-mediated increases in vagal tone, and this concurrent high sympathetic and vagal activity is thought to be particularly proarrhythmogenic [278]. For these reasons it is likely that the negative effect of AD on cardiac electrophysiological parameters and markers of risk for arrhythmia would be greater than with DOB.

Finally, we measured the risk for cardiac arrhythmia, rather than documenting the incidence of cardiac arrhythmia. This is because we were interested in evaluating cardiac electrical remodelling. It is not possible to say for certain whether increases in these markers of risk for arrhythmia would necessarily translate into an increased incidence of arrhythmia. However, we believe this is likely because these indices are well known to predict future arrhythmic events [279–283], and because of the high documented incidence of cardiac arrhythmia in both preclinical [65,284] and clinical SCI [27–29,31,189,190].

6.7 Conclusions

Individuals with high-level SCI have an increased risk for cardiac arrhythmia, particularly during periods of high sympathetic discharge, such as during AD. We showed that ECG markers of arrhythmia are negatively impacted by experimental SCI, and further exacerbated by sympathetic stimulation. We also showed that exercise training using PHLC did not improve resting cardiac electrophysiological parameters. However, the further increase in risk for ventricular arrhythmia with sympathetic stimulation was blunted in exercise trained animals. These data highlight the validity of this preclinical model to recapitulate the effects of traumatic SCI on cardiovascular regulation, permitting translatable research, and evaluation of effective treatment and management options to minimise CVD risk in individuals with SCI.

Chapter 7

Discussion

This thesis comprised a series of investigations using a variety of different but complimentary research methodologies, through which many novel discoveries into physiology and behaviour change after SCI were made. Taken together, these investigations provide a unique, translational perspective into central issues surrounding bowel care and cardiovascular function after SCI. As mentioned in Chapter 1, the experimental chapters were written with the intent that they could be considered independently. This present chapter provides commentary on the connections that exist between these research studies, their strengths and limitations, and the groundwork they have laid for future investigations within the field.

7.1 Novel insights into autonomic pathophysiology following SCI

7.1.1 Autonomic classification

Classification and quantification of the impact of SCI on autonomic function remains a considerable challenge, with a lack of consensus and applicable tools with which to measure autonomic dysfunction after SCI, little knowledge of the natural progression and evolution of autonomic dysfunction after injury, and few translatable markers of autonomic function. This thesis evaluated the use of a discrete non-invasive marker of quantitative cardiovascular autonomic function after SCI (Chapter 3). Using this approach we showed that cardiovascular dysfunction is evident and measurable as early as one-month post injury and did not improve over the first year after injury. This marker, LF SAP, was linked to self-reported symptoms of cardiovascular dysfunction, and these symptoms which were also reported after bowel care routines (Chapter 4) and in conjunction with many other activities of daily living [43]. These discoveries highlight the critical need for a discrete marker of cardiovascular autonomic (sympathetic) function after SCI. While measures of supine BPV (LF SAP) were able to identify those with severe lesions to cardiovascular autonomic pathways and were associated with the severity of cardiovascular symptoms after SCI, measures derived from supine HRV (LF RRI) were

not able to discriminate as well, particularly in the acute phase after injury (Chapter 3). However, LF RRI did became more informative in those with chronic SCI. Both of these metrics are applicable to rodent models of SCI, and our investigation using a rodent model of injury made use of LF RRI, as blood pressure was not assessed during these recordings, a clear caveat in this study. We found differences in HRV metrics between our human and rat studies (Chapter 6), and compared to prior experiments in conscious freely moving rats [114]. This suggests that the translatability of HRV, and perhaps BPV, may be less robust in anaesthetised animal preparations. In addition, because LF RRI contains a component related to vagal innervation of the heart it may be a less informative marker of the autonomic (sympathetic) completeness of injury than LF SAP. LF SAP, as a marker of autonomic cardiovascular dysfunction, if adopted by the SCI community, would have the capacity to inform clinicians and researchers as to who is most at risk for experiencing cardiovascular autonomic dysfunctions such as AD, OH, and cardiac arrhythmias, and potentially for tracking the impact of treatment or management interventions.

It is important to note that data for this longitudinal study (Chapter 3) was collected while the participant was in a supine position, which limits the influence of sympathetic stress on these recordings. It would be interesting and informative to conduct similar investigations in the seated position, or while performing a supine-to-sit test.

The relationships between HR and blood pressure were assessed using known assessments of baroreflex functioning. Here too we saw aberrant sympathetic control, further underscoring the pervasive nature of autonomic dysfunction. It was promising that there were improvements to baroreflex control over the course of acute injury (Chapter 3). However, the evolution of reflex regulation into the chronic phase of injury remains poorly understood, as changes to sympathetic cardiovascular function and increases in vagal modulation are not assessed clinically.

Based on the robustness of our findings using LF SAP as a marker of autonomic severity of injury in the acute phase (Chapter 3) we also utilised measures of LF SAP to assess autonomic completeness of injury during cardiovascular assessments during at-home bowel care (Chapter 4). However, in this study, it is plausible that, during the baseline recordings sympathetic outflow was elevated due to low-grade AD as a result of bowel distension (by definition participants had not yet completed their necessary bowel

care). Accordingly, in this case we conservatively changed our threshold for autonomic completeness of injury (from 2.0mmHg^2 to 3.75mmHg^2) for these recordings.

The ability to use LF SAP to assess impairments to descending cardiovascular (sympathetic) control after SCI cannot be over emphasised. This method provides a simple, translatable metric that can be readily adopted in both the research and clinical communities and is a prime candidate to fill the current gap in the quantitative assessment and classification of SCI.

7.1.2 Autonomic dysreflexia

We both assessed autonomic injury using LF SAP, and also evaluated the presence of autonomic disorders, including AD, particularly in the context of bowel care. AD during bowel care was prevalent, and in some cases associated with dangerously high blood pressures (exceeding 300mmHg SAP). These were the first measurements of continuous non-invasive blood pressure collected during at-home bowel care. These high pressures were quite well tolerated despite the magnitude of the increase in blood pressure. These pressures are especially alarming given that supine hypotension and OH are quite common in high-level SCI, suggesting a larger magnitude of change in blood pressure for these individuals. Only a 20mmHg rise in blood pressure is necessary to be classified as an AD response [21]. Given these high pressures, it is also possible that AD is underestimated in self-reported measures. Silent AD has been reported previously [21,65,85] and given the reasonably well-tolerated symptoms, is likely to be pervasive in high-level SCI.

Additionally, we saw that AD was exacerbated with lidocaine use. This is important because current bowel care guidelines still advocate for the use of lidocaine to mitigate AD during bowel care [57,261]. This study highlights the challenges with recommendations that are theory-based rather than evidence-based, and underscores the need for rigorous approaches to mitigate AD during personal care routines. Knowledge surrounding access to bowel care options and resources was also identified as barrier to changing bowel care, and healthcare providers were described as ill-informed (Chapter 5). This suggests that ongoing review of current practice guidelines is much needed, along with concerted effort to raise awareness of this knowledge both for individuals with SCI and their health care providers.

7.1.3 Orthostatic hypotension and fatigue

We also reported a high prevalence of OH after acute SCI (Chapter 3) and this is in keeping with prior research [43,53]. However, contrary to prior reports that suggest OH is most severe acutely after SCI [24], in fact OH did not improve over time after injury, and was severe even in those with chronic SCI. It should be noted that, although we did not measure the prevalence or severity of OH in the rodent-based studies in the present work, links between OH and level of SCI have been identified previously in pre-clinical models [114]. Interestingly, we also showed a strong relationship between OH and validated self-reported measures of fatigue (Chapter 3). Fatigue after acute injury could be a result of trauma, or infection. However, our data suggests a link between fatigue and autonomic dysfunction, perhaps as a consequence of associated hypotension and cerebral hypoperfusion [216]. This is important because the association between fatigue and autonomic function is often under-recognised and extends beyond “tiredness” and mental fatigue. This is of particular concern given prior reports that fatigue and OH significantly impair quality of life [285] and ability to participate in rehabilitation [286]. Fatigue was also tangentially discussed in the behaviour change interviews (Chapter 5) as competing interests (such as activities of daily living, time spent on care routines, and other SCI-specific considerations) were discussed as barriers to changing care. As time to complete bowel care, fatigue, and cardiovascular symptom burden have been previously shown to impact quality of life after SCI [43], these findings further highlight the need for proper assessment and consideration of these symptoms.

7.1.4 Cardiac arrhythmias

A prevalent symptom that was commonly reported throughout our investigations was the sensation of cardiac palpitations, particularly during episodes of AD. In addition to self-reported measures of palpitations, we also observed a high incidence of cardiac arrhythmias during bowel care and increases in markers of risk for cardiac arrhythmia both within the acute phase after SCI (both in clinical and pre-clinical studies) (Chapters 3 and 6) and chronically (Chapter 4). The presence of cardiac arrhythmia was further increased with lidocaine use during bowel care, further contraindicating its use (Chapter 4). In this thesis we assessed both the risk of arrhythmia (using ECG markers) and presence of arrhythmia. Similar findings between the two approaches, combined with repeated self-reports of palpitations adds to our understanding of cardiac electrical activity after SCI. It

is possible that the cardiac electrical remodelling that we documented occurs prior to functional or structural remodelling, which is also adversely affected after SCI, but at later time points following injury [287]. Given the association between autonomic dysfunction and cardiac arrhythmias, there is sufficient rationale to suggest screening for cardiac arrhythmias in individuals with high-level autonomically-complete SCI.

Cardiac arrhythmias and exercise

The general beneficial effects of exercise have been reported in both the able-bodied [266] and in individuals with SCI [277,288]. More specifically, part of this thesis explored the role of passive exercise training in mitigating cardiac arrhythmias after SCI. Investigations in Chapter 6 revealed the potentially beneficial impact of exercise on cardiac arrhythmia risk during sympathetic stimulation using a preclinical model of contusive SCI. Given that there are several well-appreciated and unavoidable triggers for AD, if exercise training were to be effective at ameliorating arrhythmia during AD the effects throughout the course of a typical day would be profound. This is timely given the introduction of new exercise guidelines for individuals with SCI, that are currently being expanded to incorporate many modalities of exercise [38,242]. The translatability of our findings, in addition to the level of exercise prescription needed for enhanced cardiovascular health need to be further studied.

7.1.5 Cardiovascular symptom burden

Chapters 3, 4, and 5 all highlighted the prevalent and devastating impact of cardiovascular symptoms for individuals with SCI, both in terms of their prevalence and progression in acute injury and association with bowel care. These results are consistent with our previous reports [43], with a high prevalence of multiple cardiovascular symptoms including those associated with OH, AD, arrythmia and fatigue. Not only does this speak to the reproducibility of our past work, but also the strength of the present investigations. Symptom reporting provides us with a personal perspective on the burden of cardiovascular dysfunction and underscores the priority placed on the resolution of autonomic dysfunction and cardiovascular abnormalities by individuals living with SCI [6,43,44]. As mentioned previously, silent AD is particularly concerning because severe untreated AD can be life threatening [21,65]. Given that both AD and OH evolve post injury, and can both present silently in the SCI population, quantitative assessments must

be established to classify autonomic injury, as self-reported measures may underestimate the extent of dysfunction present.

7.2 Novel insights into behaviour change

It was evident from our prior investigations that there were key problems when it came to changing bowel care to improve quality of life. Chapter 5 introduced the use of behaviour change science to assess the barriers and facilitators to changing bowel care. Barriers and facilitators to change bowel care related to one's environment, preconceptions, knowledge about bowel care, and social influences. This novel investigation has initiated a cascade of subsequent studies external to this thesis, including expansion to assessing the barriers and facilitators to changing bowel care among caregivers and health care professionals, in addition to designing and implementing relevant interventions to empower individuals with SCI to change bowel care routines. We used tools that provide methods for reproduction and evaluation to increase the validity of this work by grounding this work in theoretical frameworks while incorporating the use of critical friends, openness, transparency, self-reflection [145,199].

The behaviour change work included in this thesis was conducted using a patient-oriented approach and supported through a fellowship with the BC SUPPORT (SUpport for People and Patient-Oriented Research and Trials) Unit, a subset of Canadian Institute for Health Research's Strategy for Patient-Oriented research. This is important because it highlights the priority placed by key funding agencies and stakeholders on patient-oriented research who have launched programs to expand knowledge translation activities [289].

7.3 Novel insights into translational aspects of SCI research

This thesis provided a true bench-to-bedside-to-backyard approach by using a variety of research methods aimed at answering questions surrounding autonomic dysfunction after SCI. In order to bridge the gap between these different methodologies, these thesis findings need to be disseminated, translated, and applied. Interestingly, despite repeated efforts from our research team, new iterations of bowel guidelines still advocate for the use of lidocaine during bowel care [261]. We have, at the very least, provided conflicting evidence that should warrant caution for this claim. This study

(Chapter 4) highlights the need for the scientific research community to regard the impact that negative results can have on guidelines and care.

On the topic of relevancy, the use of an integrated knowledge translation approach employed in our behaviour change investigation (Chapter 5) ensured that the results are relevant and feasible. Given that there is, on average, a 17-year implementation (knowledge-to-action) gap from scientific discovery to clinical practices [290], the use of integrated knowledge translation aims to support the production of research that is timely and relevant for the research users. It should be emphasized that research users are present in any research setting, not just qualitative behaviour change research. This means that as scientists, to create meaningful change in our fields, there are obvious advantages to engaging our research users in our research design and discovery.

7.3.1 Knowledge to action cycle: the thesis in context

To contextualise the impact that different research designs can have on a specific field of study, the knowledge-to-action cycle outlined in Chapter 1 was used extensively throughout this thesis. This tool was developed to close the knowledge-to-action gap [166]. The two phases of the knowledge-to-action cycle (knowledge phase and action phase) can occur either simultaneously or sequentially. Investigations working with the knowledge creation phase (Chapters 3, 4, and 6), as well as the action cycle (Chapter 5) were performed to apply and assess knowledge and action within this thesis. **Figure 7.**1 highlights the knowledge-to-action framework in the context of this thesis work. This tool has been adopted by major federal funding agencies to explore and implement knowledge translation perspectives [165]. It is important to note that the knowledge-to-action cycle also incorporates an evaluation component that was not considered in the present work. It is imperative that further work continues to assess and evaluate the findings in this thesis. As science is a dynamic and iterative process, we must also work towards refining our understanding of these processes, in order to fully evaluate our interventions and re-evaluate the knowledge we have created.

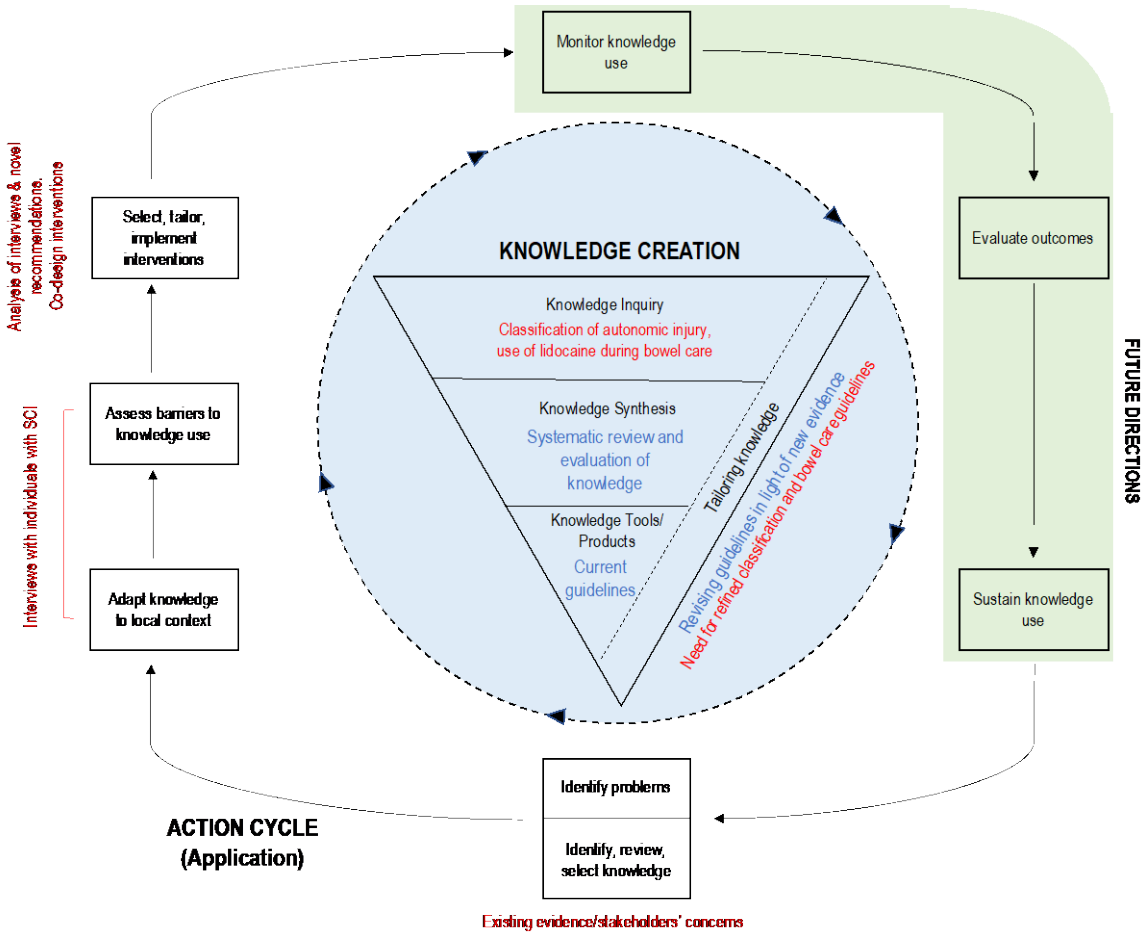

Figure 7.1 – The knowledge-to-action cycle in practice.
The knowledge-to-action cycle has been used within this thesis to guide novel investigations into autonomic dysfunction after SCI. Functions of the knowledge creation phase (blue circle) are outlined in blue text. Application of this thesis work can be found in red text. Abbreviations: SCI, spinal cord injury

7.4 Strengths and limitations

7.4.1 Considerations within the data

SCI is remarkably heterogenous. Differences in both level and severity of injury between individuals has several implications for the assessment of motor, sensory, and autonomic function. This heterogeneity provides unique challenges for researchers. In particular, the assessment of cardiovascular function depends on both level and completeness of injury, in addition to pre-existing cardiovascular comorbidities and general cardiovascular health. Participant stratification by homogenous features of SCI (groupings by level, severity, duration, etc.) can help to control heterogeneity and variability. This has important implications for research study design and data analysis.

Key considerations must be made to ensure representation, balance heterogeneity, and achieve a significant level of statistical power. Given this heterogeneity, an astute and comprehensive understanding of the strengths and limitations of various research approaches must be appreciated within this population in order to conduct rigorous research.

Additionally, the reality of clinical research is that studies will have challenges with attrition and retention, which we observed in our longitudinal study design (Chapter 3). Despite this, we continued the study until appropriately powered at each timepoint, thus ensuing robust and rigorous results. In Chapter 4, a community-based clinical trial was conducted. There were specific challenges regarding the collection of cardiovascular measurements in participants' homes while they complete their unique bowel care routines. We carefully designed our study to account for variability within the data. Despite these challenges, and because of our rigorous research design, we saw clear evidence of the adverse impact of lidocaine use emerge from the data.

We also considered the role of bias in our studies. The concern is that individuals with particularly poor autonomic control or those particularly dissatisfied with bowel care would more willingly elect to participate in our research. Though the extent of this can never be fully captured, community consultation has suggested that our results resonate with the SCI community in British Columbia at large. Of note, in Chapter 5, there was almost complete parity between the number of discussed facilitators and barriers suggesting that, despite high reports of dissatisfaction in bowel care, there are strategies that also facilitate change, and a broad representation of viewpoints was achieved.

7.5 Future directions

7.5.1 Creating bowel care interventions

We now know which important TDF domains to consider when designing interventions aimed at changing bowel care (Chapter 5). We also discovered which common bowel care strategies actually worsen cardiovascular dysfunction. Given the high priority of bowel care concerns for individuals with SCI [6,43,44], these findings provide unique opportunities to increase knowledge of bowel function and optimal management after SCI, understand the impact that autonomic completeness of injury has on bowel

functioning, and leverage these findings to further inform intervention design. What is abundantly clear from our research is that these interventions must be co-developed with clinicians, community support providers, and individuals with SCI using an integrated knowledge translation approach, as outlined above.

7.5.2 Continued research into autonomic dysfunction

In recent years there has been a growing interest in therapies that may mitigate autonomic dysfunction after SCI. Emerging therapies such as functional electrical stimulation (either implanted or transcutaneous) and advancements in exoskeletons all have the potential to impact autonomic control [240,265,291]. However, it is important to appreciate that not all members of the SCI community support these technologies [292]. Given the repeated call for “nothing about us without us”, it is important that all advancements in SCI research include research users in the entire process, so that these concerns are addressed. Preclinical work also suggests that prophylactic gabapentin, a drug commonly used to treat neuropathic pain, has the potential to prevent the development of severe autonomic dysfunction [293]. The success of these therapies may be reliant on our ability to accurately quantify the severity and progression of cardiovascular autonomic impairment after SCI. This further underscores the need for a robust quantitative measure of autonomic function after SCI.

AD commonly presents with concurrent bradycardia due to associated baroreflex-mediated increases in cardiac vagal tone triggered by the hypertensive crisis. Recently, direct in vivo recordings of single-unit vagal nerve activity using ultrasound-guided microneurography have been reported for the first time in awake humans [101]. This is a promising field of research that could provide mechanistic insight into vagal nerve activity, and its role in AD. If coupled with direct sympathetic recording, this technique has potential to shed light on autonomic conflict, a physiological state present during episodes of AD and known to promote arrhythmogenicity.

7.6 Final thoughts

Autonomic injuries present several challenges for individuals adjusting to, and living with SCI. This thesis explored the specific implications SCI poses on two key concerns for those with SCI, cardiovascular autonomic control and bowel care practices.

These data also have significant implications for how we treat, manage, and research autonomic dysfunction associated with SCI. We have demonstrated the importance of engaging research users in the research process, and the need to evaluate and implement new strategies for the management of autonomic dysfunction. Finally, it is imperative that we use our results to first and foremost benefit and improve the lives of individuals living with SCI. Their priorities should guide research and our collective findings need to be recognised and translated.

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Appendix A.

Questionnaires

1. Cardiovascular symptoms 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 ☐

1

2. How often do you experience the following symptoms of autonomic dysreflexia?

	Daily	Weekly	Monthly	Rarely	Never
Profound headache	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐
Nasal congestion	☐	☐	☐	☐	☐
Goosebumps	☐	☐	☐	☐	☐
Blurred vision/visual sensitivity	☐	☐	☐	☐	☐
Visual tunnelling	☐	☐	☐	☐	☐
Facial flushing	☐	☐	☐	☐	☐
Profuse sweating	☐	☐	☐	☐	☐
Difficulty breathing	☐	☐	☐	☐	☐
Spasticity	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Shortness of breath/chest tightness	☐	☐	☐	☐	☐
Chest pain	☐	☐	☐	☐	☐
Palpitations	☐	☐	☐	☐	☐
Uncomfortable fast heart rate	☐	☐	☐	☐	☐
Uncomfortable slow heart rate	☐	☐	☐	☐	☐
General unwellness	☐	☐	☐	☐	☐
Seizure	☐	☐	☐	☐	☐
Other (please specify)	☐	☐	☐	☐	☐

3. What sorts of things trigger these symptoms?

	Yes	No	N/A
Bladder trigger	☐	☐	☐
Bowel trigger	☐	☐	☐
Sexual activity	☐	☐	☐
Pain	☐	☐	☐
Pressure sores	☐	☐	☐
Spasticity	☐	☐	☐
Ingrown nails	☐	☐	☐
Fracture	☐	☐	☐
Tight clothes/devices	☐	☐	☐
Menstrual cramps	☐	☐	☐
High/low temperatures	☐	☐	☐
Blood clot	☐	☐	☐
Other (please specify)	☐	☐	☐

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

	Yes	No	N/A
Activities of daily living	☐	☐	☐
Work	☐	☐	☐
Exercise	☐	☐	☐
Sexual activity	☐	☐	☐
Rehabilitation	☐	☐	☐
Household chores	☐	☐	☐
Driving	☐	☐	☐
Social activities	☐	☐	☐
Sleep	☐	☐	☐
Other (please specify)	☐	☐	☐

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?

	Daily	Weekly	Monthly	Rarely	Never
Dizziness	☐	☐	☐	☐	☐
Fainting/Blackouts	☐	☐	☐	☐	☐
Lightheadedness	☐	☐	☐	☐	☐
Blurred vision	☐	☐	☐	☐	☐
Visual Tunneling	☐	☐	☐	☐	☐
Profuse sweating	☐	☐	☐	☐	☐
Profound tiredness/lethargy	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐
Palpitations	☐	☐	☐	☐	☐
Uncomfortable fast heart rate	☐	☐	☐	☐	☐
Uncomfortable slow heart rate	☐	☐	☐	☐	☐
Extreme pallor	☐	☐	☐	☐	☐
Seizure	☐	☐	☐	☐	☐
Other (please specify)	☐	☐	☐	☐	☐

4. What sorts of things trigger these symptoms?

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

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

	Yes	No	N/A
Activities of daily living	☐	☐	☐
Work	☐	☐	☐
Exercise	☐	☐	☐
Sexual activity	☐	☐	☐
Rehabilitation	☐	☐	☐
Household chores	☐	☐	☐
Driving	☐	☐	☐
Social activities	☐	☐	☐
Other (please specify)	☐	☐	☐

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 ———————————X 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.

2. Cardiovascular symptoms during bowel care questionnaire

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CARDIOVASCULAR SYMPTOMS DURING BOWEL CARE

Identification Number _____ Date completed DD/MM/YYYY
Date of Birth DD/MM/YYYY Date of Injury DD/MM/YYYY
Lubrication Tube Number _____

1. Today, what steps did you sue to empty your bowel? Check all that apply.

	Main	Supplementary
Normal defecation/straining/bearing down	☐	☐
Drink/food before bowel management	☐	☐
Massaging or rubbing abdomen	☐	☐
Touching the skin around the anus	☐	☐
Digital stimulation	☐	☐
Manual evacuation	☐	☐
Suppositories	☐	☐
Laxatives	☐	☐
Enemas	☐	☐
Stool softeners	☐	☐
Other, please specify; _____	☐	☐

2. What was your body position during your bowel care, today?
- ☐ Sitting on toilet chair/commode
- ☐ Sitting on a raised toilet seat
- ☐ Lying in Bed
- ☐ Other, please specify:_____

3. What assistance did you require for your bowel care, today?
- ☐ Required total assistance
- ☐ required partial assistance; did not clean self
- ☐ Required partial assistance; cleaned self independently
- ☐ Performed care routine independently in all tasks but needed adaptive devices or special setting (e.g., bars)
- ☐ Performed care routine independently; did not need adaptive devices or special setting

4. Total time required for defecation, today (not including cleaning):
_____minutes

5. Total time required for today's bowel care (including defecation and cleaning):
_____minutes

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6. **During today's bowel routine, did you experience any heart palpitations, irregular heartbeats or a feeling of "fluttering in your chest"?**
   ☐ Yes ☐ No

   If yes, how often do you experience this during bowel care?
   ☐ Rarely ☐ Monthly ☐ Weekly ☐ Daily

7. **How would you rate the following symptoms during today's bowel routine?**

	Not experienced	Mild	Moderate	Severe	Very severe
Headache	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐
Nasal congestion	☐	☐	☐	☐	☐
Goosebumps	☐	☐	☐	☐	☐
Blurred vision/visual sensitivity	☐	☐	☐	☐	☐
Visual tunneling	☐	☐	☐	☐	☐
Facial flushing	☐	☐	☐	☐	☐
Profuse sweating	☐	☐	☐	☐	☐
Difficulty breathing	☐	☐	☐	☐	☐
Spasticity	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Pain	☐	☐	☐	☐	☐
Other, please specify: _____	☐	☐	☐	☐	☐

Autonomic dysreflexia (AD) 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.

8. **Do you think you experienced autonomic dysreflexia since during your bowel care today?**
   ☐ Yes ☐ No

   If yes, how often do you experienced this?
   ☐ Rarely ☐ Monthly ☐ Weekly ☐ Daily

9. **Was there anything different about today's bowel routine than your normal management?**

Thank you for taking the time to complete this questionnaire

Appendix B.

Interview supplementals

1. Interview guide

Purpose	Questions
ID Code & Recording	Please confirm that you consent to have our conversation recorded. Your personal information has been assigned the random ID number _____. To insure confidentiality and anonymity this data will be stored under the same number in a secure, password-protected location inside our locked laboratory. I will not use your name as we are talking, to help protect your confidentiality.
Overall perspective	How do you feel about your bowel care?
Outcomes	What does your typical bowel care routine look like? - Who performs your routine? - What time of day is it done? - How often do you perform your bowel care? - What level of assistance are you receiving? - How flexible is your bowel care routine?
Behaviours	When was the last time you made a significant change to your bowel care routine? - Can you tell me more? - Why did you make this change? What helped you make this change? - Did this change improve your bowel care? When was the last time you wanted to make a change to your bowel care routine but didn't? - Can you tell me more? - Why have you not made this change? What are some ways you think you can change your bowel care to be more effective for you? - Can you tell me more?
Barriers and Facilitators	Can you tell me about some things that make changing your bowel care a difficult thing to do? - Can you tell me more? Can you tell me about some things that would make changing your bowel care an easier task to do? - Can you tell me more? (Additional prompts may be used to elaborate on barriers or facilitators mentioned e.g.) - Knowledge:

	○ Do you know of any options to change your bowel care? ○ Do you know where to look for information about changing your bowel care? ○ Where would you most like to receive information about bowel care? - Goals: ○ Do you/Have you planned or set a date to change your bowel care? - Skills: ○ Do you feel you have the skills you need to change your bowel care? ○ Do you know of any other methods to perform bowel care? - Beliefs about capabilities: ○ Do you feel confident in your ability to carry out bowel care changes despite difficulties? ○ How easy is it for you to make changes to your bowel care? - Behavioural Regulation/Reinforcement: ○ Do you see any benefits to changing your bowel care? - Intentions: ○ Do you feel as though you are motivated to make a change to your bowel care? ○ Do you want to change your bowel care? → Can you tell me more? - Memory, attention, and decision processes: ○ Is it [mode of bowel care] something that you usually do? ○ Is it [CHANGING YOUR BOWEL CARE] something that you remember to do? - Environmental Context and Resources: ○ Are there competing tasks or time constraints that impact changing your bowel care? ○ Do you feel like you have the resources to change your care? - Social Influences: ○ Do you feel like you are supported by others to change your bowel care? ▪ Who supports you? - Optimism ○ Do you feel that changing your bowel care will work out for the best? - Beliefs about consequences: ○ What do you think will happen if you change your bowel care? - Emotions ○ Does thinking about changing your bowel care bring up certain emotions?
Intervention	If there were an ideal intervention to improve your bowel care routine, what would that look like?

	- What would the overall intervention aim to do? - In what format might the intervention be delivered? - Who would deliver the intervention?

Closing Comments

Thank you so much for participating in this interview. I would be happy to send you a summary of the results when we have finished the analysis if you would like. What is the best way that I could send that to you? Do you have any further questions about the interviews or the study? If like I can provide you with our lab's phone number and Dr. Claydon's phone number again (Lab phone: 778-782-8560) in case you want to contact us again in the future. Participants in this study receive a $20 gift card as a thank you for taking the time to take part in the study. What type of gift card would you like and how should I send it to you?

2. Coding manual

BARRIER: Anything that hinders making changes to bowel care

FACILITATION: Anything that helps making changes to bowel care

Coding Manual

TDF Domain	Coding Rules
1. Knowledge (Know) (An awareness of the existence of something)	
2. Skills (Skills) **(An ability or proficiency acquired through practice)**	
3. Social/Professional Role and Identity (SPRI) (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	
4. Beliefs about Capabilities (BCap) **(Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)**	**Self-efficacy (confidence in ability)**
5. Optimism (Opt) (The confidence that things will happen for the best or that desired goals will be attained)	Things will turn out okay Willingness to continue to try despite failure
6. Beliefs about Consequences (BCon) **(Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)**	
7. Reinforcement (Rein) (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)	Barrier: Tried something before that didn't work out Accepting what is - if a routine is "okay", it is a lack of reinforcement to change Coping well at the time (apathy to change)
8. Intentions (Int) **(A conscious decision to perform a behaviour or a resolve to act in a certain way)**	**Need or motivation** See ECR
9. Goals (Goals) (Mental representations of outcomes or end states that an individual wants to achieve)	Description of what someone wants for or as an outcome of their bowel routine (e.g. I want it to be faster/makes their life easier) Unclear goal setting/aspirations
10. Memory, Attention and Decision Processes (MADP) **(The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)**	**Do not think about changing** **Not even on their radar**
11. Environmental Context and Resources (ECR) (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	Can't find help or information to do x Lack of help to make a change (perceived or real) Physical changes due to SCI or changes related to current bowel routine causes the need to change their bowel routine My current routine isn't working for me anymore, I need to do something about it Context forces adaptive behaviour
12. Social influences (SI) **(Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)**	**Social comparison** ****Need to have an interpersonal interaction (not an assumption)****
13. Emotion (Emo) (A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)	
14. Behavioural Regulation (BReg) **(Anything aimed at managing or changing objectively observed or measured actions)**	**If combined with Bcon, code just Breg (if they talk about a way to mitigate Bcon)** **Really hard for Breg to be a barrier. Breg is a strategy to OVERCOME a barrier (therefore facilitator) unless Breg reinforces barrier**