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Development, prevalence and treatment of blood pressure abnormalities in spinal cord injury

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August 2019

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Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

Abstract

Disorders of blood pressure control arise from disruption of the autonomic nervous system and result in symptomatic orthostatic hypotension and large fluctuations in blood pressure. Ambulatory blood pressure monitoring is used in the general population for assessment of blood pressure control and to detect episodes of hypotension.

In spinal cord injury (SCI), impaired control of the sympathetic nervous system leads to orthostatic intolerance and autonomic dysreflexia. Smaller studies in restricted populations have examined ambulatory pressures in SCI and observed abnormalities in diurnal blood pressure variation in complete cervical SCI. Altered diurnal blood pressure is associated with abnormalities in diurnal urine production and orthostatic intolerance in autonomic failure. This triad may also occur in SCI to explain the orthostatic intolerance.

A retrospective examination of ambulatory pressures of patients with SCI referred for clinically significant blood pressure disorders revealed a high prevalence of abnormalities in diurnal blood pressure and urine production in acute and chronic tetraplegia and in acute paraplegia.

To characterise the course of diurnal blood pressure, urine production and orthostatic symptoms in SCI, two prospective studies were performed. First, consecutive patients admitted with acute SCI were screened for recruitment, and consenting volunteers were compared with immobilised and mobilising controls. In the second study, people with chronic SCI (>1 year) living in the community were compared with mobilising controls.

Compared with mobilising and immobilised controls, there was a high prevalence of abnormal diurnal blood pressure variation in SCI. The abnormalities were most prevalent and marked in higher and earlier SCI. Abnormalities persisted over time in both complete and incomplete cervical SCI. Abnormalities in high paraplegia were no different to that of cervical SCI in early SCI, but were no different to that of controls in chronic SCI. Nocturnal hypertension occurred in the absence of day hypertension in

SCI, thus clinic pressures may miss elevation in blood pressures and ambulatory monitoring may be beneficial in assessment of blood pressure in SCI.

Abnormalities in diurnal urine production were present and persisted over time in cervical SCI, but appeared to improve over time with thoracic SCI, mirroring changes in diurnal blood pressure. Orthostatic hypotension and orthostatic intolerance were more prevalent in SCI than in controls. Mild orthostatic intolerance is common in chronic SCI and a small proportion had more severe symptoms. A single centre study to investigate a drug treatment for orthostatic intolerance in the setting of a loss of diurnal blood pressure variation was unsuccessful due to low recruitment rates.

As life expectancy increases in the SCI population, there is evidence of increased rates of cardiovascular disease. Similar to the general population, the loss of diurnal blood pressure variation and elevated nocturnal pressures may be a contributor to the increased cardiovascular disease in SCI, and thus a potential therapeutic target. Ambulatory blood pressure monitoring may be useful to detect these changes and examination of a larger SCI population with a longer duration of follow up for cardiovascular disease may help to determine this.

Declaration

This is to certify that:

- i. this thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the preface;
- ii. due acknowledgement has been made in the text to all other material used; and
- iii. this thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Min Yin Goh

Preface

Studies in this thesis were conducted as part of a large project comprising many programs, funded by the Victorian Neurotrauma Initiative which supports research in traumatic brain and spinal cord injury (SCI).

A/Prof Chris O’Callaghan and Ms Melinda Millard were responsible for the concept and design for Studies 2 and 3, with input from associate investigators, A/Prof Doug Brown, Prof David Berlowitz and Dr Edmund Wong. I provided input to protocol revisions. I set up Studies 1 and 4 together with A/Prof Chris O’Callaghan, Ms Melinda Millard and A/Prof Doug Brown.

Screening and recruitment for all inpatients and some outpatients for Studies 2, 3 and 4 was done by Ms Melinda Millard and Ms Janette Alexander, the Spinal Research Liaison Coordinators, as there were several concurrent studies recruiting these patients. Ms Melinda Millard assisted with participant recruitment and assessment through the project. Dr Edmund Wong performed assessments in 2010 prior to my starting with the project. Dr Mariannick Le Guen assisted with data collection from a few participants who were also undertaking a research study she was conducting. Ms Samantha Lawford and Ms Stephanie Zhao assisted with patient list cleaning and telephone screening for Study 4. Mr Oliver Lukis assisted with data entry. I carried out participant assessments, and recruitment and screening of the outpatients not covered by the Spinal Research Liaison Co-ordinators; some of this was done in 2011 and 2012, prior to my enrolment towards the degree in 2013.

Prof David Berlowitz, Dr Rachel Schembri and Dr Marnie Graco assisted with access to a database, database setup and maintenance, and a statistician during the studies. Statisticians Dr Steve Vander Hoorn provided guidance in data cleaning, manipulation and preliminary data analysis planning, and Dr Sue Finch provided guidance with data analysis. With this assistance, I set up and maintained the database, extracted information for data analysis, performed data cleaning, manipulation and analysis; data analysis and interpretation was conducted with A/Prof Chris O’Callaghan.

Collaboration with other research programs run by Prof Mary Galea, Dr Jo Spong, Dr Mariannick Le Guen and Prof Ego Seeman facilitated participant recruitment.

I collected data for the three publications included in this thesis, with help as described above, did the data cleaning, manipulation and analysis with guidance from statisticians as above, wrote initial drafts of all papers and revised manuscripts after feedback from all co-authors and reviewers. A/Prof Chris O’Callaghan helped with data interpretation for all papers. All co-authors as listed on the co-author authorisation forms were involved in manuscript revision.

The three articles included in Chapters 3, 4 and 5 were published online in Spinal Cord on 11 November 2014, 28 June 2016 and 2 March 2018 respectively.

Funding

Funding for these studies was provided by the Victorian Neurotrauma Initiative (VNI) and Transport Accident Commission (TAC) (DP174). I was supported by a scholarship (Australian Postgraduate Award, APA) through the University of Melbourne and a stipend through the Spinal Research Institute.

Acknowledgements

My heartfelt thanks to many for their support through these studies:

A/Prof Chris O’Callaghan for continued and invaluable support, guidance, encouragement and patience; Prof Albert Frauman for advice and supervision; Prof Ingrid Scheffer and Dr William Korim as my advisory committee. Ms Jo Mayall, for help with university related queries.

Ms Melinda Millard for all project related tasks and continued support; Ms Janette Alexander for co-ordinating participant recruitment and assessments. The Departments of Clinical Pharmacology and Medicine, especially Dr Edmund Wong, Ms Samantha Lawford, Ms Stephanie Zhao, Ms Lesa Marr, Dr Andrew Ellis, Ms Jenni Caulfield for help with research related tasks. Mr Oliver Lukis, for help with data entry.

The Spinal Unit and the Spinal Research Institute (SRI), with special mention to A/Prof Doug Brown and Dr Andrew Nunn; staff at the Spinal Units for their help and patience with my repeated requests for urine collection and scheduling of monitors/interviews.

Prof David Berlowitz, Dr Rachel Schembri, Dr Marnie Graco and the IBAS for access to a database, statistician and support. Dr Steve Vander Hoorn and Dr Sue Finch for statistics related guidance, and the former for introduction to the world of R. The SCI Autonomic Group and the VNI Program and other collaborators, for facilitating recruitment of participants - Prof John Furness, A/Prof James Brock, Prof Mary Galea, Dr Jo Spong, Dr Mariannick Le Guen, Prof Ego Seeman.

Participants for their time and effort, and giving me a glimpse into life with SCI.

Family, friends and rats, for being there for me.

The Transport Accident Commission (TAC) and Victorian Neurotrauma Initiative (VNI) for project funding; APA scholarship through the University of Melbourne and the SRI for financial support.

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Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACh	Acetylcholine
ADH	Antidiuretic hormone
AIS	American Spinal Injury Association Impairment Scale
ANS	Autonomic nervous system
BP	Blood pressure
bpm	Beats per minute
DBP	Diastolic blood pressure
ECG	Electrocardiogram
GCS	Glasgow Coma Scale
HR	Heart rate
MSA	Multiple system atrophy
POTS	Postural orthostatic tachycardia syndrome
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SCI	Spinal cord injury
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SEM	Standard error of the mean
VSCS	Victorian Spinal Cord Service

Chapter 1. Introduction

Orthostatic intolerance is a condition in which there are symptoms of low blood pressure (BP) on assuming or maintaining the upright position.^{1, 2} The severity of orthostatic intolerance can range from mild to severe. When severe, it can cause symptoms which can be disabling or even dangerous, e.g. syncope (also known as fainting). Thus, orthostatic intolerance has the potential to significantly impair daily function and quality of life.

Abnormal diurnal BP and urine output are associated with orthostatic intolerance.³⁻⁸ Abnormal diurnal variation of BP is associated with poorer cardiovascular outcomes, in both hypertensive and normotensive populations.⁹⁻¹²

Orthostatic intolerance and abnormal diurnal variation of BP and urine output are seen in several disease states. This thesis explores potential mechanisms by which these disease states affect cardiovascular control.

Specifically, I have examined the prevalence and mechanisms of abnormalities in BP, abnormalities of urine output and orthostatic intolerance in people with traumatic SCI. I chose to study people with traumatic SCI for several reasons. Their disease is typically caused by a known, definable neurological lesion. Their injury typically occurs at a younger age than most of the other neurological diseases that affect BP control, and therefore they are a population with relatively few confounding health issues. Also, with traumatic SCI, there is a discrete time of injury, as opposed to medical illnesses such as

diabetic autonomic neuropathy or Parkinson's disease whereby the onset of illness is gradual and often insidious.

1.1. Orthostatic hypotension

Postural hypotension was documented as early as 1925 by Bradbury and Eggleston¹³ who described this phenomenon in three cases and postulated impairment of the sympathetic vasoconstrictor function. The patients they studied described symptoms including dizziness, syncope, sensations of weakness and increased urination in the supine position. The patients were also observed to have wide variations of BP with postural change.

Subsequent studies observed orthostatic hypotension in association with a number of other neurological conditions. It was described as an unexpected finding in association with diabetic autonomic neuropathy in a series of 125 cases of diabetic neuropathy by Rundles.¹⁴ Other studies described the relationship between postural hypotension and autonomic disorders of various causes, including idiopathic orthostatic hypotension, multiple system atrophy (MSA, also known as Shy-Drager syndrome), idiopathic Parkinsonism, amyloidosis and spinal cord lesions of various causes.¹⁵⁻²⁰

Disorders of the autonomic nervous system (ANS) may be classified according to cause. 'Structural' disorders are a consequence of identifiable central or peripheral damage to the ANS, such as occurs in SCI. In 'functional' disorders, the location of damage to the ANS has not been identified. Diseases that have been included in this group include chronic fatigue syndrome and postural orthostatic tachycardia syndrome (POTS).^{19, 21}

Orthostatic hypotension is defined as a sustained fall in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing or head up tilt to at least 60 degrees on a tilt table. Orthostatic hypotension may be symptomatic or asymptomatic.^{22, 23}

Orthostatic intolerance on the other hand, refers to the symptoms of low BP in the upright position, which may or may not be accompanied by orthostatic hypotension.^{1, 2} Both commonly occur together, but one may occur in the absence of the other. For example, orthostatic intolerance is a feature of POTS, wherein postural change produces symptoms, i.e. orthostatic intolerance, but this is not accompanied by a fall in BP (rather, it is associated with a marked rise in heart rate (HR)).

The severity of symptoms that occur in orthostatic intolerance and thus the impact on quality of life, is variable. Orthostatic intolerance can range from a fleeting lightheadedness that occurs only infrequently with postural change, to symptoms that are severe and occur with virtually every episode of orthostasis and can thereby impact a person's independence and lifestyle. In addition, orthostatic intolerance can be associated with episodes of syncope, which can cause trauma and temporary or permanent injury, or even death, and thus add to the burden of disease.²⁴

Orthostatic intolerance and orthostatic hypotension are observed in a variety of populations, ranging from otherwise healthy young individuals to the elderly population, those with diabetes mellitus or Parkinson's disease, or temporary health conditions such as dehydration or a severe infection. In people with autonomic failure,

orthostatic intolerance is often observed as part of a triad which also includes abnormal diurnal variation of BP and urine production.⁶⁻⁸

1.2. Regulation of the cardiovascular system

Regulation of the cardiovascular system occurs through several interacting pathways, including the central, peripheral and autonomic nervous systems, neurohormonal pathways and baroreflex pathways. These mechanisms will be discussed in the following sections.

1.2.1. Autonomic Pathways

The 'autonomic nervous system' was named in 1898 by Langley, a physiologist from Cambridge University, who identified its two main divisions, the sympathetic and parasympathetic nervous systems as well as the third division which is termed the enteric nervous system.²⁵ Defined anatomically, the sympathetic nervous system represents the thoracolumbar outflow of the ANS, whereas the parasympathetic nervous system is composed of the craniosacral outflow. The sympathetic and parasympathetic nervous systems play largely opposing roles in cardiovascular control. The sympathetic nervous system has the main role in regulating circulation. The role of the parasympathetic system in affecting the cardiovascular system is largely limited to control of heart function.^{26, 27}

Sympathetic system

Efferent nerves of the sympathetic nervous system arise as 'pre-ganglionic' neurons in the intermediolateral nucleus of the lateral grey column of the spinal cord. The pre-ganglionic neurons synapse with post-ganglionic neurons which innervate effector organs (Figure 1.1). The only exception to this are the pre-ganglionic nerves that run directly to the adrenal gland, which, in essence, is a specialised ganglia. The preganglionic neurons receive descending input from the hypothalamus and brainstem, including the pons and ventral lateral medulla.²⁷⁻²⁹

In more detail, the efferent preganglionic neurons of the sympathetic nervous system have cell bodies within the intermediolateral cell column of the spinal cord between T1 and L2-3. These neurons leave the spinal cord at these levels and synapse in

paravertebral, prevertebral and previsceral (terminal) ganglia with postsynaptic neurons that innervate the target organs such as vascular smooth muscle, cardiac muscle, parenchymal organs including genito-urinary organs and the gut, and glands.^{28, 30}

- Paravertebral ganglia are situated on either side of the vertebral column, extending from the three cervical ganglia (superior cervical ganglia located at the bifurcation of the internal carotid arteries, middle cervical ganglion and inferior cervical ganglion) to sacral ganglia.
- Prevertebral ganglia are situated in the midline, anterior to the aorta and vertebral column, and consist of the coeliac ganglia, aortico-renal ganglia and superior and inferior mesenteric ganglia.
- Previsceral ganglia are small collections of sympathetic ganglia close to target structures.

Preganglionic fibres tend to be short and thinly myelinated, while the postganglionic fibres are long, with small, unmyelinated axons. Interruption can occur anywhere along the lengthy course of these postganglionic fibres, causing autonomic dysfunction.^{28, 29}

There is an overlapping innervation of ganglionic neurons by more than one spinal segment. Presynaptic fibres exit ventral roots via white rami communicantes to join the paravertebral chain, then either innervate the respective ganglion at the same level or a target ganglion many levels away.^{27, 29, 30}

Sympathetic vasomotor fibres pass into the sympathetic chain, then either go through specific sympathetic nerves that innervate the target organs, blood vessels and heart, or travel almost immediately into peripheral portions of the spinal nerves distributed to the vasculature of the peripheral areas. Sympathetic stimulation increases HR and contraction, mediated by noradrenaline. Innervation to the heart travels from the spinal cord between T1 to T4 levels, whereas those to the vascular bed exit between T1 to L2.^{30, 31} Thus disruption to the cervical or higher segments of the thoracic region may affect both cardiac and vascular innervation, while disruption to lower thoracic segments may leave cardiac innervation intact.

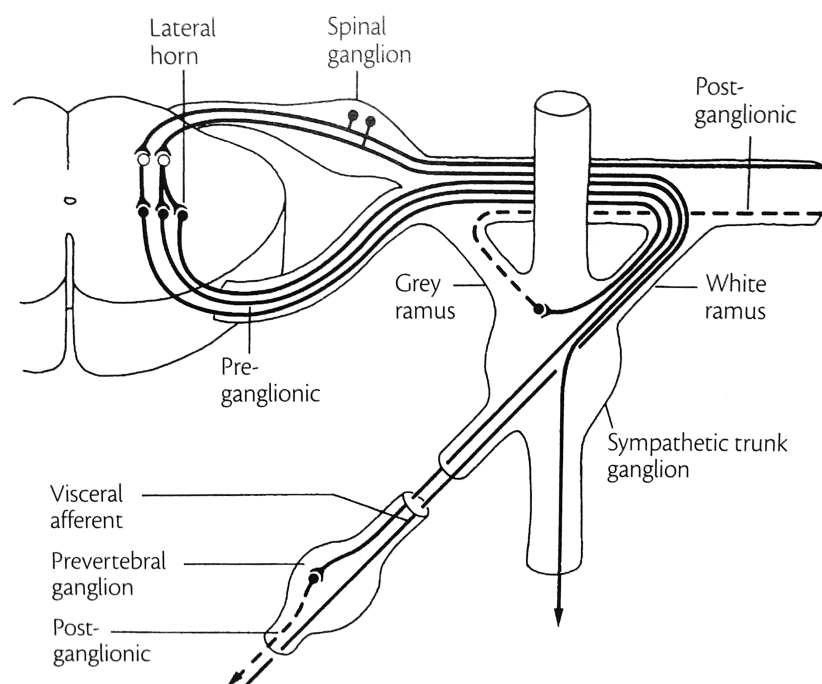


Figure 1.1 Pathway of preganglionic and postganglionic neurons.

Reprinted from *Autonomic Failure*, 5th ed, Mathias, CJ, Bannister R, Introduction and classification of autonomic disorders, 3-9, Copyright 2013, with permission from Oxford University Press.³²

Sympathetic nervous system innervation extends to all levels of the vasculature other than capillaries and venules. Innervation of small arteries and arterioles permits increased resistance and reduced rates of blood flow. Innervation of the large vessels and veins causes reduction of volume within these capacitance vessels, such as the splanchnic veins, and thereby increases return of blood to the heart.^{31, 33}

Acetylcholine (ACh) is the preganglionic neurotransmitter for sympathetic (and parasympathetic) nerves whereas noradrenaline is the main neurotransmitter at sympathetic nerve endings. Noradrenaline acts on alpha adrenergic receptors of vascular smooth muscle to cause vasoconstriction. The adrenal medulla can also cause vasoconstriction by releasing noradrenaline and adrenaline directly into venous blood.^{28,}

29

Plasma levels of noradrenaline are increased by conditions that increase sympathetic neural activation, such as a head up tilt. Other than noradrenaline secretion, the concentration of plasma noradrenaline is also dependent on neuronal uptake, metabolism and clearance.^{19, 28, 29}

Parasympathetic system

The parasympathetic nervous system neurons leave the central nervous system in cranial nerves III, VII, IX, X and in the sacral region S2-4. They are grouped in distinct nuclei in the brainstem and travel along cranial nerves III, VII, and IX to ocular smooth muscles, nasal and palatal and other glands, and along cranial nerve X via the vagus nerve to thoracic and abdominal organs. The parasympathetic cell bodies in the spinal

cord are located in the sacral parasympathetic nucleus of S2-4 segments. These neurons send preganglionic nerve fibres via the pelvic nerve to ganglia located in or very close to the pelvic organs they supply, thus the postganglionic fibres are relatively short compared to that of the sympathetic nervous system; they supply the bowel, bladder and reproductive organs. Parasympathetic ganglia are found in the head and near or in the wall of effector organs, such as the heart, digestive and reproductive organs.²⁸⁻³⁰

Preganglionic parasympathetic neurons may project to the gut and synapse directly with neurons that are part of the enteric nervous system. Other preganglionic neurons of the pathways to the colon/rectum synapse with the postganglionic neurons in the pelvic plexus, which then synapse with enteric neurons.

Similar to the sympathetic nervous system, the preganglionic neurotransmitter is ACh, which also acts at the postganglionic neurotransmitter.^{28, 29}

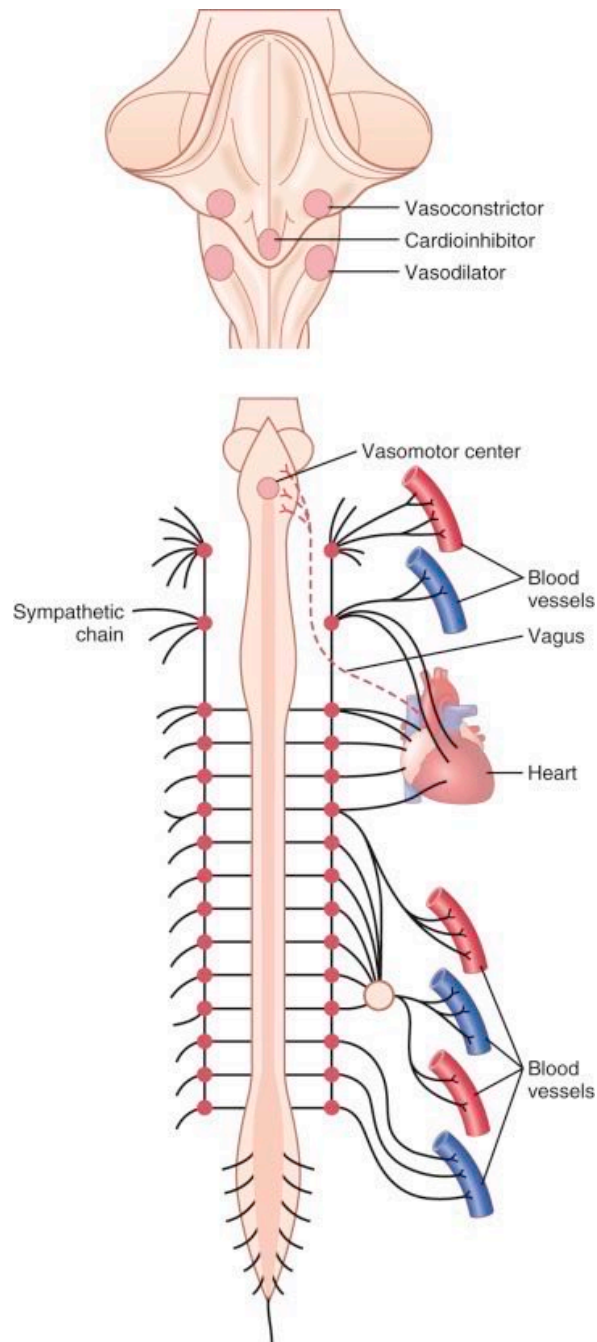


Figure 1.2 Anatomy of the sympathetic nervous control of the circulation.

The red dashed line shows the parasympathetic pathways to the heart. Reprinted from Guyton and Hall Textbook of Medical Physiology, 13th ed, Hall, JE, Nervous Regulation of the Circulation and Rapid Control of Arterial Pressure, 215-225, Copyright 2016, with permission from Elsevier.³¹

Central vasomotor control

The vasomotor centre (Figure 1.2), which is situated bilaterally in the reticular substance of the medulla and in the lower third of the pons, carries autonomic signals to and from the spinal cord to regulate blood vessels. It contains (i) vasoconstrictor areas which cause vasoconstriction via the sympathetic nervous system and maintain basal vasomotor tone, (ii) vasodilator areas which inhibit the vasoconstrictor area, and (iii) a sensory area which receives afferent signals from the vascular system, such as baroreceptor inputs via the vagus and glossopharyngeal nerves, and can relay signals to the vasoconstrictor and vasodilator areas to augment control of the BP. These functions have been attributed to the neurons in the rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM) and nucleus tractus solitarius (NTS) respectively. HR and contractility usually increase with increased vasoconstriction and decrease with inhibition of vasoconstriction.^{26, 28, 31, 34, 35}

The vasomotor centre is under the influence of neurons located throughout the reticular substance of the pons, mesencephalon and diencephalon. The hypothalamus and cerebral cortex can also cause excitation or inhibition of the vasomotor control centre.^{26,}

31

Enteric nervous system

The enteric nervous system is made up of a complex circuit of neurons extending from the oesophagus to the rectum. The Auerbach's (myenteric) plexus is located between the longitudinal and circular muscle layers, while the Meissner's (submucosal) plexus is located in the submucosa; these two plexuses of ganglia are interconnected. Neurons

from either plexus may project circumferentially, orally or caudally. These plexuses contain sensory, motor and interneurons to regulate usual gut functions including motility and digestive functions, and electrolyte regulation, in combination with inputs from the central nervous system.^{31, 36, 37}

Interstitial cells of Cajal, which are of mesenchymal origin, form networks of pacemaker cells which are electrically coupled to contractile smooth muscle cells of the gastrointestinal tract to regulate propulsive peristalsis.^{36, 38}

1.2.2. Baroreflex pathways

The arterial baroreflex pathway is an important regulator of arterial BP, especially with short term changes in BP. Sensory mechanoreceptors in the carotid sinus and aortic arch respond to an increase in BP via signals to the nucleus tractus solitarius in the medulla, resulting in a reflex reduction of sympathetic outflow and increased parasympathetic outflow. This leads to peripheral vasodilatation and reduction of cardiac contraction rate and strength, with greater responses to a more rapidly changing BP.^{26, 39}

As the opposite occurs with a reduction in BP, the baroreceptor system responds to both acute increases and decreases in BP. It thereby provides a buffer function and reduces variability in BP, such as with activity and changes in posture. Canine studies showed that denervation of baroreceptors resulted in a marked variability of BP with activity.^{26,}

40

While baroreceptors play an important role in the short-term regulation and buffering of BP, they are thought to play a less prominent role in longer term BP regulation. A reason for this is that sustained changes in BP (over days) are thought to reset the relationship between baroreceptor and BP.^{39, 40} The baroreflex response can also be modulated during prolonged periods of bed rest, and this can lead to reduced tolerance to orthostasis. This is particularly relevant for the SCI population in the early phase of rehabilitation following injury.⁴¹⁻⁴³

Baroreceptors are thought to make a longer term contribution to regulation of arterial pressure by modulating renal sympathetic activity. Prolonged increases in arterial

pressure, for example, are mediated through reduction in renal sympathetic activity, mainly through increased natriuresis and diuresis.^{31, 39}

In addition, mechanoreceptors located in the walls of low pressure vessels, namely the atria, superior and inferior venae cavae and pulmonary vein, respond to volume, rather than pressure of blood within. Increased blood volume (or other methods causing mechanical stretch to the walls) results in reflex inhibition of renal sympathetic nerve activity, and renal nerve related natriuresis and diuresis.^{40, 44}

Mechanoreceptors are also found in the somatosensory system, along with a host of other receptors in the integumentary and musculoskeletal system, such as chemoreceptors, nociceptors and thermoreceptors. Stimulation of these somatosensory receptors can cause a rise in BP, renal nerve activity and a renal nerve dependent anti-natriuresis and anti-diuresis, without significant changes in renal haemodynamics.^{40, 44}

Mechanoreceptors and chemoreceptors in visceral organs such as the gut and kidney, which have significant input into the central nervous system, also contribute to autonomic control of the cardiovascular system by regulating renal nerve activity and renal sodium and water handling. Mechanoreceptors and chemoreceptors present in the pelvis and kidney form the reno-renal reflex, which allows regulation of fluid by one kidney as a response to what occurs in the contralateral kidney. These renal afferent nerve fibres have cell bodies in the ipsilateral dorsal root ganglia from T6 to L4, and signal via the ipsilateral dorsal horn in the spinal cord to the cardiovascular and renal integration centres in the central nervous system.^{40, 44}

1.2.3. Renin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) regulates BP by interacting with the ANS to produce peripheral and central effects. Renin is generated in modified smooth muscle cells, the juxtaglomerular cells, which increase or decrease in response to demand. These are located along glomerular afferent arterioles immediately before it enters the glomerulus. For example, renin production increases if dietary sodium intake is reduced or BP falls. Renin secretion is mediated by renal sympathetic nerves that originate in the spinal segments T11 to L3. These fibers also regulate renal blood flow and thus modify fluid output and sodium and water resorption.^{40, 44, 45}

Renin is an enzyme which hydrolyses angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II. The latter causes vasoconstriction, activates the sympathetic nerves, alters baroreflex function and causes secretion of aldosterone from the adrenal cortex, leading to sodium and water resorption. All these actions lead to an increase in BP. Angiotensin II and aldosterone regulate sodium reabsorption through the renal tubules, to control BP.^{40, 45, 46}

The RAAS is activated in the event of prolonged or significant orthostatic stress, especially in the volume depleted state.^{44, 46-49}

1.2.4. Antidiuretic hormone

Antidiuretic hormone (ADH, also known as vasopressin) is another hormone that responds to changes in BP and blood volume, acting via arterial baroreceptor and cardiopulmonary reflexes. Reduction in BP or volume causes reduced stimulation of carotid sinus, aortic arch or atria baroreceptors, ADH secretion rises, which results in increased renal fluid reabsorption and vasoconstriction. A larger percentage change in blood volume than in plasma osmolarity is required for an ADH response.⁵⁰

Consistent with the baroreceptor mediated increase of ADH secretion, ADH levels increase with head up tilt. As part of the humoral response in the setting of prolonged or severe orthostatic stress, ADH is released together with the activation of the RAAS to cause resorption of sodium and water and vasoconstriction. Also, similar to the activation of RAAS is that people with tetraplegia will exhibit an exaggerated rise in ADH levels during head up tilt.^{46, 51, 52}

ADH also controls plasma osmolarity and sodium concentration by way of regulating the renal excretion of water. Secretion of ADH by the posterior pituitary gland is increased when plasma osmolarity increases, that increases permeability of distal tubules and collecting ducts, which results in increased reabsorption of water and reduced production of urine. Renal excretion of solutes is not significantly changed in this process.⁵⁰

1.3. Regulation of the upright posture

Assumption of the upright posture leads to an immediate diversion of blood, in the order of 300-800ml, away from the central compartments to the venous capacitance compartment in the lower parts of the body, including the lower limbs and abdomen. This is commonly referred to as venous pooling.^{23, 53-55} This occurs over 5-10 seconds and results in a rapid reduction of central blood volume. Neural regulatory mechanisms are the main contributors in the immediate response to orthostasis. Humoral mechanisms are mobilised if orthostasis is prolonged.

Neural regulatory mechanisms respond immediately to maintain BP by increasing HR, heart contractility and vascular tone. Insufficiency of this system can lead to syncope within minutes.⁵⁴ Postural changes in BP are rapidly detected by baroreceptors, those in the carotid sinuses playing a major role; this causes reduction of tonic inhibition of vagal efferent signals with the result that sympathetic activity increases and thus HR, heart contractility and vascular tone rise. Sympathetic responses increase splanchnic vascular resistance meaning that increased elastic recoil of venous vessels moves blood out of the large venous reservoir of the splanchnic bed, allowing maintenance of cardiac filling pressures and stroke volume during orthostatic stress.^{31, 56}

This sympathetic mediated control of the vascular tone is the main contributor to maintenance of BP with postural change. The baroreceptors also contribute to a reduction of the variability of BP with environmental changes.^{40, 57}

Failure of these systems has clinical consequences. Reduced orthostatic tolerance after immobilisation is attributed to a reduced efficiency of the carotid sinus baroreflex. Hill⁵⁸ observed that deficiency of this compensatory effect of vasomotor tone results in gravity mediated sequestration of blood to dependent parts of the body, leading to reduced cerebral circulation.

Other mechanisms that contribute to maintaining BP in the upright position include the skeletal muscle pump acting to move pooled blood up to the chest to increase cardiac output, and the humoral mechanisms in the setting of prolonged orthostasis.⁵⁹ Mechanisms contributing to overall cardiovascular regulation were discussed in the earlier sections.

1.4. Diurnal blood pressure

It has long been observed that BP and other bodily functions exhibit a diurnal variation.^{58, 60-63} Interest in chronobiology, circadian rhythms and clock genes has increased in recent decades, particularly in BP management. As well as changes in BP, diurnal variation also affects depth of respirations, body temperature, circulatory flow and metabolism or energy requirements.⁵⁸

The variability of BP and hence the importance of repeated measurements of BP was appreciated by Theodore Janeway in 1904.⁶⁰ The repeated measurements made during the study of diurnal BP confirmed a variety of stressors that affected the BP readings, ranging from levels of activity to proximity of medical personnel.

BP follows a diurnal pattern of falling overnight during sleep, and rising in the morning when, or just before, one rises. This has been observed in a number of ways including by plethysmography,⁶³ non-invasive BP monitoring by sphygmometry⁵⁸ and in the 1960s, by invasive arterial BP measurements on ambulant hypertensive and normotensive outpatients.^{60, 62}

Marian Blankenhorn was credited with the use of one of the first devices to obtain repeated automated BP measurements in normal subjects, to observe the effects of sleep on BP in 1921.^{60, 64} Non-invasive ambulatory BP devices came into use in the 1960s. However, these early devices required cuff inflation by the wearer and were therefore limited to measuring day pressures.⁶⁵⁻⁶⁷ The late 1970s saw the availability of a fully

automated system capable of intermittent measurement and recording of pressures over 24 hours. These devices allowed further study of the diurnal variation of BP, its relation to cardiovascular disease and the effects of antihypertensive medications.

Many contemporary ambulatory and automated BP monitors use the oscillometric method of measurement. This method relies on a pressure transducer connected to a tube that runs to the cuff bladder to detect pulse volume mediated pressure oscillations. These pressure oscillations are measured whilst the cuff pressure is deflated from above systolic to below diastolic pressures. During deflation, the amplitude of oscillations increases to maximal at a point corresponding to mean arterial pressure, then decrease with further cuff deflation. Manufacturing companies use proprietary algorithms to analyse these data to provide calculated systolic and diastolic BPs.^{60, 68-70}

Although initially used in research, ambulatory BP monitors have become increasingly common in research and clinical settings – especially once it was observed that ambulatory pressures were better associated than clinic pressures with complications of hypertension and cardiovascular outcomes.^{60, 67, 71} It has also been noted that the loss of the nocturnal fall in BP (known as a 'non-dipping' pattern, as opposed to a normal 'dipping' pattern) is associated with poorer cardiovascular outcomes.^{9, 10, 12} At least in part, this has led to focus on chronotherapy, or management of the BP based on the usual and impaired diurnal variation.

Diurnal variation in BP is one of the biological rhythms regulated by the suprachiasmatic nuclei (SCN), the circadian pacemaker in the hypothalamus. Factors

contributing to the diurnal variation in BP include environmental factors (e.g. sunrise and sunset), daily sleep-wake physical and mental activity, hormonal variations such as with cortisol, RAAS and melatonin, and circadian rhythm of the sympathetic nervous system.⁷²

Melatonin plays a role in regulation of the circadian rhythm, sleep-wake cycle and mood. Melatonin is produced by the pineal gland, which is innervated by the sympathetic nervous system through the superior cervical ganglia and regulated by the SCN, the circadian pacemaker in the hypothalamus. Melatonin levels tend to rise several hours before sleep, peak at about 2-4am, and fall through the rest of the night.⁷³ Melatonin synthesis is stimulated by darkness and inhibited by light, however its daily rhythm is controlled by the endogenous pacemaker, the SCN, as a circadian rhythm persists over 24 hours even in normal subjects kept in continuous darkness.⁷³

For people with tetraplegia, in whom the sympathetic pathway is disrupted, the nocturnal rise in melatonin was observed to be absent, whereas it is present in able-bodied controls and people with paraplegia.⁷⁴⁻⁸¹ In the general population, lower nocturnal melatonin levels have been noted in non-dipper hypertensive patients,^{82, 83} and administration of melatonin was observed to reduce nocturnal BP.⁸⁴⁻⁸⁷ It is proposed that this reduction in BP results from melatonin's suppression of the sympathetic system, leading to reduced vascular resistance.^{76, 85} However, it is uncertain how the lack of nocturnal melatonin affects nocturnal pressures in tetraplegia, in which sympathetic disruption is present.

1.5. Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) employs a portable machine attached to a BP cuff that automatically inflates at pre-programmed intervals during the day and night. The device is usually worn by the patient for approximately 24 hours with readings taken at 15-60 minutely intervals, often with a reduced frequency at night to reduce sleep disturbance. The output is usually read with a software program which calculates various parameters including average 24-hour, day and night BPs, and nocturnal dipping. Devices may calculate other less commonly used parameters such as hypertension loading (proportion of readings above limits that define elevated BP). Pulse rate calculations are similarly provided.

ABPM was used first primarily in research settings to observe diurnal changes in BP, and effects of antihypertensive agents on this. By the 1990s, it was recommended for clinical use.⁸⁸ Over the past few decades, it has been increasingly used and studied in clinical settings, with focus on cardiovascular conditions, especially in populations with hypertension, but also in specific populations such as those with diabetes mellitus, obstructive sleep apnoea, and renal impairment.⁸⁹

ABPM is considered superior to clinic BP measurements for prediction of cardiovascular prognosis.^{11, 71, 90} In particular, night BP along with loss of nocturnal dipping is better associated with mortality and prognosis than day BP readings.^{9, 11, 71, 90,}

It was first noted in 1988 that this loss of diurnal variation may identify individuals at a higher risk of stroke, with the terms of 'dippers' being applied to those with a normal nocturnal fall in BP and 'non-dippers' referring to those whose BPs did not fall as much overnight.⁶¹ Subsequent studies observed increased cardiovascular risk in populations with a loss of the normal dipping pattern. The extent of nocturnal dip in BP can be expressed as a ratio of night:day SBP, with a ratio of 80-90% considered normal, i.e. 'dipper' pattern, 90-100% considered non-dipping (or 'non-dipper') and >100% considered reverse dipping (or a 'reverse dipper'). Examples of such ambulatory patterns are illustrated in Figure 1.3. The significance of these categories is that patterns other than the dipper pattern are associated with worse cardiovascular prognoses.^{12, 92, 93}

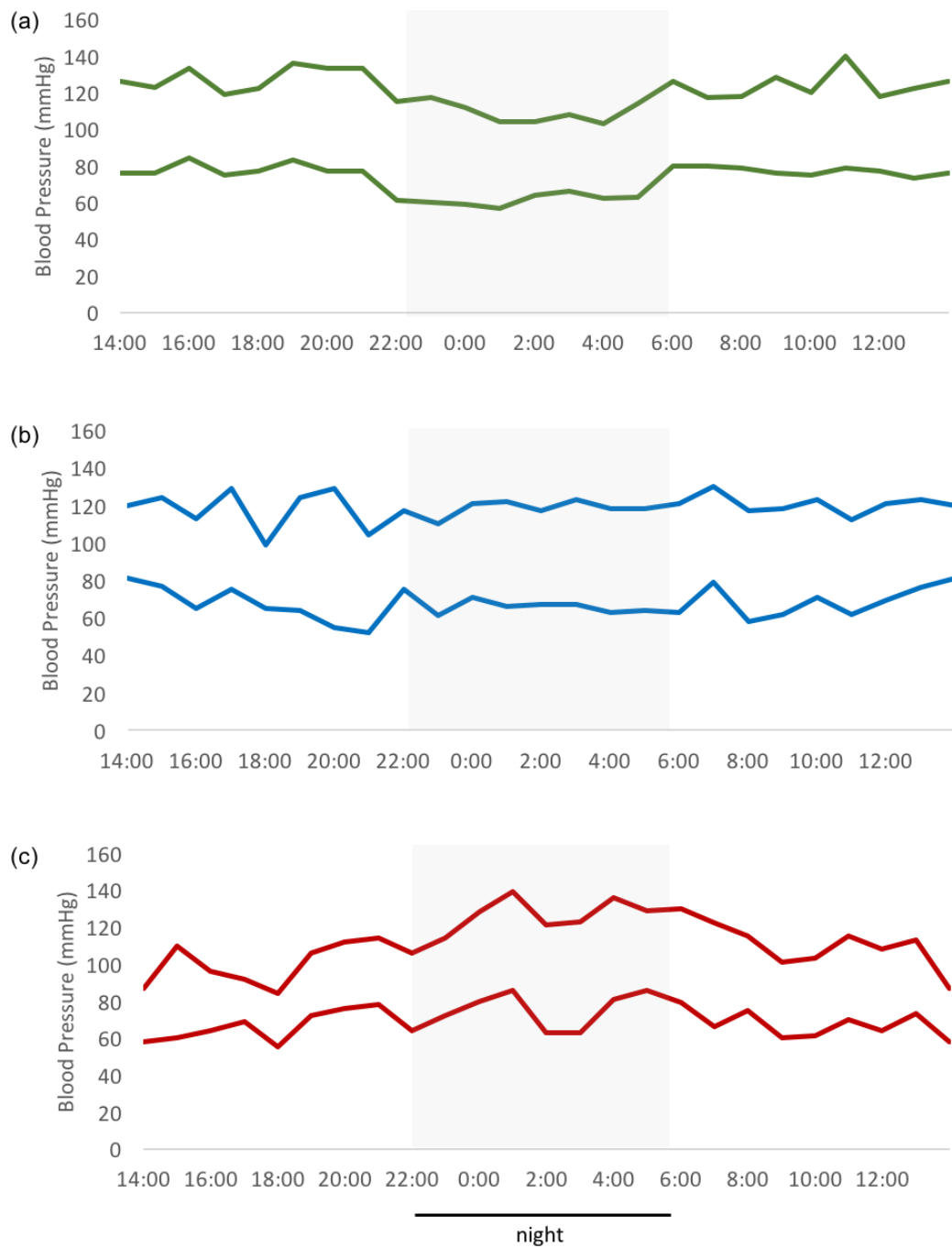


Figure 1.3 Examples of diurnal blood pressure patterns.

(a) Dipper pattern, night:day SBP 80-90% (b) Non-dipper pattern, night:day SBP 90-100% (c) Reverse dipper pattern, night:day SBP >100%. SBP, systolic blood pressure.

Nocturnal hypertension is the elevation of average night pressures above an absolute value, 120/70 mmHg;⁹⁴ it often occurs together with a loss of dipping, but can occur separately. It is also associated with poorer cardiovascular outcomes.^{9, 11, 91}

Compared to clinic BP measurements, ABPM permits the recording of a large number of readings recorded over a relatively short period, allows measurement of BP in the patient's usual environment, rather than in the relatively artificial environment of a clinic visit, and provides a measurement of diurnal changes in BP and nocturnal BP.⁸⁹

ABPM can also detect masked hypertension, the situation where clinic BPs appear within normal limits whereas ambulatory BP is elevated, and white coat hypertension, where clinic BPs appear elevated whereas ambulatory BP is not. ABPM is indicated for investigation of symptoms of hypotension, as it may be able to reveal episodes of hypotension during the period of monitoring, which may be compared against a patient diary to identify episodes of symptomatic or asymptomatic hypotension.^{94, 95}

BP may also be self-measured by patients using relatively inexpensive portable devices. The advantages of 'home' BP measurement is that like ambulatory devices, it allows measurement of BP in an environment that is perhaps more likely to reflect usual BP than measurement of BP in a medical clinic. Home BP measurement is proposed as an alternative to ambulatory BPs, especially for patients requiring long-term monitoring.^{96,}
⁹⁷ However, home measurements cannot practically measure BP during sleep, although investigation into the use of nocturnal home BPs are underway. Also, compared to home measurement, the initial diagnosis of elevated BP is better assessed with ambulatory

measurements because classification of hypertension with the latter provides better correlation with evidence of target organ effects.⁹⁸

1.6. Disorders associated with orthostatic hypotension

Orthostatic hypotension and orthostatic intolerance can occur when there is impairment in any of the physiological regulators of BP mentioned in earlier sections. This section examines orthostatic hypotension and intolerance in the context of a few of these disorders.

1.6.1. Disorders of the autonomic nervous system

As outlined above, the ANS plays a large role in homeostasis. Autonomic nerves respond to environmental stimuli and innervate organs and tissue through the body. One approach to classification of autonomic disorders is by dividing first into two groups, conditions associated with usually permanent autonomic dysfunction (e.g. Parkinson's disease, MSA, diabetic autonomic neuropathy), and conditions where dysfunction is intermittent and where the ANS appears capable of providing normal function (e.g. POTS, situational syncope). The former may also be referred to as structural disorders, whereby there is a known pathophysiological cause and usually anatomical cause. The latter is referred to as functional disorders for which the location of disorder or nature of pathology is unknown. Structural disorders can further be categorised as central (e.g. MSA) or peripheral disorders (diabetic autonomic neuropathy) with the caveat that the delineation between central and peripheral is not entirely exclusive; as generalised (e.g. MSA, diabetic autonomic neuropathy, POTS, SCI) or localised (e.g. Horner syndrome) disorders, or as primary or secondary disorders.^{19, 21, 32}

Primary autonomic disorders are those which appear to result from an underlying neurodegenerative mechanism, such as MSA, Parkinson's disease and pure autonomic failure. These are also usually regarded as central disorders, affecting the autonomic system up to a point before the sympathetic ganglion. Secondary autonomic disorders include causes such as diabetic autonomic neuropathy or familial amyloid neuropathy, where peripheral afferent or efferent fibres are affected. Intermittent autonomic dysfunction such as vasovagal syncope and POTS, and the autonomic dysfunction of SCI also fall under the classification of secondary autonomic disorders.^{19, 21, 32}

1.6.2. Cardiovascular manifestations of disorders of the ANS

Orthostatic hypotension is long known as a typical manifestation of autonomic disorders; indeed, the first cases of what is now known as pure autonomic failure were described by Bradbury and Eggleston in 1925¹³ as 'postural hypotension'. In addition to abnormal BP, dizziness and syncope, these cases were also described as exhibiting autonomic dysfunction of the urinary system, sweating and sexual function. Investigations in these three cases suggested a loss of vascular tone or response to epinephrine/adrenaline, along with the lack of variation in the HR to changes in BP and to atropine.¹³ Johnson⁹⁹ described the association between physiological findings in two cases of autonomic failure presenting with orthostatic hypotension, and the pathological neurodegeneration involving the intermediolateral columns of their spinal cords. Olivo-ponto-cerebellar atrophy was also observed in one of these cases.

ABPM has revealed a loss or reversal of diurnal BP variation in Parkinson's disease, MSA, pure autonomic failure and diabetic autonomic neuropathy.^{6, 100-104} There may be significantly elevated nocturnal BP, i.e. nocturnal hypertension, but a significant fall in BP, i.e. orthostatic hypotension, may be seen upon arising.

As discussed below, diurnal urine production is also altered in some disorders of the ANS, with the suggestion that this is related to a pressure natriuresis and diuresis from the nocturnal hypertension.

1.6.3. Spinal Cord Injury

Spinal cord injury (SCI) is another condition that is characterised by a high prevalence of orthostatic hypotension, especially in lesions affecting the higher levels of the cord.¹⁰⁵⁻¹⁰⁷ Interruption of spinal autonomic pathways results in impaired cardiovascular control which contributes to orthostatic intolerance.¹⁰⁸⁻¹¹⁰ Other autonomic functions are also affected, including bladder and bowel control, and thermoregulation.^{111, 112} All these present significant challenges to the rehabilitation and adjustment in acute and chronic SCI.^{105, 113, 114} This section explores the cardiovascular effects of SCI.

1.6.3.1. History of SCI

The earliest known documentation of SCI dates back to approximately 2500 BC, from a series of 48 traumatic cases recorded on surgical papyrus that were obtained by Edwin Smith, an American Egyptologist. Of these cases, it was thought that 6 involved the cervical spine, with 2 of these clearly implicating SCI.¹¹⁵ Additional comments related to wound management and other medical treatments but comments on the cases suggested that these two cases of SCI were "an ailment not to be treated". A final case in the series was incompletely described but appeared to be one of incomplete SCI, described to have a favourable prognosis with treatment recommended.^{115, 116}

This nihilistic view of SCI was maintained by well-known people including British naval hero Lord Admiral Sir Horatio Nelson (1758-1805) and James A. Garfield, President of the United States of America in 1881. To some extent this view explains the death of commander of United States Armies in WWII, General George Patton, who, like many of his soldiers, died soon after sustaining a SCI.¹¹⁵

It was only in 1936 that the first SCI unit was set up in the United States by Donald Munro, dubbed the "father of paraplegia".¹¹⁷ He is credited with recognising the need to treat the whole person, including multiple affected organ systems and psychological and social issues surrounding SCI. Following this, there was a gradual change in the attitude and management of SCI. It was increasingly recognised that after the initial surgical management of the SCI and its complications and consequences, rehabilitation could provide a reasonable prognosis. Factors that contributed to this change included advancement in other fields of medicine, such as in anaesthesia and radiology, and the

availability of antibiotics which controlled infection which previously caused a high mortality in SCI. Today, SCI is a survival injury, and there is increasing work on improving the lives and mortality of people with SCI.¹¹⁵⁻¹¹⁷

1.6.3.2. Cardiovascular disorders in SCI

Abnormal locomotion and sensation are the most obvious manifestations of SCI. Less visible, but clearly of importance, are the manifestations of disruption of the ANS.^{112, 118} These manifestations include disruption of gastro-intestinal function, resulting in constipation and potentially socially disabling faecal incontinence.^{119, 120} Genito-urinary function is also abnormal, and may necessitate urinary catheterisation and pre-dispose to potentially fatal urinary tract infections.^{121, 122} Of course, cardiovascular function can be significantly disrupted¹⁰⁸⁻¹¹⁰ and thereby produce significant morbidity and potentially mortality. These have been observed to be more prominent in higher and more complete SCI.¹⁰⁵⁻¹⁰⁷

The SCI population is difficult to study due to the relatively small population and its heterogeneity. The worldwide incidence and prevalence of SCI is estimated to be in the order of 13 and 368 per million respectively, while figures for Australia are 23 and 742 per million.¹²³ The small population base makes recruitment of participants challenging, especially at a single centre, and for studies involving early SCI.¹²⁴

Local or nationwide registries and databases in various countries around the world have been set up to better characterise the demographics and characteristics of the SCI population, in order to facilitate research and improve patient management. However, maintaining useful and relevant registries that allow international or national collaboration require standardisation between countries or states, and maintaining such registries require effort of participating institutions, adequate infrastructure and sufficient funding.¹²⁵⁻¹²⁸

There are multiple possible causes of SCI such as different forms of traumatic injury or disease. The SCI can be complete or incomplete, and can occur at any level from cervical to sacral. The affected person can require ventilation and be fully dependent, or independent.^{129, 130} Care for the SCI patient involves multiple disciplines, from the acute intensive care and surgical units to the rehabilitation units, and includes medical, nursing and a wide range of allied health staff. Thus, SCI is not a single entity but is heterogeneous and has various manifestations and care needs.^{112, 131, 132} A sufficiently large population is required for examination to adjust for these differences. The disability and morbidity of the SCI itself may be a factor that impedes patient participation in studies. Studies are often conducted out of tertiary centres, and require engagement of the SCI patient with such services.^{128, 133}

In the acute phase of injury, the spinal cord is in a transient state of hypoexcitability, known as spinal shock, characterised by flaccid paralysis of the muscles and a lack of tendon reflexes, occurring over days to weeks or months. There remains controversy regarding the clinical definitions of spinal shock and its recovery. Concurrently, neurogenic shock occurs due to impairment of sympathetic function with preservation of vagal or parasympathetic function, manifesting as hypotension and bradycardia. Cardiovascular support may be required in the form of fluids and vasopressors. The neurogenic shock generally resolves in days to weeks, but hypotension and bradycardia can persist into the chronic phase of injury.^{134, 135}

The chronic phase of SCI sees some return of activity and reflexes in the intact remnant of the spinal cord distal to the lesion, but of course, without complete control being provided by the proximal part of the cord or the brain. It is most commonly in this stage of SCI that autonomic dysreflexia occurs, after resolution of spinal shock, although early episodes have been documented.^{136, 137}

Cardiovascular disease, i.e. coronary heart disease and strokes, is a leading contributor of morbidity and mortality in the SCI population.¹³⁸⁻¹⁴⁰ In a cross-sectional nationwide survey in Canada involving over 60, 000 subjects, SCI was independently associated with more than 2- and 3-fold increases in heart disease and strokes after adjustment for age and sex, when compared with subjects without SCI.¹³⁹ Higher SCI was associated with cerebrovascular disease, dysrhythmia and valvular disease while lower SCI was associated with coronary heart disease and elevated BP.¹⁴¹ Risk factors for cardiovascular disease, such as elevated BP, dyslipidaemia, diabetes mellitus and reduced physical activity are prevalent in SCI.¹⁴²⁻¹⁴⁴ With the increasing lifespan of the SCI population, the development of strategies to improve cardiovascular outcomes has become more pertinent.

1.6.3.3. Orthostatic hypotension

Autonomic dysfunction has only more recently been recognised in both clinical and research fields as a priority for people living with SCI, due to its impact on quality of life as well as mortality.^{118, 145, 146}

Similar to primary autonomic disorders, orthostatic hypotension and orthostatic intolerance are frequently observed in people with SCI. It is most notable early after SCI, with a high prevalence during rehabilitation.^{105, 106} Illman et al observed orthostatic hypotension in 73.6% of 129 physiotherapy treatments performed on 14 inpatients undergoing rehabilitation after acute SCI, with symptoms in 59.8%, and perceived treatment limitation due to orthostatic hypotension in 43.2% of these sessions.¹⁰⁵ Several studies have observed a greater prevalence of orthostatic hypotension in high versus low SCI;¹⁰⁵⁻¹⁰⁷ whereas Illman et al found no difference between complete and incomplete SCI, Sidorov et al observed a lower prevalence of orthostatic hypotension in incomplete SCI.^{105, 106}

Studies of chronic SCI have found a lower rate of orthostatic hypotension, suggesting that it may improve over time.^{147, 148} This is in keeping with Sidorov's findings¹⁰⁶ of reduced prevalence of orthostatic hypotension in part of the SCI population by the end of the month-long rehabilitation period. Orthostatic hypotension is observed to become worse with periods of bed rest, potentially due to alterations of the baroreflex system or fluid shifts.^{41-43, 54}

Symptoms experienced are similar to that previously described of dizziness, visual disturbances, neck discomfort and syncope. It has also been observed that some patients do not experience symptoms despite measured postural hypotension, suggesting autoregulation of cerebral pressures to adjust to low arterial pressures.⁵

Orthostatic hypotension arises from the impaired control of the ANS, with a greater disruption to sympathetic functions in higher lesions. Lesions above T5-6 are more likely to cause orthostatic hypotension, due to involvement of the splanchnic circulation.^{109, 147, 149}

Other than the impact of symptoms on quality of life and safety, concerns have been noted about the possible contribution of chronic hypotension and orthostatic hypotension to poorer cardiovascular health. This is thought to be mediated by way of an increase in activation of the RAAS.^{147, 150, 151}

Management of this condition in SCI includes non-pharmacological methods of a head up tilt at night, abdominal binders, increased salt and water intake, and compression of the lower limbs by elastic stockings or thigh cuffs. Avoidance of precipitating factors such as straining, prolonged recumbency or rapid postural change, and hot temperatures is suggested. Pharmacological therapy aims to increase salt and water retention (fludrocortisone), cause vasoconstriction (ephedrine, pseudoephedrine, midodrine, droxidopa) or reduce vasodilatation (NSAIDs, beta-blockade). There have been few well conducted trials of pharmacotherapy in the SCI population, with the best evidence being for midodrine currently, based on a 4 subject double-blind randomised controlled

study, a 10 subject prospective dose-response trial and a few case studies.¹⁵²⁻¹⁵⁴ Information on pharmacotherapy for orthostatic hypotension in SCI is based on small numbers of studies with low numbers of participants or case studies, and knowledge from pharmacological therapy of autonomic dysfunction from other causes (e.g. diabetic autonomic neuropathy or Parkinson's disease). Of non-pharmacological therapy, functional electrical stimulation shows benefit in reduction of orthostatic hypotension, while spinal cord stimulation has had promising results.¹⁵⁵⁻¹⁵⁷

1.6.3.4. Autonomic dysreflexia

Autonomic dysreflexia is defined, in the International Standards to document remaining Autonomic Function after SCI, as an increase in SBP by 20 mmHg above baseline, with or without symptoms.¹⁵⁸ Extreme elevations to SBP of 300 mmHg have been reported,^{159, 160} which can lead to intracranial haemorrhage, seizures and death. It is more prevalent in more rostral levels of SCI, but its relation to motor completeness of SCI is not consistently observed in studies.¹⁶¹⁻¹⁶³ While it typically occurs in the chronic phase of SCI, after resolution of spinal shock, it was also documented in acute SCI.^{136,}

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Common causes of autonomic dysreflexia are bladder, bowel and skin issues, such as blockage of a catheter or a pressure ulcer. Symptoms experienced include a pounding head, sweating above the level of the lesion and facial flushing. Cold extremities result from reduction in peripheral blood flow. Episodes can be asymptomatic.¹⁶³

Autonomic dysreflexia occurs in the setting of an insult to the body below the level of the SCI lesion. Due to loss of descending inhibitory neural transmission, uninhibited local spinal reflex arcs produce increased sympathetic activity, vasoconstriction and elevation of BP below the level of the SCI lesion; this occurs in the splanchnic, muscle and cutaneous vascular beds.¹⁶⁴ In a healthy individual, stimulation of baroreceptors in the aortic arch by elevated BP results in increased parasympathetic activity and dampening of the sympathetic response. However, in people with high SCI, efferent sympathetic signalling is impaired and unable to suppress peripheral sympathetic tone, but the efferent increase in vagal activity is intact, and thereby can suppress HR. Thus,

the resultant picture is of an exaggerated increase in BP accompanied by decreased HR.¹⁶⁴

Management of autonomic dysreflexia involves primarily removing the cause. When this takes some time to occur, raising the head helps to lower BP, and antihypertensive agents can be used; nifedipine, nitrates and captopril are most commonly used in acute management of autonomic dysreflexia, while prazosin was observed to be effective without bringing on orthostatic hypotension as prophylactic management.^{160, 165, 166}

1.6.3.5. Mechanisms of cardiovascular disease in SCI

These abnormalities in BP after SCI are likely contributors to the increased prevalence of premature cardiovascular deaths observed in this population, along with other known risk factors for cardiovascular disease that apply to the general population.

The significant BP elevation of autonomic dysreflexia presents a risk of sudden severe hypertension that can lead to cerebral haemorrhage and death, in addition to the discomfort of symptoms. Studies done using animal models also suggest that the episodes of autonomic dysreflexia are associated with endothelial dysfunction, which may be a contributor to cardiovascular disease.¹⁶⁷ Silent episodes of autonomic dysreflexia were observed, which may also contribute to the increased cardiovascular risk.¹⁶⁸

Orthostatic hypotension in middle age is independently associated with increased cardiovascular risk in the general population, so the high prevalence of orthostatic hypotension in SCI may account for this being a significant risk factor in the SCI population.¹⁶⁹⁻¹⁷³

Increased variability in BP may be a risk factor for cardiovascular disease in the general population¹⁷⁴⁻¹⁷⁶ so this is likely to apply in the SCI population as well. The loss of autonomic function already leads to increased variability of BP, but in those with the combination of orthostatic hypotension and autonomic dysreflexia, there would be a further increased variability of BP.

In addition to BP disturbances, risk factors for cardiovascular disease in the general population are prevalent in SCI, such as dyslipidaemia, insulin resistance, obesity and reduced physical activity.^{142-144, 177, 178} Elevated BPs and pulse rates, known risk factors for cardiovascular disease in the general population, were prevalent in people with low SCI.¹⁴¹

As the BP disturbances are both a consequence of SCI, affecting quality of life, and also a potential risk factor for further cardiovascular disease in SCI, I aimed to examine the development, prevalence and treatment of orthostatic intolerance and abnormal diurnal variation in SCI, as there has been some success in treatment of the same in patients in our clinic with autonomic dysfunction without SCI.

In these patients, abnormalities in urine production accompanied the BP abnormalities. Furthermore, abnormalities in diurnal urine production were reported in those with SCI, therefore I wanted to examine the relationship between the abnormal diurnal variation of BP and that of urine production.

Finally, as there have been observations of an elevated HR being a risk factor for cardiovascular disease in the general population,¹⁷⁹ I examined the pulse rate along with ABPM data to see if my observations may correspond to the relation of pulse rate being a possible mechanism for cardiovascular disease in SCI.

1.6.3.6. Blood pressure in SCI

The various causes of SCI such as traumatic and non-traumatic causes, and the effects of different levels and completeness of SCI lead to variable patient characteristics to control for in studies; this is made more difficult by the relatively smaller numbers of participants available.

Prior studies have largely examined clinic pressures in people with SCI, with a smaller number of studies using ABPM to examine smaller cohorts of people with SCI, but usually limiting participants to those without cardiovascular disease or symptoms of BP abnormalities and orthostatic intolerance, and often to those with complete SCI.¹⁸⁰⁻¹⁸³

The additional requirements of keeping an ambulatory BP monitor on for 24 hours, and two visits for application and removal/return may be a barrier to participation. Unlike clinic pressures, ambulatory pressures are not a part of usual clinical care, so this information is more difficult to obtain for larger sets of patients. Considering the increased variability of BP in autonomic dysfunction, including in SCI, ABPM is an important tool in the examination of how BP affects a person with SCI.

Resting supine arterial diastolic BPs are lower than normal in acute cervical SCI.¹⁸⁴ The low basal BP and low levels of plasma noradrenaline and adrenaline were identified as early as the second day after SCI. It is thought to be a consequence of reduced sympathetic nervous system activity, which usually contributes to maintenance of vascular tone. Another potential contributor is skeletal muscle paralysis, however people with tetraplegia due to poliomyelitis often have a normal or higher BP.⁴³

The chronic phase of SCI is characterised by a correlation between lower resting systolic and diastolic clinic BPs and higher level of SCI.^{185, 186} Similarly, the prevalence of hypotension falls with a decrease in the level of SCI. These phenomena may relate to cervical and high thoracic lesions having lost sympathetic control of the splanchnic circulation, cervical lesions having also lost sympathetic control of the heart and low thoracic lesions having preserved sympathetic control of both cardiac function and splanchnic circulation.¹⁴⁸ ABPM indicates loss of the usual dip in BP overnight in complete cervical SCI.^{180, 183} Because of absent tonic supraspinal sympathetic input and reduced peripheral sympathetic activity, basal levels of noradrenaline and adrenaline in tetraplegia remains low, similar to levels observed during the phase of spinal shock. Compared to controls, microelectrode recordings in patients with SCI (C5-T8) show lower levels of spontaneous muscle sympathetic activity and a lack of arterial baroreflex modulation of muscle sympathetic activity. Bladder stimulation resulted in marked hypertensive reactions that were not matched by similarly significant increases of muscle sympathetic activity, suggesting that exaggerated sympathetic outflow was not the cause for the episodes of high BP in SCI.¹⁸⁷

1.6.3.7. Diurnal blood pressure in SCI

A small number of studies have examined the diurnal BP in people with SCI, employing the use of ABPM.

To date, the summary of observations from past studies is that people with complete, but not incomplete, tetraplegia lose the diurnal variation in BP, whereas those with high or low complete paraplegia have preserved diurnal variation.^{180-183, 188} Previous papers have mostly evaluated the presence of nocturnal dipping by determining whether the day pressures differ from the night time pressures, rather than examining the degree of nocturnal dipping for an individual or group according to whether it falls in the category of dipper, non-dipper or reverse dipper, which is widely used both in research and clinically in the general population. To reiterate, the extent of nocturnal dip in BP can be expressed as a ratio of night:day SBP, with a ratio of 80-90% considered normal ('dipper'), 90-100% considered non-dipping and over 100% considered reverse dipping.^{12, 92, 93} Non-dipping (including reverse dipping) and nocturnal hypertension have independently been associated with poorer outcomes in normotensive as well as hypertensive able-bodied populations.^{11, 189} Their impact on cardiovascular risk and whether treatment to normalise them will improve outcomes has not been examined in people with SCI.

Rosado-Rivera et al¹⁸³ presented figures for the nocturnal BP dip expressed as a percentage. In a group of participants with high and most complete paraplegia, the average nocturnal BP dip fell into the non-dipping category, however attention was only drawn to the statistically higher (more abnormal) nocturnal dip of the group with

tetraplegia – which fell into the reverse dipper category. The low paraplegia group, and the control group who were confined to wheelchairs, had normal dipping status on average.

Table 1.1 presents the night:day SBP for these studies organised according to the dipping categories, using the group summary day and night SBP presented in each paper. (Note that mathematically this is slightly different from the average of individual dipping status.) It appears that there is some loss of diurnal variation in high paraplegia and incomplete tetraplegia.

Table 1.1 Dipping categories in previous studies of diurnal variation in SCI

Study	Level, AIS	Dip%	Level, AIS	Dip%	Level, AIS	Dip%		Dip%
<i>Rosado-Rivera</i> ¹⁸³	tetra, A-D	103	high para, A,B	94	low para, A	89	controls	90
<i>Frisbie</i> ¹⁸⁸	tetra, A	101			low para, A	88		
<i>Munakata</i> ¹⁸²	tetra, A	101			low para, A	90	controls	85
<i>Nitsche</i> ¹⁸⁰	tetra, A	104	tetra, B-D	92	low para, A	90		
<i>Krum</i> ¹⁸¹			tetra	98			controls	90
<i>Seabra-Garcez</i> ¹⁹⁰			tetra A, para A	98				

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; Dip, night:day systolic blood pressure; A-D, AIS A-D; A, AIS A; A,B, AIS A and B; B-D, AIS B-D; tetra, tetraplegia; para, paraplegia.

Therefore, the overall observations are

- There is a loss of nocturnal dipping in SCI groups, with the exceptions of
 - complete low paraplegia group in whom diurnal variation is intact, and;
 - people with incomplete tetraplegia or high paraplegia in whom data is inadequate to draw conclusions.
- Greater abnormalities in BP diurnal variation are observed in people with complete tetraplegia, to the point of a reversal of diurnal variation.

- People with incomplete tetraplegia or high paraplegia also fall within the non-dipping category.

Given that the non-dipping was associated with poorer cardiovascular prognoses in the able-bodied population, and that cardiovascular disease was observed to be elevated in the SCI population, the extent to which the loss of nocturnal dipping affects these subgroups of patients may be a significant contributor to their cardiovascular disease. Seabra-Garcez et al¹⁹⁰ examined 32 people with chronic complete tetraplegia and paraplegia, without cardio-metabolic risk factors, and observed no correlation between nocturnal dipping status, defined as a nocturnal fall in BP of at least 10%, and carotid ultrasonography or echocardiography parameters. They found 24-hour DBP to be the only variable associated with carotid intima-media thickness after adjusting for level of injury and nocturnal dipping status. Thus, in this initial investigation, an association was observed between a marker of atherosclerosis and 24-hour DBP but not dipping status. However, the association between diurnal variation of BP and cardiovascular disease in the SCI population has not been studied.

Other than dipping status, the absolute mean values of 24-hour, day and night BPs have been compared between groups of people with SCI.

- Munakata et al found no difference in mean 24-hour BPs between complete tetraplegia, complete paraplegia and controls.
- Rosado-Rivera et al found a lower mean 24-hour BP in tetraplegia with post hoc analysis but not when comparing average values across groups.

- Generally, the night BPs are similar between all groups including complete and incomplete tetraplegia or high or low paraplegia and controls, while day BPs are lower in complete tetraplegia than complete low paraplegia and/or controls.^{182, 183,}

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This might be explained by the impairment in the sympathetic system which prevents the rise in BP with activity during the day. In addition, the lower activity levels of people with tetraplegia may also contribute to the lower day time BP.¹⁸²

Studies done to date have often been limited to people with chronic SCI, and excluded those with cardiovascular disease or 'orthostatic dysregulation', although a few have included and studied autonomic dysreflexia. Some have focused on complete injuries to minimise the variability of the extent of spinal cord dysfunction in the different groups, and compared complete tetraplegia and paraplegia to controls.¹⁸² Rosado-Rivera's group confined controls to a wheelchair (and included only SCI participants reliant on wheelchairs) to avoid the influence of orthostatic changes with standing on the cardiovascular haemodynamics.¹⁸³ Complete transection of the spinal cord at different levels allows for comparison between groups with differing sympathetic activity, since people with tetraplegia have a lesion above the sympathetic chain and would be expected to have little sympathetic activity, whereas those with low paraplegia are expected to retain sympathetic function. Given this aim, the exclusion of participants with cardiovascular disease or symptoms of BP abnormalities is logical.

However, in addition to the information provided by previous studies, it would be useful from an epidemiological point of view to examine the diurnal BP of the SCI population

as a whole, in order to observe correlations between the BP profile and cardiovascular prognosis and BP related symptoms, so as to facilitate management goals and options. The patients with BP related symptoms, namely autonomic dysreflexia, and orthostatic symptoms, and those with cardiovascular disease, are perhaps the ones who are most in need of BP monitoring as a tool to aid management. Indeed, orthostatic hypotension is an indication for ABPM on current clinical guidelines.⁹⁴ Hubli et al recently explored the use of ABPM to determine associations with symptoms and occurrence of both autonomic dysreflexia and orthostatic hypotension, finding a relationship between the occurrence of autonomic dysreflexia and events on the monitor, but this was not so for orthostatic symptoms.¹⁹¹ It would have been interesting to see what the diurnal patterns of BP were in these patients, because the loss of diurnal variation and nocturnal hypertension, along with nocturnal polyuria, was found in some patients with autonomic failure who have orthostatic symptoms.^{6, 192}

As mentioned above, non-dipping is associated with poorer cardiovascular outcomes in the able-bodied population, and in subpopulations such as diabetes mellitus and renal failure in which there is an increased cardiovascular risk,^{9, 10, 12, 193-195} given that the SCI population is observed to be associated with an increased cardiovascular risk, but mechanisms for these observations may be different in SCI compared to the general population, it is of importance that this gap in knowledge of population SCI diurnal BP profiles is filled. To begin this process, and to characterise the course of abnormalities in diurnal BP and urine output in SCI, is one of the purposes of the studies in this thesis. The observations obtained in this study will form the basis for further examination of

how diurnal BP relates to cardiovascular prognosis in longer-term prospective follow up, and from there, management goals may be determined.

1.6.3.8. Urine production

Abnormalities in diurnal urine production were observed alongside abnormal diurnal variation in BP and orthostatic hypotension (and orthostatic intolerance) in people with autonomic dysfunction.^{5, 6, 8} Specifically, nocturnal polyuria, an increased production of urine overnight, results from recumbency in autonomic failure, and contributes to orthostatic hypotension in the morning.¹⁹⁶ This is mediated by an increase in ADH during the day while upright.¹⁹⁷

Abnormalities in diurnal urine production, attributed to a lack of diurnal variation of ADH, have also been observed in patients with complete SCI above and below the T6 level in early SCI, and complete tetraplegia in early and chronic SCI.^{198, 199} Day ADH was higher in SCI than in controls.¹⁹⁸ A marked increase in ADH during upright tilts demonstrated in cervical SCI was absent in controls.^{51, 200, 201}

Recumbency in tetraplegia induces a diuresis but not a natriuresis, whereas both occur in primary autonomic failure.²⁰² In tetraplegia, where there is an absence of adequate resting sympathetic tone, the RAAS plays an important role in maintaining BP, through direct pressor effects of angiotensin II and salt retaining effects of aldosterone. An exaggerated elevation in renin is noted in people with tetraplegia undergoing a head up tilt,^{52, 203-205} whereas a reduced renin response has been observed in some with primary autonomic failure.^{206, 207}

Whereas disruption of diurnal variation of urine had been examined in high SCI,^{198, 199} it has been less commonly measured in lower SCI and not in relation to diurnal BP in

SCI. Given the potential relation with altered diurnal BP and orthostatic hypotension (and orthostatic intolerance) seen in autonomic failure, this thesis sought to examine the diurnal pattern of urine production in early and chronic SCI, and to determine its association with diurnal BP and orthostatic intolerance.

1.6.3.9. Heart rate

Elevated HR has been associated with cardiovascular morbidity and mortality in the general population, and may thus be another contributing factor to the increased risk of cardiovascular disease in SCI. In the general population, elevated HR has been associated with future development of hypertension, potentially as both could be due to an increased sympathetic tone.^{179, 208, 209} Elevated resting HR has been noted to correlate with worse cardiovascular prognoses especially in males, while elevated ambulatory HR has been observed to be associated with non-cardiovascular mortality.^{179, 209-211} A number of mechanisms may be contributory, and similar processes may be applicable to the SCI population. One of these mechanisms is thought to be the contribution of an elevated HR to arterial stiffness, which is of significance as increased arterial stiffness was observed in SCI compared with non-SCI populations, and both elevated HR and paraplegia have been associated with increased arterial stiffness in an SCI population.²¹²⁻²¹⁵ Thus, an elevated HR may be a potential mechanism contributing to elevated BP and cardiovascular risk in SCI.

Whereas bradycardia was noted in tetraplegia, tachycardia was noted in paraplegia.

In cervical SCI, resting pulse rate tends to sit at the lower end of the normal range compared to controls, due to the impairment in sympathetic drive and predominance of the vagal tone. This was not observed to change over time.^{148, 216} There was also an observation of increased rate of arrhythmias in cervical SCI, but how this relates to cardiovascular prognosis is uncertain.¹⁴¹

In paraplegic SCI however, elevated resting HR has been noted on both clinic and ambulatory measurements. Wecht et al²¹⁶ noted a high prevalence of high normal HR (HR > 80 bpm), or tachycardia (HR >100 bpm) in both high and low paraplegia. This is unexpected considering that people with high paraplegia, with injury between T1-T6, would be anticipated to have some impairment of sympathetic activity and therefore have HR that fall in between that of people with tetraplegia or low paraplegia. However, this observation is consistent with that of other studies. Ravensbergen et al found elevated HR in low paraplegic SCI, but the prevalence of this decreased with time after SCI, suggesting that some factors such as rehabilitation and reconditioning, along with improved blood volume status and medications, might have contributed.¹⁴⁸ Rosado-Rivera et al similarly found increased HR using ambulatory monitoring in high and low paraplegia as compared to tetraplegia, and to able-bodied controls restricted to wheelchair activity. They postulated that the elevation in HR may reflect dysfunction of the ANS with a shift toward sympathetic predominance, but were unable to ascertain whether this elevated HR was an independent cardiovascular risk factor to the autonomic dysfunction.¹⁸³ In support of the hypothesis of increased sympathetic activity, elevated resting catecholamine concentrations have been observed in low paraplegia.^{217, 218} In both animal and human studies, vagal dysfunction has also been observed, supporting this as a contributing factor to the elevation in HR.^{183, 219, 220}

In this thesis, although examination of the HR was not the primary aim, ambulatory pulse rates were available along with the ambulatory BPs, so these were also examined.

1.7. Conclusion / summary

In summary, orthostatic intolerance occurs in traumatic SCI, in which there is impairment of autonomic control of the cardiovascular system, leading to disruption in BP control, including increased variability in BP, severe hypotension and autonomic dysreflexia.^{109, 151} Smaller studies in restricted populations have employed the use of ABPM and identified abnormal diurnal variation of BP in complete cervical SCI.^{180-183, 188} With increasing life expectancy of the SCI population, evidence of an increased cardiovascular risk is emerging in this population.¹³⁸⁻¹⁴⁰

In the general population with and without autonomic disorders, ABPM has been used to identify abnormalities in diurnal BP and is used for both symptom management, and assessment and management of cardiovascular risk. Ambulatory pressures are better associated with cardiovascular prognoses than clinic pressures, and able to assess nocturnal pressures and dipping.^{11, 71, 90}

The role of ABPM in SCI is not well defined but has the potential to also be useful in the management of symptoms and cardiovascular risk, in a similar way that it has been applied in other populations. Examination of the diurnal BP alongside urine production and orthostatic intolerance, may be beneficial in SCI as it has been in autonomic failure.

This project aims to characterise the course of diurnal BP patterns over the first year of a SCI and to examine diurnal BP in chronic SCI in a relatively unselected population, as

a framework upon which further research work and clinical guidelines can be developed.

Thus, the aims of this thesis were:

- 1) To examine the prevalence and extent of abnormal diurnal variation of BP and urine production in patients with SCI who were referred for clinically significant disorders of BP control.
- 2) To verify that abnormal diurnal variation of BP occurs in SCI, particularly tetraplegia, and not in healthy people with intact sympathetic systems, in early and chronic SCI.
- 3) To examine the association of the diurnal variation of BP with diurnal urine production, orthostatic hypotension and orthostatic intolerance in SCI, particularly in tetraplegia.
- 4) To develop a protocol for management of orthostatic intolerance in people with SCI, to assist with improvement of quality of life.

Chapter 2. Methods

This chapter describes the methods used in the following sections of the thesis.

2.1. Study Population

The main population of interest in this thesis are people with traumatic SCI. Specific study populations are outlined within each chapter. The Victorian Spinal Cord Service (VSCS) at the Austin Health is a tertiary centre for management of acute SCI for the states of Victoria and Tasmania, Australia, therefore many of these study participants have had contact through this service. This multidisciplinary service provides inpatient and outpatient care, and rehabilitation for people with traumatic and non-traumatic SCI, and is one of six such specialist services in Australia. It provides specialty medical services such as the spinal urology service and upper limb program, as well as community based services to optimise medical and social outcomes.

Study 1 was a retrospective analysis on medical records of patients with acute or chronic SCI who had been referred to the Blood Pressure Clinic at the Department of Clinical Pharmacology between June 2008 and May 2011. The study examined abnormalities in diurnal BP and urine production in a referred population.

Study 2 examines these parameters in consecutive consenting patients admitted to the VSCS with acute, traumatic SCI, between February 2010 and December 2013. A comparator group recruited contemporaneously comprised otherwise healthy patients who were required to remain immobilised with bed rest while awaiting orthopaedic surgery. A further control group was also recruited contemporaneously and comprised healthy, able-bodied volunteers without SCI. They were recruited by advertisements

which were placed in the hospital and nearby universities. This group served as a control group for this study and Study 3.

Study 3 examines these parameters in volunteers with chronic traumatic SCI (at least one year duration) recruited prospectively by advertisements placed in the hospital and community, alongside invitations to previous and current patients of the hospital via letters and telephone calls. Comparisons were made with healthy able-bodied volunteers (described above).

Study 4 was designed to investigate the use of a novel treatment for orthostatic intolerance in people with SCI of at least one year duration. In screening for participants for this study, a telephone survey was conducted to examine participants' symptoms and function in relation to symptoms of orthostatic intolerance.

In addition, participant eligibility for Study 2, 3 and 4 were defined as follows:

All participants:

- Aged at least 16 years and able to provide consent

Exclusion criteria for all participants:

- Significant head injury (GCS <8 at the time of injury)
- Inability to participate in ABPM because of issues such as trauma to arms including bilateral limb amputation, fistulae.
- Significant medical conditions likely to influence ability to complete study protocol
- Pregnancy or breastfeeding

Participant grouping was defined as follows:

A) Tetraplegia

- Traumatic SCI in the cervical region
- As assessed by the American Spinal Injury Association Impairment Scale (AIS) according to inpatient notes for Study 2, or medical history for Studies 1 & 3.

B) Paraplegia

- Traumatic SCI in the thoracic, lumbar or sacral region, as assessed by the AIS according to inpatient notes for Study 2, or medical history for Studies 1 & 3.
- Participants were further sub-grouped as *high paraplegia* if the SCI lesion was between T1 to T6, and *low paraplegia* if the lesion was below T6.

C) Immobilised controls (Study 2 only)

- Expected immobilisation of at least 24 hours for injury not involving the spinal cord such as orthopaedic injuries whilst awaiting surgery

D) Healthy able-bodied volunteers without SCI (Studies 2 and 3)

Complete and Incomplete SCI

The terms complete and incomplete SCI in the following studies refer to neurological completeness according to motor and sensory deficits, as assessed by the AIS, where AIS A is considered a complete injury and AIS B, C and D are considered incomplete injuries.²²¹ This differs from autonomic completeness of injury, which may not correlate with the neurological completeness.¹⁴⁷ Whereas neurological completeness is routinely

assessed clinically, and there are efforts to standardise recording of autonomic function alongside this, bedside assessment of autonomic completeness is still not routine in clinical practice.²²² I aimed to examine study variables in subgroups of SCI participants according to their usually clinically defined characteristics.

Acute and chronic SCI

Rowland et al²²³ outlines pathophysiological changes occurring after SCI, defining immediate (up to 2 hours), early acute (up to 48 hours), secondary subacute (up to 14 days), intermediate (up to 6 months) and chronic (>6 months) phases of injury according to early mechanical changes and later tissue destruction. In this thesis, the term *acute SCI* is applied to the group of participants with SCI who had a duration of SCI of less than a year. *Chronic SCI* was applied to the group of participants with SCI of duration of more than a year. The one year demarcation was arbitrarily chosen based on the observation that rehabilitation after SCI was expected to be complete within about 6 months, and while a small proportion of patients have delayed discharges due to social issues, most would be discharged and living in the community by a year after the SCI. Thus, the acute SCI group would mostly be in the subacute or intermediate physiological phase of injury and in acute medical care or inpatient rehabilitation following the SCI, while those in the chronic SCI group would be expected to have completed rehabilitation after SCI and be living in the community.

2.2. Ambulatory blood pressure monitoring

ABPM employs a portable machine attached to a BP cuff that automatically inflates at pre-programmed intervals during the day and night. The device is usually worn for about 24 hours, with readings taken at 15-60 minutely intervals, often with a reduced frequency at night to reduce sleep disturbance. The output is read with a software program which calculates various parameters, including average 24-hour BP, day and night BPs, nocturnal dipping, and other parameters such as hypertension loading. Pulse rate calculations are similarly provided.

The Spacelabs 90207 (Spacelabs Inc, Redmond, WA, USA) and Card(X)plore (Meditech, Hu) ambulatory monitors used in the studies in this thesis both measured BP by the oscillometric method. These devices fulfil the validation protocol and satisfy accuracy criteria in accordance with the Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS).²²⁴⁻²²⁶

Study 1 was a retrospective study. Patients underwent ambulatory monitoring with either the Spacelabs 90207 device or Card(X)plore monitor – which were the devices which were used for clinical service in Austin Health's Hypertension Clinic at the time the study was conducted. Studies 2, 3 and 4 were prospective studies which employed the use of the Card(X)plore monitor.

2.2.1. Analysis of ambulatory blood pressure monitoring data

Although the method of measuring BP using ambulatory devices has been extensively evaluated and there are standardised validation protocols for monitors,²²⁷⁻²³⁰ consensus is yet to be developed for the optimal method for analysing data generated by ambulatory monitors.^{89, 231-233} Examples of this have been highlighted by O'Brien et al and Rossen & Hansen who documented significant errors in reports with figures differing from on-screen numbers.^{89, 231}

2.2.1.1. Determination of averages

ABPM has been used relatively commonly for research and clinical purposes for many decades. When reporting ambulatory BP data, scientific publications frequently refer to 'average' 24-hour, day and night BP values. However, relatively few papers define the method used to calculate 'average' values. As recently as 2010, Octavio et al²³² pointed out a lack of consensus in the method of calculation of 'average' ambulatory BP, and demonstrated that time-weighted calculations of ambulatory BP avoids overestimation of 24-hour BP – especially in people who have a 'dipper' pattern of diurnal variation. The importance of weighted averages is amplified when a higher frequency of measurements is recorded during the day compared to at night. The authors believe that the conventional method of calculating the 24-hour average, used in most ABPM software, is based on averaging the total readings across 24 hours of recording, and a time weighted average is the exception. Further variation in calculating ambulatory BP measurements can arise when different frequencies of measurement are employed and when day and night periods are differently defined. The commonly used frequencies are 2-4 times/hour during the day and 1-4 times/hour during the night, where day and night are also defined differently at different centres. Weighted averages are recommended.⁸⁹

In these studies, raw values of systolic and diastolic ambulatory BP and pulse rate data were downloaded from the Spacelabs 90207 and Card(X)plore devices and hourly averages were calculated for each parameter using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and R software (<http://www.r-project.org>). From these hourly values, the mean 24-hour, day and night BP were calculated for each participant. From these figures, group statistics were derived as presented in the chapters.

2.2.1.2. Definitions of day and night

Other than the advantage of a large number of readings over time, ABPM allows for examination of the diurnal BP pattern. The usual circadian rhythm is such that the BP usually falls during sleep, to a level that is 10-20% of the daytime BP. This is known as the nocturnal dip, and people with this normal pattern are known as *dippers*.^{12, 92, 93}

The day and night periods of the ABPM duration usually correspond to awake and asleep periods. The definitions of day and night for the purposes of examination of the ABPM can be defined in different ways, but the most commonly used methods are by means of a patient kept diary, or by a fixed time clock method. The activity diary is thought to be the most accurate, provided the patient keeps a detailed record of posture, activity, sleep and wake times for the duration of the ambulatory monitor. This would allow correlation of BP data with sleep and wake states, along with time. In some studies, daytime napping or night time awakenings are excluded from data analysis.^{234,}

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The fixed clock time method uses a particular time period to define night and day, regardless of when the patient was actually awake or asleep. It has been found that using a narrow fixed clock duration corresponds better to the actual awake-sleep time for most patients, as compared to a broad fixed clock time interval.^{235, 236} Specifically, the period of 1000-2000 for daytime and 0000-0600 for night time excludes the morning and evening periods when patients tend to be awakening or going to bed, as compared to using 0600-2200 for the day period and 2200-0600 for the night period.²³⁶ This narrow fixed clock time has also been observed to be compatible with the living

habits of the majority of people in various populations.²³⁴ Another fixed time range used is 0900-2100 for the day and 0100-0600 for the night, with the aim of eliminating variations between young and old, and in different cultures to some extent.^{89, 237} Some studies found no major differences whether patient diary, fixed time or actigraphy based definitions of day and night were used.^{238, 239}

In the retrospective examination in Study 1, the wide fixed clock time method was used as that was the convention in clinical use at the time, with day defined as 0700-2300 and night as 2300-0700. Thereafter, it was recognised that this wide fixed clock time method would lead to inclusion of variable portions of the day and night period containing asleep or awake data for some participants.

The intention was to use diary times to define individual day and night periods, however as diary entries for sleep-wake times were not well completed, the narrow fixed clock time was used as the main method of defining day and night time periods for BP monitoring for Studies 2 and 3, taking the discussion above into account. This method was chosen because it may accommodate for the behavioural patterns that patients with SCI frequently have, i.e.

- Patients with acute SCI are resident in hospital in the period immediately after injury and until rehabilitation is completed. During that time, they are required to adhere to the routine of the hospital.
- Patients with acute SCI (Study 2) typically only gradually progress from being fully recumbent in the period immediately after the injury, to being upright for the

majority of the day. Early in the rehabilitation period they may only spend 2 hours out of bed each day

- Rather than changing rapidly between erect and supine as they retire to or leave bed, patients with SCI often undertake a series of postural changes in the morning and evening. For example, after awakening for the day, a patient with SCI may sit in bed for breakfast, then shower seated in a commode, then return to bed to dress and/or rest, and then transition to their wheelchair for the day. At night, a patient with SCI may gradually transition from being upright in a wheelchair to being partly recumbent for some time, and then being fully recumbent when initiating sleep.
- The duration and timing of transitioning between bed and upright may be influenced by the availability of carers. These transitions may take several hours.

One of the commonly used fixed clock times of 1000-2000 for day time and 0000-0600 for night time²³⁴ was selected because in the hospital, patients tended to return to bed by 8 pm, were awoken from 6am due to nursing rounds and got out of bed usually between 8 and 10 am to attend rehabilitation programs starting from 9am.

The European Society of Hypertension (ESH) previously recommended a minimum of 14 daytime and 7 night time measurements for ABPM,²³⁷ however an updated position paper in 2013⁸⁹ (after commencement of the studies) suggests a minimum of 70% of expected measurements, or 20 daytime measurements and 7 night time measurements, based on half hourly automated readings from the monitor over the day and night, and the use of fixed time periods 0900-2100 for the day and 0100-0600 for the night.

The definitions of day and night used for reasons described above would give a maximum of 21 readings in the day and 7 readings overnight, as half hourly pressures were taken during the day and hourly pressures taken during the night. Therefore, considering the recommendations of the ESH, monitors with a minimum of 15 day readings and 5 night readings, i.e. at least 70% of expected measurements, were included for analysis.^{89, 237}

2.3. Orthostatic blood pressure measurements

To determine the prevalence of orthostatic hypotension, BP was measured during orthostasis. Orthostatic hypotension is defined as a sustained reduction of SBP of at least 20 mmHg or DBP of at least 10 mmHg within 3 minutes of standing.²²

Orthostatic BP was measured by participants using the Card(X)plore device. On the morning after fitting of the device, participants were requested to obtain three measurements of BPs taken whilst they were supine and another three measurements after they assumed the upright position. The measurements were performed upon first leaving bed in the morning. Each set of readings were to be taken by pressing a button on the monitor at one minute intervals. These readings were recorded as manual readings on the ambulatory monitor. Patients who were able to stand for the upright readings were asked to, while those who were unable to stand were asked to do the upright measurements while seated.

The change in postural BP was calculated by determining the difference between the lowest upright BP and the mean supine BP for systolic and diastolic measurements. The change in pulse rate was calculated by determining the difference between the maximum upright pulse rate and the mean supine pulse rate. These differences were expressed as a mean for each study group for between group comparisons. The prevalence of participants in each group with a fall in at least 20 mmHg SBP or 10 mmHg DBP was also noted.

2.4. Diurnal urine production

In healthy individuals, urine production follows a diurnal pattern with reduced volumes overnight. At least in part, the diurnal variation is mediated by changes in secretion of anti-diuretic hormone. The diurnal rhythm of urine production was previously observed to be disrupted along with BP in autonomic failure.^{6, 196, 197, 240} In SCI, there was a loss of diurnal variation in both urine production and ADH levels.¹⁹⁸ A diuresis due to recumbency may also contribute to this effect in SCI.²⁰²

In the following studies, measurement of diurnal urine volumes over three days and nights were performed by participants, with help from carers where required. Participants were instructed to record the time of voiding or emptying of catheter bags on waking for the morning of Day 1, then to record the time and urine volume for each subsequent void or catheter bag emptying until and including the measurement on first waking on Day 4. To determine day and night periods, participants were asked to indicate the time of arising and retiring to bed each day. A measuring jug was provided for measurement of the urine volumes.

The day and night rates of urine output were calculated by dividing the volume of urine by the duration between measurements, and expressed as ml/minute. Average values for the 3 days and nights were used in analyses.

2.5. Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and R software (<http://www.r-project.org>). Methods of analysis for each study are detailed within each chapter. The Student's t-test, ANCOVA, ANOVA or linear mixed models were used for comparison of continuous variables BP, pulse rates and urine output across study groups, with pairwise comparisons between groups. Normality of data was assessed by visual inspection of plots of paired differences or residuals. The Kruskal-Wallis and Wilcoxon signed-rank tests were used to compare symptom scores, while the Chi-square or Fisher test was used for categorical variables such as comparison of gender or dipping status. Significance was set at $p < 0.05$.

2.6. Ethics Approval

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The protocol for each study was approved by the Human Research Ethics Committee of the Austin Health.

Chapter 3. Retrospective review of diurnal blood pressure in symptomatic patients with SCI

Study 1. It has been increasingly recognised that in people with SCI, quality of life is significantly affected by not only the effects of motor and sensory impairments, but also by autonomic dysfunction.^{118, 145, 146} This includes disorders of control of the cardiovascular system, urinary system as well as gastrointestinal system.

Previous examinations of diurnal BP in SCI populations have excluded people with cardiovascular disease or symptoms of impaired BP control. In order to characterise the extent of abnormalities in diurnal BP and urine production patterns in people who are affected by the autonomic impairment associated with SCI, I began my studies with a retrospective examination of the diurnal BP and urine production patterns in patients with SCI who were referred to the BP Clinic for clinical reasons - largely orthostatic intolerance.

A manuscript describing the results of this study was published in *Spinal Cord*. The following is a reprint of the manuscript as published.

Goh MY, Wong EC, Millard MS, Brown DJ, O'Callaghan CJ. A retrospective review of the ambulatory blood pressure patterns and diurnal urine production in subgroups of spinal cord injured patients. *Spinal Cord* 2015; **53**(1): 49-53. doi:10.1038/sc.2014.192

ORIGINAL ARTICLE

A retrospective review of the ambulatory blood pressure patterns and diurnal urine production in subgroups of spinal cord injured patients

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Study design: Retrospective study.

Objectives: To quantify diurnal blood pressure (BP) patterns and nocturnal hypertension and to measure diurnal urine production in spinal cord injury (SCI) patients with clinically significant disorders of BP control.

Setting: A specialist state-based spinal cord service in Victoria, Australia.

Methods: Medical records of patients with traumatic SCI who were referred to a specialist service for management of a BP disorder were examined. Ambulatory BP and nocturnal urine production were compared between groups of patients classified according to level, completeness and chronicity of SCI. Patients with night:day systolic BP <90% were classified as dippers, 90–100% as non-dippers and >100% as reversed dippers.

Results: Patients (44 tetraplegic, 10 paraplegic) were predominantly males (92.6%) aged 41 ± 2.5 years (mean $\pm$ s.e.m.). Referral was for orthostatic intolerance ($n=37$), autonomic dysreflexia ($n=6$), nocturnal polyuria ($n=4$), elevated BP ($n=1$) and peripheral oedema ($n=1$). The average BP was $111.1 \pm 1.4/65.0 \pm 1.2$ mm Hg. In 56% of patients ($n=30$), BP at night was higher than during the day and another 37% ($n=20$) were non-dippers. Nocturnal hypertension was present in 31% ($n=17$) of the patients. In the tetraplegic patients, urine flow rate was greater during the night than day (121 ± 9.5 ml h⁻¹ vs 89 ± 8.2 ml h⁻¹, $P=0.025$).

Conclusion: Ambulatory BP monitoring in patients with SCI and clinically significant BP disorders detected a high incidence of reversed dipping and nocturnal hypertension. We postulate elevated nocturnal BP may contribute to nocturnal diuresis that might cause relative volume depletion and thereby contribute to daytime orthostatic hypotension.

Spinal Cord (2015) **53**, 49–53. doi:10.1038/sc.2014.192; published online 11 November 2014

INTRODUCTION

Abnormal blood pressure control resulting in orthostatic intolerance is a common and distressing disorder for both able-bodied and spinal cord injury (SCI) patients. At least for able-bodied patients with orthostatic hypotension, guidelines recommend measuring blood pressure over 24 h using an ambulatory device.^{1,2} Monitoring of ambulatory blood pressure in autonomic neuropathy detects episodes of otherwise undetectable hypotension and it can also determine whether night pressures are elevated, which is particularly important when contemplating drug treatments that may further increase already elevated nocturnal pressures. Also, it has been postulated that elevated nocturnal pressures in autonomic neuropathy may contribute to nocturnal diuresis and natriuresis, which in turn is proposed to cause volume depletion which may exacerbate postural hypotension.^{3–5} Thus, in addition to assisting in management of blood pressure disorders, measurement of ambulatory blood pressure may provide insight into the mechanisms contributing to orthostatic hypotension.

Although abnormalities in diurnal blood pressure have been found in patients with SCI, and clinical use of ambulatory blood pressure monitoring has been advocated,⁶ the clinical application of ambulatory blood pressure monitoring in SCI has been incompletely studied. This

is partly because previous studies have specifically excluded patients with 'orthostatic dysregulation' or 'cardiovascular disease'.^{7–9} Whether patients with symptomatic blood pressure disorders have abnormal diurnal variation or nocturnal diuresis, which could potentially contribute to orthostatic hypotension, has not been determined.

In this study, we examined the 24-h ambulatory blood pressure patterns in patients with SCI who had clinically significant problems with blood pressure control. We also measured the nocturnal urine production in a subset of those patients—17 tetraplegics—most of whom had long-term catheters (2 had condom drainage and 1 male did not use voiding aids). Patients included in this study had tetraplegic or paraplegic SCI, complete and incomplete SCI and acute and chronic SCI.

MATERIALS AND METHODS

The protocol for this study was approved by the Human Research Ethics Committee of Austin Health.

A retrospective review of the records in the Blood Pressure Clinic database identified patients with a history of traumatic SCI who were referred to our Blood Pressure Service for blood pressure management between June 2008 and May 2011.

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Received 27 March 2014; revised 6 October 2014; accepted 6 October 2014; published online 11 November 2014

Demographic details of SCI (date, mechanism of injury, level and completeness of injury), ambulatory blood pressure monitoring results and diurnal urine production were obtained from medical records. The level and completeness of injury were evaluated according to the international standards for neurological classification by the American Spinal Injury Association (ASIA) on admission to the hospital with SCI and on discharge from rehabilitation. The most recent level and ASIA impairment scale (AIS) noted in the medical history were recorded for the purposes of this study.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitor results were analysed according to mean 24-h, day (0700–2300) and night (2300–0700) values for systolic blood pressure, diastolic blood pressure and pulse rate, obtained from half-hourly measurements during the day and hourly measurements overnight during 24 h of monitoring.

The nocturnal dip was the ratio of night to day systolic blood pressure, expressed as a percentage. Patients with a nocturnal dip of <90% (the normal pattern) were classified as 'dippers', 90–100% as 'non-dippers' and >100% as 'reversed dippers'.¹⁰ Hypertension was defined as a 24-h blood pressure greater than 130/80 mm Hg, daytime hypertension as a daytime blood pressure above 135/85 mm Hg and nocturnal hypertension as a night blood pressure above 120/70 mm Hg.¹

Nocturnal urine production

Urine volumes were recorded over three consecutive days, generally within a week of blood pressure monitoring. Measurements reported were average values for the 3 days. Nocturnal urine production was the volume of urine produced overnight, including urine passed on first waking for the day, expressed as a percentage of the entire day's urine output. Nocturnal polyuria was defined as a nocturnal urine volume being >33% of the total daily volume.¹¹

Study groups

Patients were divided firstly according to level of injury, where tetraplegia was defined as a level of injury above T1 and paraplegia, T1 and below. These were then subdivided into patients with complete (AIS A) and incomplete (all others) injury. Next, they were grouped according to whether the SCI was acute (occurring within the past 1 year) or chronic (occurring more than 1 year before the blood pressure monitoring).

Statistical analysis

Analysis was performed using Microsoft Excel. The Student's *t*-test was used to compare continuous variables between study groups (such as blood pressure and nocturnal urine production). The chi-square test was used for categorical variables (such as gender and dipping status). Significance was set at $P < 0.05$. Range intervals represent standard error of the mean (s.e.m.).

RESULTS

Study group characteristics

The patients ($n = 54$) were predominantly male (92.6%), aged 41 ± 2.5 years (mean $\pm$ s.e.m.) and mainly tetraplegic (Table 1). Of the 10 patients with paraplegia, 7 had SCI between T3 and T5, most were complete and all had acute injuries; therefore, paraplegics were only considered as a single group, with insufficient numbers for subgroup

Table 1 Characteristics of study group

	Tetraplegia ($n = 44$)	Paraplegia ($n = 10$)
Level of SCI	C1–C7	T3–T5
Complete/incomplete	22/18	9/1
Acute/chronic	29/15	10/0

Abbreviation: SCI, spinal cord injury.

analysis. Records of nocturnal urine production were available for 17 patients with tetraplegia.

Referral to the Blood Pressure Service was for clinically significant blood pressure management issues with referring clinicians specifically requesting assistance with orthostatic intolerance ($n = 37$), autonomic dysreflexia ($n = 6$), nocturnal polyuria ($n = 4$), elevated blood pressure ($n = 1$) and peripheral oedema ($n = 1$). Co-morbidities include sleep apnoea ($n = 6$), hypertension ($n = 3$), diabetes mellitus ($n = 3$), atrial fibrillation ($n = 2$) and congestive cardiac failure ($n = 1$). Medications taken by patients during ambulatory blood pressure monitoring included anti-hypertensives ($n = 4$), pseudoephedrine 30–60 mg daily ($n = 4$) and sodium chloride and/or fludrocortisone 0.1–0.2 mg daily ($n = 3$).

All patients

Of the 54 patients studied, only 4 (7%) had the normal dipping pattern of blood pressure. Thirty (56%) patients had higher pressures at night than during the day (Table 2). Reversed dipping patterns tended to be more common amongst the tetraplegics than paraplegics. Nocturnal hypertension was present in 17 (31%) patients (2 of whom were paraplegic), whereas daytime hypertension and elevated 24-h blood pressure were only present in 2 and 3 tetraplegic patients, respectively. The pulse rate was lower in the tetraplegic compared with the paraplegic patients and both groups had a nocturnal fall in pulse rate.

Mean total daily urine volume in the 17 tetraplegics was 2570 ± 164 ml. An average of $50 \pm 3.3\%$ volume of urine was passed overnight. Urine flow rate was higher during the night than day (121 ± 9.5 ml h^{-1} vs 89 ± 8.2 ml h^{-1} , $P = 0.025$). The proportion of

Table 2 Blood pressure and pulse rate for all patients, tetraplegics and paraplegics

	All patients ($n = 54$)	Tetraplegics ($n = 44$)	Paraplegics ($n = 10$)	P-value
Age (years)	40.8 ± 2.5	42.8 ± 2.9	32.4 ± 4.2	0.113
Systolic BP (mm Hg)				
24 h	111.1 ± 1.4	110.5 ± 1.6	113.5 ± 2.1	0.392
Day	110.5 ± 1.5	109.5 ± 1.7	114.9 ± 2.1	0.162
Night	112.0 ± 1.6	112.2 ± 1.8	110.7 ± 2.8	0.717
Night:day (%)	101.7 ± 1.3	102.9 ± 1.5	96.5 ± 2.2	0.055
Reversed dippers	30 (56%)	27 (61%)	3 (30%)	0.072
Diastolic BP (mm Hg)				
24 h	65.0 ± 1.2	65.1 ± 1.3	64.4 ± 2.6	0.826
Day	65.9 ± 1.3	65.7 ± 1.4	66.8 ± 2.6	0.736
Night	63.3 ± 1.2	64.0 ± 1.4	59.8 ± 2.9	0.188
Hypertension				
24 h	3 (5.6%)	3 (7%)	0	0.396
Day	2 (3.7%)	2 (5%)	0	0.492
Night	17 (31.5%)	15 (34%)	2 (20%)	0.387
Pulse rate (bpm)				
24 h	72.3 ± 1.9	70.1 ± 1.9	82.1 ± 4.4	0.011
Day	74.4 ± 1.9	71.8 ± 1.9	86.0 ± 4.3	0.002
Night	68.5 ± 2.2	67.0 ± 2.3	74.4 ± 6.2	0.205
Day-Night	5.9 ± 1.4	4.6 ± 1.3	11.6 ± 4.9	0.053

Abbreviation: BP, blood pressure. *P*-values are for comparison between tetraplegics and paraplegics. *P*-values <0.05 are indicated in bold.

urine produced at night was inversely correlated with the 24 h systolic pressure ($r^2=0.25$, $P=0.043$) and day systolic pressure ($r^2=0.30$, $P=0.022$) and there was a trend to a direct correlation with the night: day systolic pressures ($r^2=0.19$, $P=0.078$).

Complete vs incomplete tetraplegia

Compared with those with incomplete injuries, tetraplegic patients with complete injuries were younger, had lower day blood pressures and a greater incidence of reversed dipping (Table 3). In incomplete injuries, pressures at night were lower than day values for both diastolic ($P<0.001$) and systolic pressure ($P=0.166$), whereas night systolic pressures were higher than the day measurement for complete injuries ($P=0.003$). Compared with day values, the pulse rate fell in both groups at night ($P<0.05$).

There was a higher total daily urine volume in patients with a complete injury, and their urine flow rate at night was significantly higher than in the day ($P=0.035$).

Table 3 BP and urine measurements for complete and incomplete tetraplegics

	Complete (n = 22)	Incomplete (n = 18)	P-value
Age (years)	37 ± 3.4	51 ± 4.3	0.011
Systolic BP (mm Hg)			
24 h	109.0 ± 2.3	113.0 ± 2.5	0.255
Day	106.5 ± 2.3	114.3 ± 2.9	0.037
Night	113.4 ± 2.9	110.7 ± 2.6	0.449
Night:Day (%)	106.7 ± 1.9	97.2 ± 1.9	0.002
Reversed dippers	16 (73%)	7 (39%)	0.031
Diastolic BP (mm Hg)			
24 h	63.7 ± 1.7	68.3 ± 2.1	0.101
Day	63.1 ± 1.6	70.5 ± 2.3	0.011
Night	64.9 ± 2.1	64.1 ± 2.0	0.805
Hypertension			
24 h	1 (5%)	2 (11%)	0.433
Day	0	2 (11%)	0.109
Night	10 (45%)	4 (22%)	0.125
Pulse rate			
24 h	70.9 ± 2.7	69.7 ± 2.9	0.759
Day	72.7 ± 2.6	71.1 ± 3.0	0.688
Night	67.6 ± 3.3	66.9 ± 3.1	0.880
Urine Measures	Complete (n = 10)	Incomplete (n = 7)	P-value
Volumes (ml)			
Total	2867 ± 193	2140 ± 206	0.023
Day	1439 ± 198	1123 ± 160	0.265
Night	1428 ± 105	1017 ± 197	0.065
Nocturnal (%)	52.0 ± 4.0	46.1 ± 5.7	0.399
Flow rates (ml h ⁻¹)			
Day	95 ± 12	80 ± 11	0.378
Night	132 ± 7.0	105 ± 20	0.172
Night:Day	1.6 ± 0.2	1.5 ± 0.4	0.789

Abbreviation: BP, blood pressure. P-values <0.05 are indicated in bold.

Acute vs chronic tetraplegics

Patients with acute injuries were younger than those with chronic injuries (Table 4). The average time between monitoring and SCI was 3.1 months (1.1–6.0 months) in the acute group. Patients in the chronic group had had SCI for an average of 32.5 years (4–48 years).

Compared with patients with chronic injuries, patients with acute injury had lower blood pressure, particularly the diastolic pressure, higher night:day systolic pressure and a greater proportion of reversed dippers. Pulse rates for both groups were similar, including the presence of nocturnal fall.

Compared with the chronic tetraplegics, acute tetraplegics had lower day urine production and passed a greater proportion of their urine at night, and had a significantly higher night urine flow rate than that in the day ($P=0.002$).

Table 5 summarises the nocturnal blood pressure dipping ratios and nocturnal urine volumes for subgroups of tetraplegics.

Table 4 BP and urine measurements for acute and chronic tetraplegics

	Acute (n = 29)	Chronic (n = 15)	P-value
Age (years)	38 ± 3.8	52 ± 3.2	0.029
Systolic BP (mm Hg)			
24 h	109.4 ± 1.8	112.7 ± 3.2	0.326
Day	107.4 ± 1.6	113.7 ± 3.8	0.084
Night	113.1 ± 2.4	110.6 ± 2.9	0.526
Night:Day (%)	105.4 ± 1.6	98.1 ± 2.7	0.017
Reversed dippers	21 (72%)	6 (40%)	0.036
Diastolic BP (mm Hg)			
24 h	62.8 ± 1.3	69.6 ± 2.6	0.011
Day	63.0 ± 1.3	70.9 ± 3.1	0.008
Night	62.4 ± 1.6	67.1 ± 2.4	0.104
Hypertension			
24 h	1 (3%)	2 (13%)	0.218
Day	0	2 (13%)	0.044
Night	9 (31%)	6 (40%)	0.552
Pulse rate			
24 h	71.9 ± 2.2	66.6 ± 3.6	0.191
Day	73.7 ± 2.1	67.9 ± 3.6	0.141
Night	68.8 ± 2.9	63.9 ± 3.8	0.319
Urine Measures	Acute (n = 12)	Chronic (n = 5)	P-value
Volumes (ml)			
Total	2448 ± 172	2854 ± 374	0.272
Day	1133 ± 123	1731 ± 297	0.040
Night	1315 ± 126	1123 ± 235	0.447
Nocturnal (%)	54.1 ± 3.4	38.8 ± 5.6	0.029
Flow rates (ml h ⁻¹)			
Day	77 ± 6.6	117 ± 19	0.019
Night	127 ± 12	106 ± 16	0.319
Night:Day	1.8 ± 0.2	1.0 ± 0.2	0.051

Abbreviation: BP, blood pressure. P-values <0.05 are indicated in bold.

Table 5 Nocturnal dipping ratio and urine volumes for subgroups of tetraplegics

	Complete	Incomplete
<i>Night:Day SBP (%)</i>		
Acute	108.5 ± 1.8 (n = 16)	98.9 ± 2.5 (n = 9)
Chronic	102.1 ± 5.1 (n = 6)	95.5 ± 3.0 (n = 9)
<i>Nocturnal urine volume (%)</i>		
Acute	53.1 ± 4.3 (n = 8)	56.0 ± 6.0 (n = 4)
Chronic	47.5 ± 13.5 (n = 2)	33.0 ± 0.6 (n = 3)

Abbreviation: SBP, systolic blood pressure.

DISCUSSION

In our population of SCI patients who were referred for blood pressure management, ambulatory monitoring revealed a substantial prevalence of reversed dipping or nocturnal hypertension, despite a relatively low prevalence of 24-h or daytime hypertension, and these abnormalities tended to be more frequent amongst patients with acute, complete or tetraplegic injuries. In addition to the higher incidence of reversed dipping of blood pressure, we also found higher nocturnal urine production in patients with acute or complete SCI when compared with patients with chronic or incomplete injuries, respectively (Table 5).

The mechanisms explaining these findings are uncertain. One explanation for the reversed diurnal variation of blood pressure is that interruption of sympathetic nervous system tracts rendered our patients unable to maintain blood pressure when upright during the day. This is in keeping with the observation that patients with incomplete SCI, who presumably have more intact sympathetic nervous system tracts, tended to have a lower incidence of non-dipping. It is also consistent with the high incidence of non-dipping seen in autonomic neuropathy, which is another condition associated with impaired orthostatic blood pressure control.^{12,13} However, in both SCI and autonomic failure, not all patients have non-dipping, implying that factors other than damage to the autonomic nervous system cause changes in diurnal blood pressure profiles. For example, the lower incidence of abnormal blood pressure or urine production in our patients with chronic injury suggests that at a time that is more than 6 months after SCI, adaptive mechanisms unrelated to spinal cord function might develop to modulate blood pressure control.

Similarly, the mechanism explaining nocturnal polyuria is unclear. In general, the patient groups in our study that had a higher incidence of non-dipping also had a relatively higher rate of nocturnal urine flow, raising the possibility that the diuresis may have been directly related to renal perfusion pressures. However, at least in patients with autonomic failure, natriuresis can be independent of elevated nocturnal pressures.⁵

The importance of these findings relates to a potential role for nocturnal blood pressure elevation in orthostatic intolerance. It has been proposed that attenuating the excessive natriuresis of autonomic failure by selectively reducing nocturnal blood pressure may provide relief from orthostatic symptoms. In autonomic neuropathy, sleeping with a head up tilt was suggested to attenuate orthostatic hypotension by reducing renal perfusion pressure and thereby reducing diuresis.¹⁴ Similarly, short-acting nocturnal anti-hypertensive agents have reduced nocturnal blood pressure and nocturnal natriuresis in patients with primary autonomic failure.^{15–17} However, head up tilt is problematic in the SCI population, because their sleeping position is determined by other considerations, such as prevention of pressure

injury. Short-acting nocturnal anti-hypertensives are a potential pharmacological alternative to head up tilt, but their role in SCI has not been examined.

Our results differ from previous studies that found a loss of diurnal variation in blood pressure only in patients with chronic and complete tetraplegics, but not in incomplete tetraplegics or complete paraplegics.^{7–9} To some extent, this difference may be explained by those studies excluding patients with conditions such as known cardiovascular disorders, autonomic dysreflexia and orthostatic dysregulation, thus potentially excluding a population of patients in whom disruption of blood pressure control may be greatest.

The other interesting aspect of our study is our measurement of the prevalence of nocturnal hypertension in patients with SCI, a parameter that has not previously been reported in similar studies. Reversed dipping and nocturnal hypertension may have implications for risk of cardiovascular disease, which may be elevated in patients with SCI.¹⁸ Studies in the general population have found that night blood pressure and reversed diurnal variation are important factors in predicting cardiovascular risk^{19–21} and it may be that the results of ambulatory monitoring can be used to detect patients who would benefit from treatments aimed at reducing cardiovascular risk.

In addition to orthostatic intolerance, autonomic dysreflexia is the other major blood pressure problem seen in SCI. It has been proposed that the loss of diurnal blood pressure variation may be a feature of tetraplegic patients with dysreflexia.²² However, autonomic dysreflexia was a relatively uncommon cause of referral in our study group (6 of 44 tetraplegic patients), yet almost all patients exhibited an abnormal diurnal blood pressure pattern. Further studies should be directed towards examining whether abnormalities of diurnal blood pressure variation are more common or contribute to autonomic dysreflexia in SCI.

Although our study was retrospective and limited to a relatively small number of patients, its strength was that it only included patients who had a clinical reason for measurement of ambulatory blood pressure. The high incidence of abnormalities in this group suggests that the role of measuring ambulatory monitoring should be further explored in these patients.

CONCLUSION

We conclude that ambulatory blood pressure monitoring is a useful diagnostic method for nocturnal hypertension and reversed dipping in patients with SCI who are referred for blood pressure management. The reversal of diurnal blood pressure variation, elevation of nocturnal blood pressure and increased night urinary flow rates support the nocturnal blood pressure as a potential therapeutic target.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Transport Accident Commission (DP174). MYG is supported by a scholarship and stipend through the University of Melbourne and Spinal Research Institute.

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Chapter 4. Natural History of diurnal blood pressure and urine production in SCI

As described in the previous chapter, Study 1 demonstrated a high prevalence of abnormalities in diurnal BP and urine production, and nocturnal hypertension in patients with SCI who had clinical manifestations of altered BP regulation, present in both tetraplegia and paraplegia. This compared with previous studies that had mainly documented BP abnormalities in patients with chronic complete tetraplegia.

This led to further questions which I examined in the thesis. When do these abnormalities occur after SCI and how do they evolve over time? How prevalent are they in the population with SCI?

Study 2 examines the diurnal BP and urine production patterns, along with postural BP changes, in consecutive patients admitted for acute traumatic SCI to a state-wide SCI service. These patients were compared with able-bodied controls. A group of immobilised controls are also included to determine the contribution of immobilisation as opposed to the presence of SCI. Participants had measurements taken at baseline - as soon as practicable after the injury, and a year later. Those with tetraplegia had five measurements taken over a year.

A manuscript describing the results of this study was published in *Spinal Cord*. The following is a reprint of the manuscript as published.

Goh MY, Millard MS, Wong EC, Brown DJ, Frauman AG, O'Callaghan CJ. Diurnal blood pressure and urine production in acute spinal cord injury compared with controls. *Spinal Cord* 2017; **55**(1): 39-46. doi:10.1038/sc.2016.100

ORIGINAL ARTICLE

Diurnal blood pressure and urine production in acute spinal cord injury compared with controls

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Study design: This is a prospective observational study.

Objectives: The objective of this study was to determine time-dependent changes in diurnal blood pressure (BP) and urine production in acute spinal cord injury (SCI).

Setting: This study was conducted in a specialist, state-based spinal cord service in Victoria, Australia.

Methods: Consenting patients admitted consecutively with acute SCI were compared with patients confined to bed rest while awaiting surgery and with mobilising able-bodied controls. Participants underwent ambulatory BP monitoring (ABPM), measurement of diurnal urine production and rated orthostatic symptoms over 1 year. Participants with night:day systolic BP (SBP) <90% were classified as dippers, 90–100% as non-dippers and >100% as reverse dippers.

Results: Participants comprised tetraplegics ($n=47$, 40.0 ± 17.3 years), paraplegics ($n=35$, 34.4 ± 13.9 years), immobilised ($n=18$, 30.9 ± 11.3 years) and mobilising ($n=44$, 33.1 ± 13.5 years) controls. At baseline, 24-h BP was significantly lower in tetraplegics ($111.8 \pm 1.9/62.1 \pm 1.1$ mm Hg) but not in paraplegics ($116.7 \pm 1.4/66.0 \pm 1.1$ mm Hg), compared with controls ($117.1 \pm 1.3/69.1 \pm 1.1$ mm Hg), adjusting for gender. This difference was not observed at 1 year. The average night:day SBP in mobilising controls was $86.1 \pm 0.7\%$, differing from paraplegics ($94.0 \pm 1.5\%$, $P<0.001$) and tetraplegics ($101.5 \pm 1.5\%$, $P<0.001$). Urine production in tetraplegics and paraplegics did not fall at night compared with the day. Abnormal diurnal BP and orthostatic symptoms in tetraplegics persisted throughout the study. Nocturnal hypertension was observed in 27% ($n=9$) of tetraplegics, of whom only 2 had day hypertension. All mobilising controls with nocturnal hypertension ($n=6$, 14%) had day hypertension.

Conclusion: People with SCI have a high prevalence of isolated nocturnal hypertension, reverse dipping, orthostatic intolerance and nocturnal polyuria. Cardiovascular risk management and assessment of orthostatic symptoms should include ABPM.

Spinal Cord (2017) 55, 39–46 doi:10.1038/sc.2016.100; published online 28 June 2016

INTRODUCTION

Disruption of the neural pathways that regulate cardiovascular function markedly impairs blood pressure (BP) control. The clinical consequences of autonomic damage in spinal cord injury (SCI) are well recognised and include severe hypotension and persistent bradycardia, large daily fluctuations in BP, autonomic dysreflexia and potentially premature arterial disease and increased cardiovascular risk.^{1–4}

When autonomic disease affects the able-bodied population, it produces similarly severe clinical impairment. In this cohort, measurement of BP during ambulation has been proven to be invaluable in the management of symptoms, control of cardiovascular risk and identification of potential mechanisms, which may contribute to orthostatic intolerance. In particular, ambulatory BP monitoring (ABPM) has been instrumental in identifying the disruptions of diurnal variation of BP and the role that elevated nocturnal pressures may have in nocturnal diuresis and natriuresis, which have been proposed to contribute to postural hypotension.^{5–7}

The role of ambulatory monitoring in SCI is less well defined. Most investigations have been restricted to relatively healthy volunteers and usually excluded participants with cardiovascular disease and

significant BP symptoms.^{8–11} In general, these studies found that SCI was characterised by loss of the usual diurnal variation in BP. Only recently have investigations included symptomatic patients,^{12,13} including our study, which found that patients with orthostatic symptoms had similar or even more extreme abnormalities than asymptomatic patients—particularly in the period soon after injury.¹⁴

It is unknown whether abnormalities of diurnal BP and urine production, which are observed soon after SCI, persist over time or whether they contribute to symptoms of orthostatic hypotension. In this study, we examined the 24-h ambulatory BP patterns of patients admitted consecutively to our SCI service. We compared results in SCI with control participants who were able-bodied and independently mobilising and with a group of similarly able-bodied participants who were immobilised while awaiting surgical procedures and followed them up over a year.

METHODS

Screening was performed on patients who were consecutively admitted to the SCI unit between February 2010 and December 2013 for acute, traumatic SCI, and eligible consenting participants were enrolled. Immobilised control participants were otherwise healthy patients confined to bed rest while awaiting orthopaedic surgery. Healthy, mobilising able-bodied control participants

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Received 16 November 2015; revised 22 May 2016; accepted 28 May 2016; published online 28 June 2016

without known cardiovascular conditions were recruited by advertisement. Comparisons were made between tetraplegic, paraplegic (including high and low paraplegics) and immobilised and mobilising able-bodied participants at each time point and over time within each group.

Participants were interviewed and medical records were reviewed to characterise demographic details (age, gender) and details of SCI (date, mechanism of injury, level and completeness of injury), medical conditions and concurrent medications. Level and completeness of injury were extracted from the medical history, as assessed by physical examination and recorded according to the International Standards for Neurological Classification of Spinal Cord Injury during the admission.¹⁵ Imaging was not used for classification. Participants were designated as tetraplegics if their lesion was in the cervical region, and as paraplegics if their lesion was in the thoracic, lumbar or sacral region; paraplegics were further classified as high paraplegics if their lesion was between T1 and T6 or as low paraplegics if their lesion was below T6.^{1,11,16,17}

Measurements included ABPM, quantification of diurnal urine output by completion of a diary and quantification of orthostatic symptoms on a rating scale. Study assessments were undertaken for SCI groups after initial mobilisation. Participants also had another assessment performed 1 year after mobilisation, and tetraplegic participants had additional assessments at 2, 4 and 6 months after mobilisation. Assessments were delayed if an active acute medical condition precluded performance of investigations. Control groups underwent assessments at baseline and 1 year. During the course of the study, some participants underwent sleep studies either as part of clinical assessment or through participation in a concurrent study examining sleep apnoea in SCI.

Ambulatory BP monitoring

Ambulatory BPs were obtained using the Card(X)plore monitor (Meditech, Budapest, Hungary), with an appropriately sized cuff, worn by each participant for about 24 h. Measurements were taken half-hourly during the day (0600–2200 hours) and hourly at night (2200–0600 hours). Results were analysed according to mean 24-h, day (1000–2000 hours) and night (0000–0600 hours) values for systolic BP (SBP), diastolic BP (DBP) and pulse rate. Day and night were defined by fixed clock time intervals to eliminate transition periods in the morning and evening when there is considerable variation in BP¹⁸ and also in postural change among groups. This method has been found to correspond well with actual awake and asleep periods.¹⁹ This is especially applicable to the SCI population who may dress in bed after getting upright for the morning routine and may return to bed for a duration before going to sleep for the night; hence, there is a period of time over which postural change occurs.

The extent of nocturnal dip in BP was calculated as the ratio of night-to-day SBP, expressed as a percentage. Participants with a night:day SBP of <90% (the normal pattern) were classified as 'dippers', 90–100% as 'non-dippers' and >100% as 'reverse dippers'.²⁰ Hypertension was defined as a 24-h BP >130/80 mm Hg, day hypertension as BP >135/85 mm Hg and nocturnal hypertension as BP >120/70 mm Hg, according to clinical guidelines.²¹

Postural BP measurement

Participants or their carers were requested to obtain BP measurements on the ambulatory BP monitor, by pressing a button. They were instructed to obtain two supine and three upright BPs, a minute apart, on first arising from bed the morning after the monitor was applied. Participants were considered upright when either standing up or sitting up in a chair for those with SCI who were unable to stand. Orthostatic hypotension was defined as a fall in BP of 20/10 mm Hg within 3 min of assuming the upright position.²²

Urine measurements

Urine output was recorded over 3 consecutive days, generally within a week of BP monitoring. Participants were instructed to record the time that they void or empty their catheter bag on waking on the first day (Day 1) and then to record urine volumes and times at each void or each time the catheter bag was emptied, until and including the measurement on first waking on Day 4. A measuring jug was provided for measurement of voided urine or urine emptied from the catheter bag. For the purposes of this study, the terms urine output and urine production are used interchangeably and refer to the

volume of urine measured from voiding or emptying of the catheter bag. The day and night rates of urine output were calculated by dividing the volume of urine by the time between measurements and expressed as ml per minute. Measurements reported were average values for the 3 days and nights. For each group, comparisons were made between the rate of urine output during the day and the night to determine whether the rate of urine output at night was significantly different from the rate during the day.

Symptom assessment

Participants were asked to rate their symptoms of orthostatic intolerance for the past week on a scale of 0 for none at all to 10 for the worst possible. Symptoms of orthostatic intolerance were explained as symptoms (lightheadedness, dizziness) pertaining to low BP often arising from postural change or remaining upright for some time and relieved with tilting backwards, lifting up legs or lying down.

Statistical analysis

Analysis was performed using the Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and R software (<http://www.r-project.org>). For continuous variables such as BP and pulse rate, linear mixed models were used to examine the interaction between group and time point, adjusting for gender, with subjects as random effects. The interaction between group and time point was included in the model, as we aimed to examine the differences between groups at baseline and at 1 year, as well as the change over time for each group, with the hypothesis that the controls would not differ over time while the other groups may. We report the overall test of the interaction from this model, and pairwise comparisons for group at each time point were made using the Tukey's Honestly Significant Difference test. Paired *t*-tests were used to compare the day and night continuous variables (BP, pulse rate and urine output rates) within each group. The chi-square test was used for categorical variables (such as gender and dipping status). The Kruskal–Wallis and Wilcoxon signed-rank tests and Spearman's correlation test were used to compare non-parametric variables. Significance was set at $P < 0.05$. Range intervals represent s.e.m.

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The protocol for this study was approved by the Human Research Ethics Committee of Austin Health.

RESULTS

Study group characteristics

Of the 116 tetraplegic and 73 paraplegic patients with traumatic SCI who were screened, 49 and 23, respectively, were ineligible for reasons including age, medical instability or death. Participation was declined by a further 19 and 15 tetraplegic and paraplegic patients, respectively, resulting in recruitment of 48 tetraplegics and 35 paraplegics (72% and 70% of eligible participants, respectively). One tetraplegic participant was later withdrawn because of lack of data, leaving 47 tetraplegics. Of these 47 tetraplegics, 12 had not enrolled at the initial visit, predominantly because other clinical problems precluded participation or they were initially reluctant to engage in the study. Analyses performed including and excluding participants who did not enrol in the first visit were not different. There were significantly fewer male participants in the mobilising control group (Table 1).

Patients who declined to participate in the study did not differ significantly from the study group in age, gender or neurological category of SCI.

Medications

At baseline, one tetraplegic patient was taking an ACE-inhibitor (angiotensin-converting enzyme inhibitor) and four paraplegic patients were taking antihypertensive agents (beta blockers ($n=2$),

Table 1 Characteristics of the study group

	<i>Tetraplegics</i> n = 47	<i>Paraplegics</i> ^a n = 35	<i>Immobilised</i> n = 18	<i>Mobilising controls</i> n = 44
Age, years	40.0 ± 17.3	35.4 ± 13.9	30.9 ± 11.3	33.1 ± 13.5
Median	37.0	33.0	26.5	28.5
Range	16–70	16–63	19–50	16–65
Male	42 (89%)	28 (80%)	14 (78%)	25 (57%)
Level of SCI	C1–C7	T2–S2		
Complete/incomplete	20/27	25/10		
Neurological classification	C1–4, ABC: 20 C5–8, ABC: 20 D: 7	T1–6, ABC: 13 T7–S2, ABC: 20 D: 2		
SCI to mobilisation (days)	16.6 ± 12.3	13.5 ± 10.1		
Median	13	10		
Range	2–68	4–40		
Mobilisation to ABPM (days)	13.8 ± 5.9	12.6 ± 6.4		
Median	13	12		
Range	2–27	1–25		
SCI to ABPM (days)	28.3 ± 15.0	27.1 ± 13.4		
Median	26	24.5		
Range	6–92	6–58		
<i>Co-morbidities</i>				
Smoking (current)	9 (19%)	6 (17%)	4 (22%)	1 (2%)
Hypertension at baseline	6	3 (+1 suspected WCH)	0	0
Diabetes mellitus	3 (type 2)	1 (type 1)	0	0
Dyslipidaemia	2	0	0	2
OSA (preadmission)	2	2	0	0
Other		1 'small vessel atheromatous disease' on angiogram, 1 SVT/AF, 1 valvular disease in childhood		1 AF, 1 MVP repair

Abbreviations: ABPM, ambulatory blood pressure monitoring; ABC, American Spinal Injury Association Impairment Scale (AIS) A, B or C; AF, atrial fibrillation; D, AIS D; MVP, mitral valve prolapse; OSA, obstructive sleep apnoea; SCI, spinal cord injury; SVT, supraventricular tachycardia; WCH, white coat hypertension.

Age and time periods shown as mean ± s.d.

^aHigh and low paraplegics.

ACE-inhibitors ($n=1$) and calcium channel blockers ($n=1$) before admission. These patients all continued antihypertensive therapy for the duration of the study.

Antihypertensive treatments at the 1-year assessment included an ACE-inhibitor for one mobilising control and one tetraplegic patient and a calcium channel blocker and ACE-inhibitor for one paraplegic patient. Other cardiovascular medications included clonidine taken as an analgesic by one paraplegic patient. One tetraplegic patient was taking fludrocortisone.

Immobilised controls

Immobilised controls were admitted under the orthopaedic unit for lower limb fractures ($n=10$), vertebral fractures without spinal cord involvement ($n=6$) or lower limb soft tissue injury ($n=2$). They were confined to bed rest for 1–11 days (mean 2.6 days, median 2 days) before ABPM.

Population retention

Loss to follow-up over time resulted in about half the participants attending the final assessment in each group. Of participants who were lost to follow-up, 29–56% in each group were not contactable, about 33% in each group declined assessment and about 20%

(0 for immobilised controls) were in a geographically different location, making follow-up not feasible. Baseline BP, urine output rates and symptom scores were not significantly different between those who did and did not attend the final assessment.

BP: baseline

Tests of interaction for each parameter are reported in Table 2. Where the interaction is small, we expect the estimated differences between groups at each time point to be similar. Where the interaction is larger, we expect the estimated differences to be more variable. The pairwise comparisons at each time point help characterise these differences, in reference to our hypothesis.

Consistent with their age and paucity of other co-morbidities, average BPs across all groups were substantially lower than diagnostic levels for hypertension²¹ (Table 3). Nevertheless, among the mobilising control group, average day and night BPs exceeded thresholds for hypertension in 19% and 14% of participants, respectively. In the control group, average night:day SBP was 86.1% and none were reverse dippers. In control participants, 24-h SBP was significantly higher in male than in female participants, but no other BP or pulse rate parameter was affected by gender

($119.3 \pm 1.7/70.2 \pm 1.5$ mm Hg vs $113.9 \pm 2.0/67.6 \pm 1.6$ mm Hg, $P=0.044$ and $P=0.256$ for SBP and DBP, respectively).

Compared with the controls, immobilised participants had significantly higher average BPs (Table 3), with average day and night BPs exceeding the limit for hypertension in 33% and 53% of participants. The night:day SBP did not reach statistical significance when compared with that of control participants ($P=0.087$).

Table 2 Tests of interaction from linear mixed models

	$F_{3,51}$	P -value
Systolic BP		
24 h	0.533	0.662
Day	0.733	0.537
Night	0.673	0.572
Night:day (%)	1.530	0.218
Diastolic BP		
24 h	1.524	0.220
Day	1.787	0.161
Night	2.231	0.096
Pulse rate		
24 h	3.730	0.017
Day	2.433	0.076
Night	1.973	0.130

Abbreviation: BP, blood pressure.

BPs in paraplegic participants did not differ from controls, but they were significantly lower than that of the immobilised participants (Table 3). Average day and night pressures were higher than limits for hypertension in 8% and 19% of participants. The night:day SBP (94%) was significantly different from that of the controls ($P<0.001$), and 6 (23%) participants were reverse dippers.

Tetraplegics had significantly lower day BP than all other groups, whereas night pressures were not significantly different from that of mobilising controls or paraplegics (Table 3). Mean 24-h BPs were significantly lower than that of mobilising controls after adjusting for gender but not different from that of paraplegics. Average BPs exceeded limits for hypertension in 8% of participants during the day but in 27% of participants at night. The night:day SBP (101.5%) was significantly higher than the night:day SBP of each of the other groups. Reverse dipping was found in 18 (55%) tetraplegics.

Subgroups

Although the night:day SBP in all paraplegic participants was significantly different from that of tetraplegics, when analysed according to level of paraplegia, high paraplegia ($n=9$, $98.3 \pm 2.5\%$) was not significantly different from tetraplegia ($n=33$, $101.5 \pm 1.5\%$) ($P=0.753$), whereas low paraplegia ($n=17$, $91.8 \pm 1.7\%$) differed significantly from tetraplegia ($P<0.001$). Both high and low paraplegia were significantly different from controls ($n=43$, $86.1 \pm 0.7\%$) ($P<0.001$ and $P=0.033$ for high and low paraplegia, respectively, compared with controls). Differences in the day and night systolic and diastolic BPs for each subgroup are shown in Figure 1.

The night:day SBP for complete tetraplegics ($n=11$, $103.3 \pm 3.0\%$) was not significantly different from that of incomplete tetraplegics

Table 3 Diurnal blood pressure and pulse rate at baseline

	<i>Tetraplegics</i> $n = 33$	<i>Paraplegics</i> ^a $n = 26$	<i>Immobilised</i> $n = 15$	<i>Mobilising controls</i> $n = 43$
Systolic BP (mm Hg)				
24 h	$111.8 \pm 1.9^{*,\#\#}$	$116.7 \pm 1.4^{\#}$	$126.6 \pm 3.2^*$	117.1 ± 1.3
Day	$110.9 \pm 2.2^{*,\#\#,f}$	$119.6 \pm 1.7^{\#}$	$131.7 \pm 3.5^*$	123.0 ± 1.5
Night	$112.0 \pm 2.0^{\#}$	$112.2 \pm 1.6^{\#}$	$119.5 \pm 3.0^{**}$	105.7 ± 1.4
Night:day (%)	$101.5 \pm 1.5^{*,\#\#,ff}$	$94.0 \pm 1.5^{**}$	91.1 ± 1.6	86.1 ± 0.7
Reverse dippers [^]	18 (55%)	6 (23%)	1 (7%)	0 (0%)
Diastolic BP (mm Hg)				
24 h	$62.1 \pm 1.1^{*,\#\#}$	$66.0 \pm 1.1^{\#}$	72.8 ± 1.8	69.1 ± 1.1
Day	$63.1 \pm 1.2^{*,\#\#,f}$	$70.0 \pm 1.5^*$	75.0 ± 2.2	74.5 ± 1.2
Night	$60.9 \pm 1.2^{\#}$	$61.4 \pm 1.2^{\#}$	$69.0 \pm 1.8^{**}$	58.3 ± 1.2
Hypertension				
24 h	2 (6%)	0 (0%)	6 (40%)	7 (16%)
Day	3 (8%)	2 (8%)	5 (33%)	8 (19%)
Night	9 (27%)	5 (19%)	8 (53%)	6 (14%)
Pulse rate (b.p.m.)				
24 h	$68.4 \pm 1.9//$	$83.4 \pm 2.1^{*,\#\#}$	68.9 ± 2.6	70.5 ± 1.3
Day	$71.0 \pm 1.9//$	$88.8 \pm 2.2^{*,\#\#}$	72.8 ± 2.6	75.0 ± 1.4
Night	$64.0 \pm 2.1/$	$74.5 \pm 2.3^{*,\#}$	63.1 ± 3.0	61.7 ± 1.6

Abbreviations: BP, blood pressure; b.p.m., beats per minute.

Values are mean $\pm$ s.e.m.

* $P<0.05$ vs mobilising controls, ** $P<0.001$ vs mobilising controls.

[#] $P<0.05$ vs immobilised controls, ^{##} $P<0.001$ vs immobilised controls.

^f $P<0.05$ vs paraplegics, ^{//} $P<0.001$ vs paraplegics.

[^] $P<0.001$ between four groups.

^aHigh and low paraplegics.

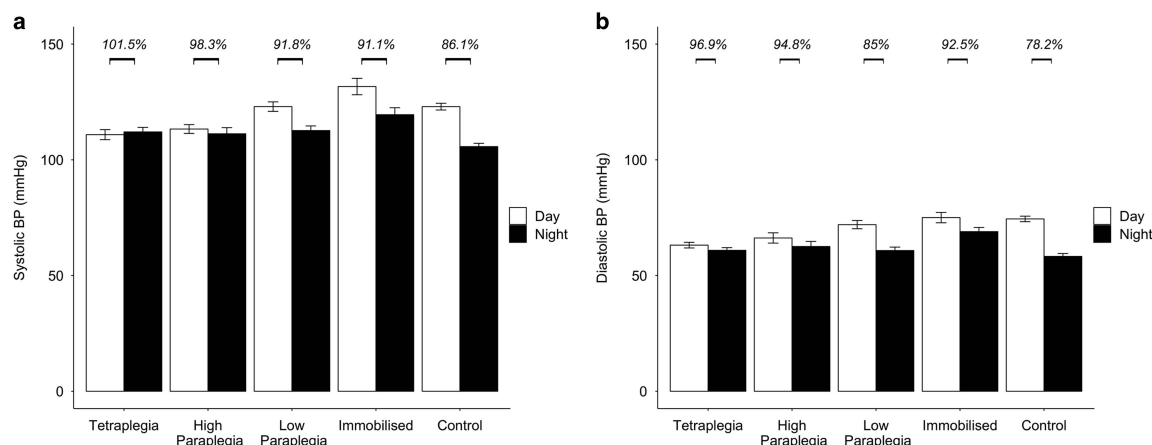


Figure 1 Day and night SBP (a) and DBP (b) for tetraplegics ($n=33$), high paraplegics ($n=9$), low paraplegics ($n=17$), immobilised controls ($n=15$) and mobilising controls ($n=43$) at baseline. Error bars represent s.e.m. Percentages above each set of bars represent night:day SBP and night:day DBP in respective graphs.

Table 4 Postural blood pressure and pulse rate changes

	Tetraplegics	Paraplegics ^a	Immobilised	Mobilising controls
Baseline	$n=3$	$n=12$	$n=0$	$n=31$
Change in SBP (mm Hg)	-26.1 ± 3.56	$-8.2 \pm 2.44^*$		-0.8 ± 1.88
Change in DBP (mm Hg)	-21.1 ± 3.50	$-2.4 \pm 1.60^*$		8.6 ± 1.51
Change in PR (b.p.m.)	12.8 ± 6.17	$16.6 \pm 3.78^*$		26.0 ± 1.88
1 year	$n=12$	$n=5$	$n=5$	$n=23$
Change in SBP (mm Hg)	$-13.4 \pm 4.32^*$	-9.5 ± 7.18	5.5 ± 3.46	-1.9 ± 1.97
Change in DBP (mm Hg)	-0.8 ± 2.20	-3.3 ± 4.12	9.7 ± 2.46	4.3 ± 1.43
Change in PR (b.p.m.)	18.0 ± 4.19	16.7 ± 6.83	22.2 ± 5.56	26.4 ± 2.97

Abbreviations: b.p.m., beats per minute; DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure.

Values are mean $\pm$ s.e.m.

* $P < 0.05$ vs mobilising controls.

^aHigh and low paraplegics.

($n=22$, $100.6 \pm 1.7\%$) ($P=0.904$). Similarly, night:day SBP did not differ significantly between complete paraplegics ($n=19$, $95.7 \pm 1.7\%$) and incomplete paraplegics ($n=7$, $89.5 \pm 2.6\%$) ($P=0.340$).

The night:day SBP was 103.5% in tetraplegics, with a sleep study that was positive for obstructive sleep apnoea ($n=16$) and 104.9% in those whose sleep study was negative for obstructive sleep apnoea ($n=5$).

Postural BPs

Postural BP was not measured at the baseline visit in immobilised controls, because of their need to maintain bed rest, and in many of the tetraplegic participants where it was precluded by clinical circumstances. Compliance with the instruction to measure postural BP was relatively low in the paraplegics and immobilised controls at 1 year.

Compared with controls, the postural fall in SBP was significantly larger in both paraplegic and tetraplegic participants at the baseline and 1-year visits (Table 4). Criteria for orthostatic hypotension were met by 25% of paraplegic participants at the baseline visit (vs 6% in controls, $P=0.12$) and 25% of tetraplegic participants at the 1-year visit (vs 5% of controls $P=0.11$). Analyses were not carried out

on paraplegics and immobilised controls at 1 year because of the small numbers of participants providing data.

Pulse rates: baseline

Paraplegics had significantly higher 24-h, day and night pulse rates as compared with each of the other groups (Table 3). Considering high and low paraplegia separately, 24-h, day and night pulse rates were significantly higher in both high paraplegics (85.4 ± 4.6 b.p.m. over 24 h, 89.1 ± 5.5 b.p.m. in day, 77.3 ± 4.4 b.p.m. at night) and low paraplegics (82.3 ± 2.2 b.p.m. over 24 h, 88.7 ± 2.0 b.p.m. in day, 72.9 ± 2.7 b.p.m. at night) as compared with each of the other groups, with the exception that night pulse rates did not differ significantly between low paraplegics and immobilised controls. The pulse rate was significantly lower at night than in the day within each group.

Urine output rates: baseline

In control participants, the urine output rate at baseline was significantly lower at night than during the day (Figure 2). However, the rate of urine output did not fall at night compared with the day in the other three groups. Similarly, there was also no significant

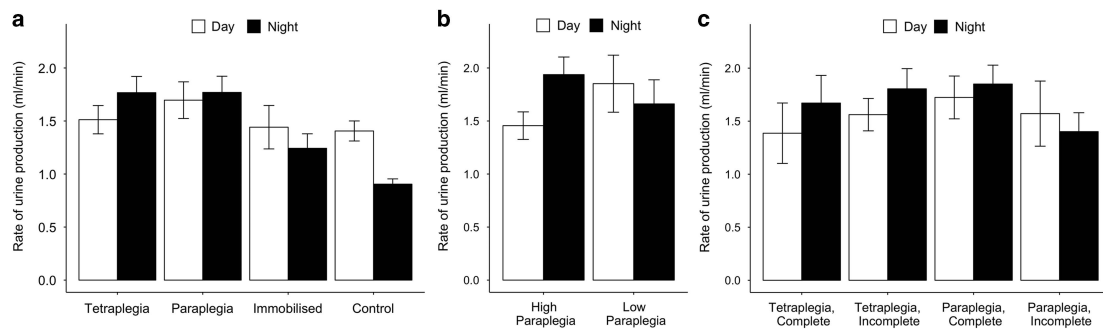


Figure 2 Day and night urine production rates at baseline for (a) tetraplegics ($n=26$), paraplegics ($n=27$), immobilised controls ($n=7$) and mobilising controls ($n=36$), $P<0.001$ for day vs night rate of urine production in the control group; (b) high ($n=10$) and low ($n=17$) paraplegics; (c) complete ($n=7$) and incomplete ($n=18$) tetraplegics and complete ($n=23$) and incomplete ($n=5$) paraplegics. Error bars represent s.e.m.

difference between the day and the night rate of urine output in high or low paraplegia and in complete or incomplete SCI.

Correlation between BP and urine output rates

The night:day SBP correlated with the night:day urine output rates ($r^2=0.30$, $P<0.0001$) when all participants were considered. The correlation was present in the tetraplegics ($r^2=0.26$, $P<0.0001$) but not in other groups.

Changes over time

Nocturnal dipping of BP (expressed as night:day SBP) was compared at baseline and 1 year for each group, using a linear mixed model described above. For the control group, immobilised participants and tetraplegics, the night:day SBP did not differ significantly between visits ($P=0.846$, $P=0.182$ and $P=0.605$, respectively). For the paraplegic group, there was a significant difference between baseline and 1 year ($94 \pm 1.5\%$ vs $88 \pm 2.2\%$, $P=0.0143$). There was no significant difference in nocturnal dip in the five assessments over a year in the tetraplegic group. The loss of diurnal variation in urine output rate persisted in both the tetraplegic ($n=6$) and paraplegic ($n=6$) participants who completed this measurement at the 1-year assessment.

Symptom scores

Symptom scores at baseline were significantly different between the four study groups. Median scores were 3, 2, 2 and 0 for tetraplegics, paraplegics, immobilised controls and mobilising controls, respectively ($\chi^2=18.26$, $df=3$, $P<0.001$). Scores were not significantly different between high and low paraplegia, complete and incomplete tetraplegia or complete and incomplete paraplegia (data not shown).

Symptom scores were completed at baseline and 1 year in 14 tetraplegics, 10 paraplegics, 5 immobilised controls and 26 mobilising controls. Although significant differences were noted across the four groups at baseline ($\chi^2=8.616$, $df=3$, $P=0.0349$), they were not significantly different at 1 year ($\chi^2=1.162$, $df=3$, $P=0.762$). Symptom scores did not differ significantly between baseline and 1 year for tetraplegics ($n=14$) ($P=0.136$).

At baseline, there was a weak monotonic relationship between dizziness and the nocturnal dipping ratio in the study population as a whole ($\rho=0.256$, $P=0.0069$) but not within each group.

DISCUSSION

This study examined the haemodynamic effects of SCI as a function of time after injury. Previous studies of cardiovascular abnormalities in SCI have predominantly been cross-sectional, conducted in chronic SCI, examined limited numbers of individuals (usually about 10 participants per SCI group) or used restricted entry criteria such as excluding people with 'orthostatic dysregulation' or 'cardiovascular disease' or including only complete SCI.^{8–11} The present study recruited large groups of tetraplegic and paraplegic patients from consecutive admissions to a state-based spinal cord service. This is the first prospective study examining ambulatory BPs soon after SCI and with repeated ABPM measurements over the first year of SCI to assess the persistence of any changes over time.

This study confirms the clinical impression that BP in tetraplegic participants is lower than in mobilising control participants in early SCI, after adjusting for gender. In previous studies, 24-h systolic and diastolic BP have not consistently differed between the tetraplegia and control groups, perhaps because participants with low BP symptoms were excluded, because they were underpowered to detect such a difference or because they were conducted on more established SCI.^{10,11} Another contributing factor may have been the inclusion of female participants in the control group, who usually have lower pressures than male participants. Indeed, when our analysis was not adjusted for gender, we were unable to detect an effect of tetraplegia on SBP.

Diurnal BP variation, particularly in tetraplegics, was profoundly and persistently disrupted for the year following acute SCI. The extent of the disruption meant the majority of tetraplegics had night pressures which exceeded day pressures, and one quarter had nocturnal hypertension. A proportion of paraplegics were similarly affected, especially those with lesions above T6. In paraplegics, there appeared to be improvement over time, so that at 1 year the average night:day SBP ratio was within the dipper category, whereas it was in the non-dipper category at baseline. Our findings in the paraplegic group are in keeping with observations in rat models of thoracic SCI, in which an initial loss was followed by return of diurnal BP variation, compared with pre-SCI patterns.^{23,24} In the general population, including normotensive populations, abnormal diurnal variation (night:day SBP $>90\%$) and elevated nocturnal BPs have independently been associated with poorer cardiovascular prognoses.^{25–28} The contribution of abnormal diurnal BP to the high rate of cardiovascular disease seen in the SCI population^{1–4} remains to be determined.

Changes in diurnal BP were paralleled by changes in diurnal urine production, but there was only a weak correlation with orthostatic symptoms. This is consistent with recent report by Hubli *et al.*¹³ that self-reported symptoms of hypotension did not correlate with episodes of hypotension detected by ABPM. In addition, in keeping with previous studies, we found that both high and low paraplegia, but not tetraplegia, caused the pulse rate to be higher than in control participants.^{11,29} This has been observed in both 24-h recordings and clinic measurements, but a clear explanation has not yet been determined.^{11,29,30} Vagal function is expected to be normal in SCI, and cardiac autonomic function is expected to be normal in low paraplegia and partially affected in high paraplegia. However, in SCI, there is some suggestion of a shift towards increased sympathetic activity or altered autonomic balance—as evidenced by increased plasma catecholamine levels in low paraplegics^{11,29,31,32} and findings suggestive of vagal pathology in SCI in both human and animal studies.^{11,33,34}

Our study included a control group consisting of otherwise healthy individuals who were immobilised in hospital while awaiting orthopaedic surgery—conditions unrelated to spinal cord function. Broadly speaking, immobilised participants had BP patterns that were similar to the mobilising control participants. This suggests that abnormalities of diurnal variation of BP and pulse rate observed in SCI were not a consequence of the experiences the SCI participants shared with immobilised control participants such as immobility, hospitalisation and pain.

Sympathetic fibres leave the spinal cord to innervate effector organs between T1 and L2.³⁵ We have made several observations supporting the concept that interruption of sympathetic fibres is more important than immobility as a mechanism contributing to BP abnormalities observed in SCI, including the following: the night:day SBP of the immobilised controls did not differ from mobilising controls; low paraplegia was associated with a lower degree of disruption of diurnal variation compared with tetraplegia; diurnal variation of tetraplegics did not change over time despite the fact that they would have spent more time mobilising as they progressed with rehabilitation; and BP and urine output patterns of tetraplegic patients resembled those seen in other diseases of the autonomic nervous system such as pure autonomic failure, diabetic autonomic neuropathy or disease of the extra-pyramidal system.^{36–39}

Nocturnal polyuria in SCI has been attributed to redistribution of fluid arising from the impaired autonomic mechanisms. The loss of vascular tone and muscle tone in the lower limbs results in venous pooling and oedema during the day in the upright position, whereas reversal of this process at night results in increased BP and reduced antidiuretic hormone levels, leading to diuresis and nocturnal polyuria.^{40,41} Studies in a rat spinal contusion model of SCI have observed polyuria in the range of mild-to-severe impairment in locomotion, which did not improve with increased muscle pump activity by step training, suggesting that other mechanisms contribute to the polyuria.⁴² It has previously been noted in separate studies in humans that there is a loss of diurnal variation in BP in tetraplegics, and a loss of diurnal variation of urine production in both tetraplegia and paraplegia.^{8–11,40} Our study examined these parameters in the same population and observed a weak correlation between the diurnal variation of BP and that of urine production in tetraplegics but not in paraplegics. This observation is in agreement with previous studies, suggesting that the regulation of urine production in SCI is determined by factors in addition to the result of the motor effects of SCI, posture and BP.

Obstructive sleep apnoea is associated with abnormal diurnal BP variation in the able-bodied population and is therefore another

potential cause of abnormal diurnal BP variation in SCI—in whom sleep disordered breathing is an almost ubiquitous finding.^{43,44} However, within the limitation of the small numbers in our study, we were unable to identify an association between abnormalities in diurnal BP and the presence of sleep apnoea in patients with SCI.

Our study included serial observations during a time when participants underwent intensive rehabilitation. Although rehabilitation is associated with a substantial increase in mobility and time spent upright, diurnal BP patterns did not improve in tetraplegic participants. In contrast, the abnormal diurnal variation of paraplegic participants showed improvement at 1 year compared with baseline and was not significantly different from the control group at the 1-year follow-up. This observation might explain why our recent study,¹⁴ which was performed in paraplegics soon after injury, reported a loss of diurnal variation in paraplegic patients, which was different from most other investigators who had performed their studies in participants with more established injuries.^{8,10,11}

Factors such as physical fitness and sleep-disordered breathing are probably different between tetraplegics and paraplegics,^{10,45,46} but our data do not provide insight as to whether either of these factors may have been a contributor.

CONCLUSION

The results of this study produce several clinical implications. They emphasise the need for ABPM in SCI to determine cardiovascular risk. However, at least for paraplegic patients, measurement might need to be repeated in order to determine that abnormalities in diurnal variation are persistent. Symptoms did not correlate well with abnormalities of BP and should therefore not be relied upon to detect patients in whom ambulatory monitoring should be performed. Finally, this study, which has demonstrated abnormalities in diurnal BP and urine output in SCI, raises the possibility that abnormal urine output may be associated with BP abnormalities as has been hypothesised in the able-bodied population with autonomic nervous system disease.³⁹

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Transport Accident Commission (TAC) (DP174). MG is supported by a scholarship and stipend through the University of Melbourne and Spinal Research Institute. We thank Dr Sue Finch and the Statistical Consulting Centre, University of Melbourne, for their assistance in statistical analysis.

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Chapter 5. Diurnal blood pressure and urine production in people with chronic SCI

From Study 1 and Study 2, I observed a high prevalence and extent of abnormalities in diurnal BP and urine production, nocturnal hypertension and orthostatic hypotension, in the SCI population as compared with mobilising and immobilised controls. This was observed in a retrospective analysis of clinically referred patients with SCI, and in a prospectively studied population being admitted for acute SCI.

Diurnal BP abnormalities occurred to a greater extent in people with SCI at higher level, i.e. cervical SCI and thoracic SCI above T6. These abnormalities are present soon after acute SCI, and persist over the first year of SCI in tetraplegia, whereas improvement over the year was observed in people with paraplegia.

The next question addressed in this thesis was, how prevalent are these abnormalities in people with chronic SCI living in the community? How do they compare with the abnormalities seen in the first year after SCI, and with people without SCI?

Study 3 examined the prevalence and extent of abnormalities in diurnal BP and urine production, along with orthostatic hypotension, in people with chronic SCI, i.e. those who have had the SCI a year or longer prior to the study. Comparison was made with healthy, able-bodied volunteers without SCI.

A manuscript describing the results of this study was published in *Spinal Cord*. The following is a reprint of the manuscript as published.

Goh MY, Millard MS, Wong ECK, Berlowitz DJ, Graco M, Schembri RM, Brown DJ, Frauman AG, O'Callaghan CJ. Comparison of diurnal blood pressure and urine production between people with and without chronic spinal cord injury. *Spinal Cord* 2018; **56**(9): 847-855. doi: 10.1038/s41393-018-0081-3



Comparison of diurnal blood pressure and urine production between people with and without chronic spinal cord injury

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Received: 22 September 2017 / Revised: 8 February 2018 / Accepted: 12 February 2018 / Published online: 2 March 2018
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Abstract

Study design Observational study.

Objectives To quantify diurnal blood pressure (BP) patterns and nocturnal hypertension and to measure diurnal urine production in people with chronic spinal cord injury (SCI), compared with controls without SCI.

Setting Chronic SCI population in the community in Victoria, Australia.

Methods Participants were recruited by advertisement, and sustained SCI at least a year prior or were healthy able-bodied volunteers. Participants underwent ambulatory BP monitoring (ABPM), measurement of urine production, and completed questionnaires regarding orthostatic symptoms. Comparisons were made between participants with tetraplegia or paraplegia and able-bodied controls. Participants with night:day systolic BP < 90% were classified as dippers, 90–100% as nondippers, and > 100% as reverse dippers.

Results Groups with tetraplegia ($n = 51$) and paraplegia ($n = 33$) were older (42.1 ± 15 and 41.1 ± 15 vs. 32.4 ± 13 years, mean $\pm$ s.d.) and had a higher prevalence of males (88 and 85% vs. 60%) than controls ($n = 52$). The average BP was $110.8 \pm 1.5/64.4 \pm 1.2$ mmHg, $119.4 \pm 2.1/69.8 \pm 1.5$ mmHg, and $118.1 \pm 1.4/69.8 \pm 1.0$ mmHg in tetraplegia, paraplegia, and controls, respectively. Of participants with tetraplegia, paraplegia and controls, reverse dipping was observed in 45, 13, and 2% ($p < 0.001$), while nocturnal hypertension was observed in 13, 23, and 18%, respectively ($p = 0.48$). A reduction in nocturnal urine flow rate compared with the day was observed in paraplegia and controls, but not tetraplegia.

Conclusions Similar to the effects of acute SCI, chronic SCI, specifically tetraplegia, also causes isolated nocturnal hypertension, reverse dipping, orthostatic intolerance, and nocturnal polyuria. Cardiovascular risk management and assessment of orthostatic symptoms should include ABPM.

Electronic supplementary material The online version of this article (<https://doi.org/10.1038/s41393-018-0081-3>) contains supplementary material, which is available to authorised users.

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Introduction

Blood pressure (BP) control is dramatically impaired by disruption of the neural pathways that regulate cardiovascular function. The clinical consequences of autonomic damage in spinal cord injury (SCI) are well recognised and include severe hypotension and persistent bradycardia, large daily fluctuations in BP, autonomic dysreflexia and potentially premature arterial disease, and increased cardiovascular risk [1–3].

Autonomic disease in the able-bodied population produces similarly severe clinical impairment. In this cohort, measurement of BP during ambulation has proven invaluable in the management of symptoms, control of cardiovascular risk, and identification of potential mechanisms which may contribute to orthostatic intolerance. In particular, ambulatory BP monitoring (ABPM) has been instrumental in identifying

the disruptions of diurnal variation of BP and the role that elevated nocturnal pressures may play in nocturnal diuresis and natriuresis—which have been proposed as contributors to postural hypotension [4, 5].

Using ambulatory monitoring, we recently documented the temporal changes in BP and urine production over the year following SCI [3]. Compared with control participants, SCI was characterised by high rates of nocturnal hypertension, reversal of diurnal variation of BP, and absent diurnal variation in urine production, especially in people with tetraplegia. Whether these effects persist beyond the first 12 months following SCI, and the extent to which people with chronic SCI are affected by them, remains unknown. In this study, we examined the diurnal BP, diurnal urine production, and orthostatic symptoms in people with chronic SCI, and compared them with that of controls.

Methods

Participants were recruited prospectively by advertisement within the hospital and in the community through general and SCI-specific services. Previous patients of the hospital were also invited by letters and telephone calls. Participants with SCI had traumatic tetraplegia or paraplegia with a duration of injury of at least 1 year, regardless of concurrent health conditions. Able-bodied volunteers without known cardiovascular conditions were recruited through advertisements in the hospital and surrounding universities.

Participants underwent an interview, and medical records were reviewed, to characterise demographic details (age, gender) and details of SCI (date, mechanism of injury, level, and completeness of injury [6]), medical conditions, and concurrent therapy. Participants were assigned the tetraplegia group if their lesion was in the cervical region, and the paraplegia group if their lesion was in the thoracic, lumbar, or sacral region. Those with paraplegia were further classified as high paraplegia if the lesion was between T1 and T6 or as low paraplegia if the lesion was below T6 [6].

Ambulatory BP monitoring

Ambulatory BP measurements were obtained using the Card (X)plore monitor (Meditech, Budapest, Hungary), with a cuff of appropriate size, worn by each participant over about 24 h in an outpatient setting. Measurements were taken half-hourly during the day (0600–2200 h) and hourly at night (2200–0600 h). Results were analysed according to mean 24-h, day (1000–2000 h), and night (0000–0600 h) values for systolic BP (SBP), diastolic BP (DBP), and pulse rate. Day and night were defined by narrow fixed clock-time intervals to eliminate morning and evening transition periods which are associated with considerable variation in BP [7] and in

postural change among groups. These correspond well with actual awake and asleep periods [8]. This is especially applicable to the SCI population who may dress in bed after getting upright for the morning routine and may return to bed for a duration before going to sleep for the night, hence there is a period over which postural change occurs.

As previously described, the extent of nocturnal dip in BP was calculated as the ratio of night SBP to day SBP, expressed as a percentage (night:day SBP). Participants with a night:day SBP of <90% (the normal pattern) were classified as “dippers”, 90–100% as “nondippers”, and >100% as “reverse dippers” [9]. Hypertension was defined as average 24-h BP greater than 130/80 mmHg, day hypertension as average day BP above 135/85 mmHg, and nocturnal hypertension as average night BP above 120/70 mmHg [10].

Postural BP measurement

Postural BP was measured upon arising from bed on the morning after the monitor was applied. Participants or their carers took manual measurements from the ambulatory device at 1-min intervals. The participants were required to be recumbent for the first two measurements and then standing (seated if participants were unable to stand) for the next three measurements. Orthostatic hypotension was defined as a fall in SBP of 20 mmHg or DBP of 10 mmHg within 3 min of assuming the upright position [11].

Urine measurements

Urine output was recorded over 3 consecutive days, generally within a week of BP monitoring. Participants were instructed to record the time that they voided or emptied their catheter bag on waking on the first day (Day 1), and then to record urine volume and time at each void or when the catheter bag was emptied, until and including the measurement on first waking on Day 4. A measuring jug was provided for measurement of voided urine or urine emptied from the catheter bag. For the purposes of this study, the terms urine output and urine production are used interchangeably and refer to the volume of urine measured from voiding or emptying of the catheter bag. The day and night rates of urine output were calculated by dividing the volume of urine by the time between measurements and expressed as ml/min. Measurements reported were average values for the 3 days and nights. For each group, comparisons were made between the rate of urine output during the day and the night.

Symptom assessment

Participants were asked to rate their symptoms of orthostatic intolerance over the preceding week on a scale of 0 for none

to 10 for the worst possible. Symptoms of orthostatic intolerance were explained as symptoms (lightheadedness, dizziness) pertaining to low BP often arising from postural change or remaining upright for some time, and relieved with tilting backwards, lifting legs, or lying down.

Study groups

The main aim was to compare tetraplegia with paraplegia and with healthy able-bodied volunteers. Additionally, high paraplegia was compared with low paraplegia, and complete with incomplete tetraplegia and paraplegia. For participants with SCI, urine production and orthostatic symptoms were compared across the three categories of diurnal BP variation—dipping, nondipping, and reverse dipping. This comparison was made for participants with: (a) SCI, (b) complete SCI, and (c) tetraplegia.

Statistical analysis

Analysis was performed using Microsoft Excel (Microsoft, Redmond, WA, USA) and R software (<http://www.r-project.org>). Participants' data was included for analysis if they had complete measurements for at least one of ABPM or urine diary. Factorial ANCOVA was used to compare continuous variables between study groups (such as BP), adjusting for gender and age; Tukey's Honestly Significant Difference tests were used for pairwise comparisons where there was a significant difference between groups. Paired *t*-tests were used to compare the day and night continuous variables (pulse rate and urine output rates) within each group. The chi-square test was used for categorical variables (such as gender and dipping status). The Kruskal–Wallis test was used for ordinal, non-parametric data (symptom rating scale). Significance was set at $p < 0.05$. Range intervals represent standard error of the mean (s.e.m.).

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The protocol for this study was approved by the Human Research Ethics Committee of Austin Health.

Results

Study group characteristics

Participants were predominantly male and middle aged (Table 1). There were significantly more males in the SCI

groups than in the able-bodied group, and participants in the SCI groups were older (Table 1).

Eight participants (three with tetraplegia, five with paraplegia) were taking anti-hypertensive medications and two (both with tetraplegia) were on pressor agents (fludrocortisone, pseudoephedrine, and liquorice root). None of the control participants were taking medications that affect BP.

ABPM data was incomplete for 4, 3, and 1 participant(s) in the tetraplegia, paraplegia, and control groups, respectively, while urine measurements were incomplete in 20, 9, and 10, respectively. This was due to insufficient readings (ABPM), inability to tolerate the monitor, or not completing urine measurements.

BP and pulse rates

The tetraplegia group had lower 24-h and day BP than the paraplegia and control groups, but night BP did not differ between groups (Table 2). Night BP exceeded day BP in 45% of participants with tetraplegia, but this was the case for only 13% of those with paraplegia and 2% of controls. Dippers comprised 26% of those with tetraplegia, 70% of those with paraplegia, and 82% of the controls. In those with elevated night BP, nocturnal hypertension was seen in the absence of day hypertension in 4 of 6 in the tetraplegia group, 5 of 7 in the paraplegia group, and 1 of 9 in the control group.

Participants with tetraplegia had lower 24 h and daytime pulse rates compared with other groups, while those with paraplegia had higher pulse rates in the day compared with other groups (Table 2). The nocturnal fall in pulse rate was observed in each group.

The differences across groups for SBP and pulse rates were present after adjusting for gender and age.

Subgroups

High and low paraplegia

Values for BP and pulse rate in participants with high paraplegia were generally located between those with tetraplegia and low paraplegia (Supplementary Table S1). There were significant differences between high paraplegia and tetraplegia for day pressures, nocturnal dipping, 24-h, and day pulse rates, and no significant differences between high and low paraplegia for BP or pulse rate parameters. Dippers comprised 74 and 65% of participants with high and low paraplegia, respectively.

Complete and incomplete SCI

Diurnal BP variation was lost in both complete and incomplete tetraplegia, with night:day SBP being in the

Table 1 Characteristics of study group

	Tetraplegia (<i>n</i> = 51)	Paraplegia (<i>n</i> = 33)	Controls (<i>n</i> = 52)
Age (years)	42.1 ± 15*	41.1 ± 15*	32.4 ± 13
Median	41	41	28
Range	16–70	22–75	16–65
Males	45 (88%)*	28 (85%)*	31 (60%)
Level of SCI	C2–C8: 51	T1–T6: 17 T7–L1: 16	–
Duration of SCI (years)	7.5 ± 9.3	5.9 ± 6.4	
Median	4	3	
Range	1–51	1–28	
Complete/incomplete	21/30	24/9	–
Neurological	C1–4, ABC: 10	T1–6, ABC: 17	
Classification	C5–8, ABC: 32 D: 9	T7–S5, ABC: 13 D: 3	
Comorbidities			
Diagnosed sleep disordered breathing [^]	25 (49%)	4 (12%)	0 (0%)
Current smoking [^]	10 (20%)	9 (27%)	3 (6%)
History of hypertension [^]	3 (6%)	5 (15%)	0 (0%)
Diabetes mellitus	3 (6%)	2 (6%)	0 (0%)
Ischaemic heart disease	2 (4%)	2 (6%)	0 (0%)
Cerebrovascular disease	2 (4%)	0 (0%)	0 (0%)
Dyslipidaemia	2 (4%)	1 (3%)	2 (4%)
Atrial fibrillation	0 (0%)	0 (0%)	1 (2%)

SCI spinal cord injury, ABC American Spinal Injury Association Impairment Scale (AIS) A, B, or C, D AIS D

**p* < 0.05 compared with controls; [^]*p* < 0.05 across groups. Data given as mean ± s.d

reverse dipper category for the complete tetraplegia group, but in the nondipper category for the incomplete tetraplegia group (Table 3). The between-group difference in night:day SBP of 7.2% (95% CI, −0.1 to 14.5), as determined in pairwise comparisons, suggests a trend towards a more abnormal diurnal BP variation for the complete compared with incomplete tetraplegia group. Reverse dipping was observed in 60 and 33% of complete and incomplete tetraplegia, respectively, while dipping was observed in 15 and 33%, respectively. Completeness of injury was not associated with statistically significant differences in BP or pulse rate parameters in paraplegia or in tetraplegia.

Postural BP

SBP and DBP were slightly higher after postural change in control participants, but in both tetraplegia and paraplegia, BP was lower (Fig. 1). Orthostatic hypotension was present in 38% (*n* = 10), 25% (*n* = 4), and 6% (*n* = 2) of participants with tetraplegia or paraplegia and the controls, respectively (*p* < 0.05).

Urine production

Urine flow rates were statistically lower at night than during the day in controls and in participants with paraplegia, but this nocturnal fall in urine flow rate was not observed in the participants with tetraplegia (Fig. 2a).

In participants with SCI, the nocturnal fall in urine production was present in those with a dipper BP pattern, in contrast to the reversal of diurnal urine production in the reverse dipper group (Fig. 2b). In participants with tetraplegia, the nocturnal fall in urine production was absent in all groups, but a reversal of diurnal urine production was observed in the group with the reverse dipper pattern (Fig. 2c). In participants with complete SCI, the nocturnal fall in urine production was present only in those with the dipper BP pattern (Fig. 2d).

No correlation was observed between night:day SBP and night:day urine flow rates.

Symptom scores

Symptoms of orthostatic intolerance were greatest in participants with tetraplegia and lowest in controls (Fig. 3).

Table 2 Blood pressure and pulse rate for all participants

		Tetraplegia (<i>n</i> = 47)	Paraplegia (<i>n</i> = 30)	Controls (<i>n</i> = 51)
Systolic BP (mmHg)	24 h	110.8 ± 1.5**††	119.4 ± 2.1	118.1 ± 1.4
	Day	111.5 ± 1.9**††	125.3 ± 2.2	124.1 ± 1.5
	Night	108.2 ± 1.7	109.6 ± 2.8	106.9 ± 1.4
	Night:Day (%)	97.8 ± 1.6**††	87.6 ± 1.8	86.2 ± 0.8
Reverse dippers		21 (45%)	4 (13%)	1 (2%) ^
Diastolic BP (mmHg)	24 h	64.4 ± 1.2**††	69.8 ± 1.5	69.8 ± 1.0
	Day	66.3 ± 1.3**††	74.9 ± 1.6	75.0 ± 1.1
	Night	60.7 ± 1.2	61.4 ± 1.8	59.2 ± 1.2
	Night:Day (%)	91.2 ± 1.3**††	82.9 ± 1.9	82.9 ± 1.2
Hypertension		2 (4%)	5 (17%)	11 (22%) ^
	Day	2 (4%)	5 (17%)	13 (25%) ^
	Night	6 (13%)	7 (23%)	9 (18%)
Pulse rate (bpm)	24 h	65.2 ± 1.5**††	78.1 ± 1.7*	71.3 ± 1.2
	Day	68.4 ± 1.5**††	83.2 ± 1.9*	75.9 ± 1.4
	Night	60.5 ± 1.6††	69.1 ± 1.9	62.5 ± 1.4
	Night:Day (%)	88.4 ± 1.6**††	86.8 ± 1.9	86.2 ± 1.2

BP blood pressure

p* < 0.05 vs. controls; *p* < 0.01 vs. controls; †*p* < 0.05 vs. paraplegia; ††*p* < 0.01 vs. paraplegia; ^*p* < 0.05 across groups. Values are mean ± s.e.m**Table 3** Blood pressure and pulse rates for complete and incomplete tetraplegia and paraplegia

		Tetraplegia, complete (<i>n</i> = 20)	Tetraplegia, incomplete (<i>n</i> = 27)	Paraplegia, complete (<i>n</i> = 23)	Paraplegia, incomplete (<i>n</i> = 7)
Systolic BP (mmHg)	24 h	108.6 ± 1.5**‡‡	112.4 ± 2.4**	120.1 ± 2.5	117.4 ± 4.2
	Day	107.0 ± 2.2**‡‡	114.8 ± 2.6**	125.9 ± 2.7	123.6 ± 3.9
	Night	108.2 ± 1.7	108.3 ± 2.7	110.2 ± 3.1	107.7 ± 6.7
	Night:Day (%)	101.9 ± 2.4**‡‡	94.8 ± 2.1**	87.7 ± 2.0	87.1 ± 4.3
Reverse dippers		12 (60%)	9 (33%)	2 (9%)	2 (29%) ^
Diastolic BP (mmHg)	24 h	63.5 ± 1.4**‡‡	65.1 ± 1.7**	70.2 ± 1.9	68.6 ± 2.2
	Day	63.8 ± 1.7**‡‡	68.2 ± 1.9**	75.3 ± 2.0	73.7 ± 2.0
	Night	61.1 ± 1.5	60.5 ± 1.7	61.9 ± 2.1	59.6 ± 3.6
	Night:Day (%)	96.1 ± 1.3**‡‡	91.7 ± 1.9	87.1 ± 2.1	86.2 ± 3.6
Hypertension		0 (0%)	2 (7%)	4 (17%)	1 (14%)
	Day	0 (0%)	2 (7%)	4 (17%)	1 (14%)
	Night	2 (10%)	4 (15%)	5 (22%)	2 (29%)
Pulse rate (bpm)	24 h	63.3 ± 1.9**‡‡	66.7 ± 2.2†	77.9 ± 2.1	78.8 ± 2.8
	Day	67.0 ± 2.0**‡‡	69.4 ± 2.1†	83.1 ± 2.4	83.2 ± 2.5
	Night	58.0 ± 1.6‡‡	62.3 ± 2.4	69.2 ± 2.2	68.7 ± 4.3
	Night:Day (%)	86.6 ± 1.6**‡‡	92.1 ± 2.4	84.6 ± 2.4	87.1 ± 4.3

BP blood pressure, bpm beats per minute

Data for control participants shown in Table 2

p* < 0.05 vs. controls; *p* < 0.01 vs. controls; †*p* < 0.05 vs. incomplete paraplegia; ††*p* < 0.01 vs. incomplete paraplegia; ‡*p* < 0.05 vs. complete paraplegia; ‡‡*p* < 0.01 vs. complete paraplegia; ^*p* < 0.05 across groups; Values are mean ± s.e.m

Scores were not significantly different between high and low paraplegia, complete and incomplete tetraplegia, or complete and incomplete paraplegia (data not shown). There was no significant difference in symptom scores among the three diurnal BP categories (dipper, nondipper, and reverse dipper).

Discussion

We previously documented the haemodynamic consequences of acute SCI by studying a large group of participants recruited from consecutive admissions to a single-site unit that had responsibility for treating people with

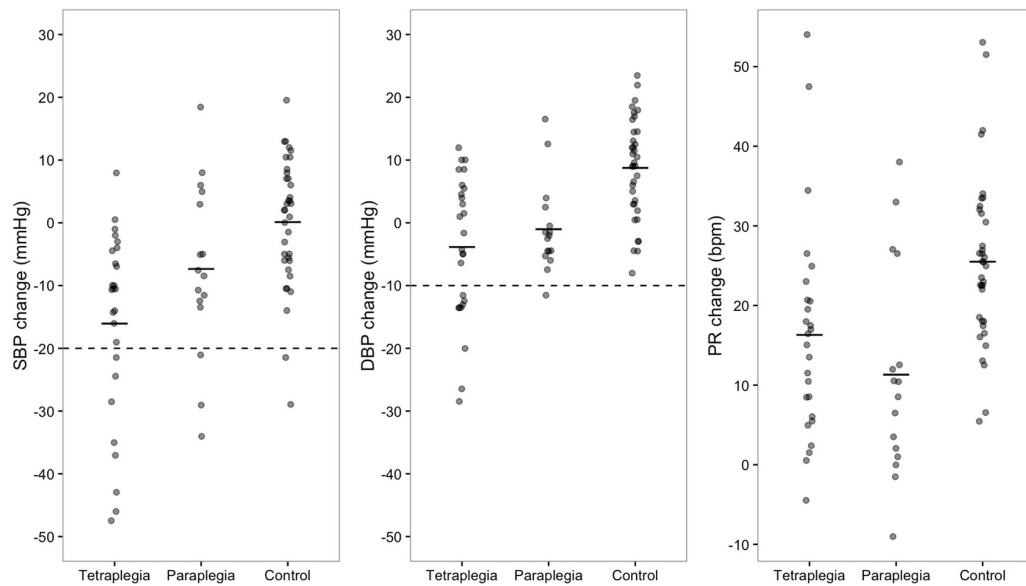


Fig. 1 Postural changes in blood pressure and pulse rates for tetraplegia ($n = 26$), paraplegia ($n = 16$), and controls ($n = 36$). Dashed line indicates limit for orthostatic hypotension. Solid short lines

represent mean. SBP systolic blood pressure, DBP diastolic blood pressure, PR pulse rate, bpm beats per minute

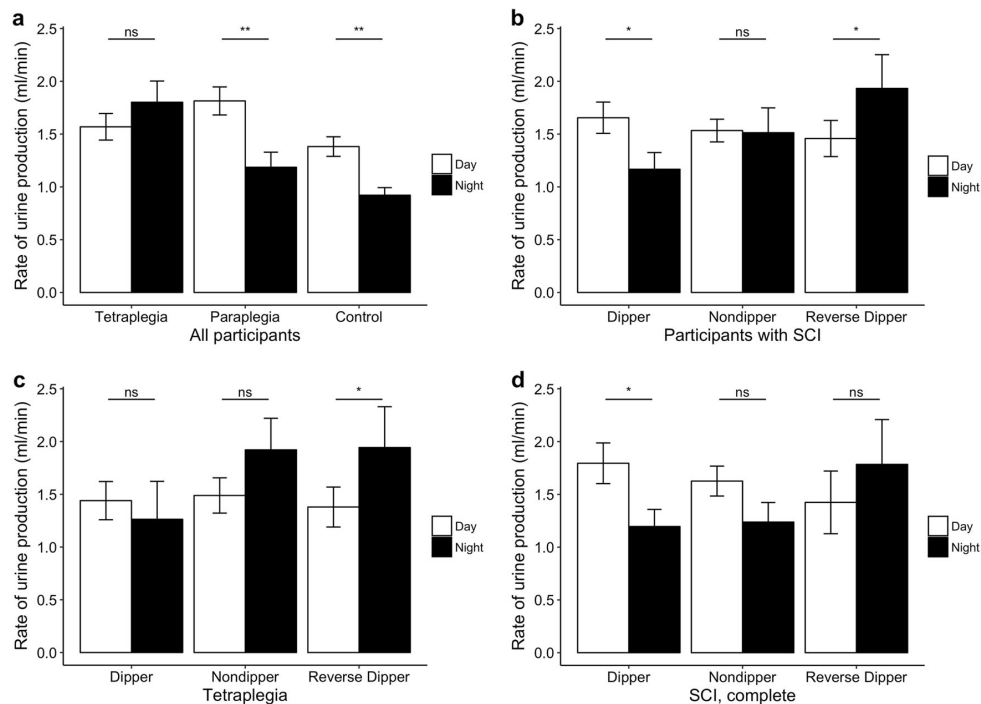


Fig. 2 a Day and night urine flow rates for tetraplegia ($n = 31$), paraplegia ($n = 24$), and controls ($n = 42$). **b** Urine flow rates for participants with SCI and dipper ($n = 19$), nondipper ($n = 13$), and reverse dipper ($n = 16$) patterns. **c** Urine flow rates for participants with tetraplegia and dipper ($n = 7$), nondipper ($n = 8$), and reverse

dipper ($n = 12$) patterns. **d** Urine flow rates for participants with complete SCI and dipper ($n = 11$), nondipper ($n = 9$), and reverse dipper ($n = 7$) patterns. Error bars represent s.e.m. Significance values above each pair of bars indicate comparison between day vs. night rate; ns not significant; * $p < 0.05$; ** $p < 0.01$

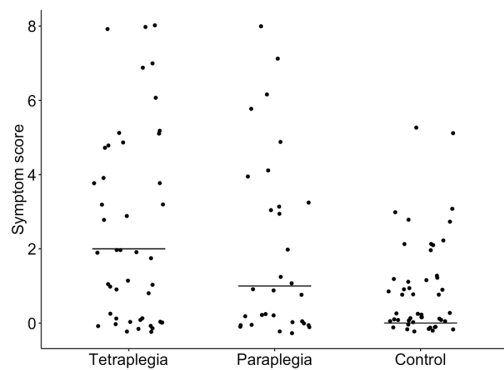


Fig. 3 Orthostatic intolerance symptom scores for tetraplegia ($n = 45$), paraplegia ($n = 31$), and controls ($n = 48$). Horizontal lines represent median scores. Chi-squared = 8.94, $df = 2$, $p = 0.0114$

traumatic SCI from a defined region of Australia [3]. The present study aimed to examine the effects of SCI on BP over the longer term. Similar to our previous study and in contrast to other investigations [12–16], we examined a large cohort of participants and employed few exclusion criteria. Also, diurnal BP was categorised according to patterns associated with poorer cardiovascular outcomes in the general population [9, 17].

We previously found that acute SCI disrupts diurnal variation of BP in 94% of participants with tetraplegia and 65% of those with paraplegia and these changes largely persisted over the 12 months after cervical injury, but they tended to improve in paraplegia [3]. In this study of participants with a longer-term injury, we again observed a high prevalence of abnormal diurnal BP variation amongst participants with tetraplegia (74%). However, abnormal diurnal BP variation was only seen in 30% of participants with long-term paraplegia, compared with 18% in the control population. This apparent time-dependent improvement in BP control following paraplegic injury is consistent with findings in animal models of mid-thoracic SCI in which diurnal BP variation returned after 5 days following incomplete T5 injury [18] and after 14–21 days following complete T3 injury [19]. Taken together, the results of these studies suggest that SCI causes substantial disruption to diurnal BP control which largely persists following tetraplegic injury, but which improves after paraplegic injury.

The return of diurnal BP variation in paraplegia could potentially be dependent on preservation of sympathetic inputs to the spinal cord below C8. The sympathetic outputs between T1–T6 regulate orthostatic vascular responses, and the severity of cardiovascular dysfunction following SCI has previously been correlated with the extent of histopathological changes in the vasomotor pathways in the spinal cord [20]. Consistent with a neurological explanation is that participants with an incomplete tetraplegic injury had

less abnormalities in diurnal variation of BP than participants with a complete injury. Also consistent with this hypothesis is the higher pulse rates observed in the paraplegic group, particularly in low paraplegia. In contrast, the pulse rate in tetraplegic participants was lower than in controls. This finding is similar to our observation following acute injury, thus it appears that the elevation in pulse rates following paraplegia begins soon after SCI and persists in the longer term. This observation would be consistent with paraplegia being in a state of increased activation of the sympathetic nervous system, and perhaps that may explain why their BP is similar to that of the controls. In contrast, in tetraplegia it appears that the ability to mount an adrenergic response has been lost.

Consistent with our previous studies [21], we found a high prevalence of sleep disordered breathing (SDB) among people with tetraplegia. Obstructive sleep apnoea, the predominant form of SDB [21], has been associated with abnormal diurnal BP variation in the able-bodied population [22] and therefore might have contributed to the BP abnormalities observed in this study. It was unfortunately outside the scope of this study to measure sleep indices on all participants, which would have allowed for a comparison of effects on sleep disturbances, including effects of any management for SDB, on diurnal BP. The lack of precision in our estimates of SDB preclude any meaningful interpretation of these differences.

The increased incidence of cardiovascular disease in SCI mandates strict control of cardiovascular risk factors. Compared with clinic measurements, ambulatory BP better predicts cardiovascular risk [23]. Although the predictive powers of ambulatory pressure have not been studied in SCI, in our population of relatively unselected participants, measurement of ambulatory pressure revealed that 17% ($n = 13$) of our SCI participants had nocturnal hypertension, but in only 5% ($n = 4$) did an elevated day pressure provide a clue about the high night pressure. While these data argue for the use of ambulatory measurements in the SCI population, it should be noted that the results of ambulatory monitoring only triggered antihypertensive treatment in one of our study participants—at least in part because relatively low day pressures produced a 24-h average that was below treatment thresholds.

Nocturnal nondipping involves the loss of decline in night BP relative to day pressure, whereas nocturnal hypertension is defined when average night BP exceeds an absolute value, thus one may occur independently of the other. We observed a high prevalence of nondipping in people with tetraplegia. While the prevalence of nocturnal hypertension was not different between SCI and controls, it was not insignificant, considering that people with long-term SCI have been observed to have a higher rate of other cardiovascular risk factors [2], which contributes to higher

absolute cardiovascular risk. Nondipping and nocturnal hypertension have independently been associated with poorer outcomes in normotensive as well as hypertensive able-bodied populations [23, 24]. Their impact on cardiovascular risk, and whether treatment to normalise them will improve outcomes in people with SCI, remains to be investigated.

Although orthostatic hypotension may be asymptomatic in SCI, it can also manifest as lightheadedness, fatigue, and syncope [1, 25]. Symptoms can affect activities of daily living, delay rehabilitation and impair quality of life [1, 25, 26]. In our previous study of a large group of unselected participants with SCI, we found a high prevalence of symptoms, particularly in those with complete cervical injury, and these were only partly improved 12 months later. Whether these symptoms would persist over the longer term is unclear, with previous smaller studies of selected people with SCI having provided conflicting results [1, 25]. In the present study we observed that participants with tetraplegia continued to be symptomatic, and at higher rate than those with paraplegia, suggesting there was not a continuous improvement in orthostatic symptoms beyond 12 months after injury. It should also be noted that although the difference in median values between those with tetraplegia and controls was relatively small, this is not to say symptoms were insignificant. Some individuals reported severe symptoms even many years after their injury (Fig. 3).

As in our previous study, we measured diurnal urine production in people with SCI. Nocturnal polyuria in SCI has been attributed to the loss of vascular tone due to impaired autonomic function, alongside lack of the skeletal muscle pump, resulting in lower limb venous pooling while upright; recumbency overnight returns circulating volume thus increasing renal perfusion pressures, which, together with a lack of nocturnal increase in antidiuretic hormone [16], leads to nocturnal diuresis. Other hormonal changes such as rises in atrial natriuretic peptide and glucocorticoid, and suppression of the renin–angiotensin–aldosterone system, have also been implicated in post-SCI polyuria in human and animal studies [27, 28]. There is also evidence for an interaction of neural networks involved in the control of the bladder function and lower limb musculature. Locomotor training, including training limited to the forelimbs, has been found to reduce post-SCI polyuria in rats. It also been associated with improvements in bladder and urinary tract function in rat studies, in keeping with a few reports in humans with SCI [29].

In previous studies [3, 16], diurnal variation of urine production was lost in both tetraplegia and paraplegia. In contrast, and within the limits of the data from our urinary measures, we observed a nocturnal fall in urine output in both high and low paraplegia and in complete paraplegia. This may be related to time after SCI as previous studies

were done on participants admitted for acute SCI or undergoing inpatient rehabilitation following admission for SCI. The compensatory neuro-hormonal mechanisms occurring over time that affect diurnal BP, described above, may also affect diurnal urine production. The ability to maintain daytime BP in paraplegia may reduce the fluid shifts seen in tetraplegia that result in nocturnal diuresis. Another factor could be the effect of physical activity over time, that leads to the changes in diurnal urine production, by its effect on the urinary tract and bladder function, as described in the rat models of thoracic SCI above.

Relative elevation of supine BP consequent upon SCI has been proposed as a cause or contributor to a nocturnal diuresis and even potentially to orthostatic hypotension [4, 5]. That hypothesis is supported by the results of the current study in which chronic tetraplegia was associated with nocturnal nondipping and diuresis. Also consistent with this hypothesis was the observation that the improvement in diurnal BP variation in participants with paraplegia was accompanied by a normalisation of the diurnal production of urine. However, in the current trial, we did not find that the improvements in these parameters in the participants with paraplegia were accompanied by an improvement in orthostatic symptoms. That being said, this trial was not designed or powered to detect such a change—and perhaps the only way of testing this hypothesis would be to determine the symptomatic effects of selectively altering nocturnal BP or diuresis.

Limitations of our study include that it examined a sample of convenience, with the population being recruited at a single centre, and willing to participate, thus findings may not be generalisable to the greater SCI population.

Conclusions

This study has found a high prevalence of abnormal diurnal variation in BP and urine output, and of orthostatic hypotension and symptoms, in tetraplegia compared with paraplegia and controls. While nocturnal hypertension was not different in prevalence between SCI and controls, daytime hypertension was lower in tetraplegia. ABPM can be used to identify these BP patterns, which are associated with poorer prognoses in the general population, and are potential contributing factors to the observed increased prevalence of cardiovascular disease in the SCI population.

Acknowledgements This research was supported by a grant from the Transport Accident Commission (DP174). MG is supported by a scholarship and stipend through the University of Melbourne and Spinal Research Institute. We thank Dr. Sue Finch and the Statistical Consulting Centre, University of Melbourne, for their assistance in statistical analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Chapter 6. Treatment of orthostatic symptoms with nocturnal antihypertensive medications in SCI

6.1. Introduction

This chapter describes my attempts to investigate the use of a novel management technique for orthostatic intolerance in people with SCI. It is based on the observation of studies in previous chapters, and on studies by other investigators, which have found a high incidence of reversal of diurnal variation in BP, with higher night time than day time BPs.^{180-183, 188} Concurrently, the rate of urine production is often also increased compared to daytime urine production.^{198, 199} A similar triad of supine hypertension, orthostatic intolerance and nocturnal polyuria is seen in autonomic failure arising from conditions such as pure autonomic failure, MSA and Parkinson's disease.^{6, 7} It is postulated that an increase in BP on returning to the supine position leads to an increased renal perfusion and thus increased urine production in the supine position.^{8, 196, 197, 241} This gives rise to nocturnal polyuria, thus leaving the patient less fluid replete in the morning when trying to assume the erect position, which therefore exacerbates the symptoms of orthostatic intolerance. This explanation is consistent with the observation that patients tend to report worse symptoms in the mornings.^{6, 8, 196, 197, 242-244}

The role of nocturnal BP reduction in patients with elevated nocturnal BP and autonomic failure has been examined by other investigators. Shannon et al²⁴⁵ tested three vasodilators applied at bedtime and observed the greatest nocturnal BP lowering effect with transdermal glyceryl trinitrate, less with minoxidil and least with hydralazine. Jordan et al⁸ found that a single dose of transdermal glyceryl trinitrate and nifedipine both reduced night BP, with the former having no effect on sodium excretion

but the nifedipine increased nocturnal sodium excretion – which was the opposite of what was expected. In a similarly designed trial by Shibao et al,²⁴¹ a single nocturnal dose of clonidine or topical glyceryl trinitrate reduced the night pressure, and the clonidine also reduced the nocturnal urinary sodium excretion. Orthostatic hypotension on the morning following drug administration was not improved when patients were treated with clonidine – which the authors concluded may have been a reflection of the long duration of action of clonidine. Arnold et al²⁴⁶ observed a reduction in nocturnal BP and urinary sodium excretion with single doses of losartan but not captopril and neither was associated with worse orthostatic tolerance in the morning. The lack of response to captopril was consistent with previously observed low renin levels in autonomic failure (in contrast to elevated renin levels in SCI), but high levels of angiotensin II and response to losartan were new findings.

Taken together, these data suggest that short term administration of nocturnal antihypertensive medications reduce night BP, and can, at least for some medications, reduce nocturnal sodium excretion. No studies have been done to investigate the long-term effects of nocturnal antihypertensive therapy on orthostatic symptoms and nocturnal hypertension in patients who have both. (Since my studies were conducted, a case series observed lowering of nocturnal ambulatory BPs following the use of nocturnal antihypertensive agents over 4 months in 3 patients, but did not assess effects on orthostatic symptoms.²⁴⁷)

Autonomic dysfunction in SCI

Other than the well known motor and sensory impairments of SCI, disturbances of autonomic function also cause significant and perhaps an even greater impact on quality of life. Bladder and bowel disturbances confer social implications as impaired control of the ANS may lead to reduced continence, and the 'bowel accident' familiar to many people with SCI, where an unexpected loss of bowel contents leads to crippling social embarrassment. At other times constipation may result in the complication of autonomic dysreflexia. Poor motility of bowel contents and sphincter dysfunction may also contribute to symptoms of hypotension during a bowel routine, which in some people can be significant enough to cause a loss of consciousness. Such issues can lead a person with SCI to avoid leaving their residence on 'bowel routine days'. This has implications on both employment or education and recreation, and thereby quality of life.^{111, 112, 118-120}

Similar conditions apply to the urinary system. Nocturnal polyuria, or a large volume of urine produced overnight, is also common in SCI, especially with cervical SCI. This can lead to difficulties for individuals who use a program of intermittent catheterisation for bladder emptying, as the need for increased frequency of nocturnal catheterisation potentially diminishes quality of sleep. For those with suprapubic or indwelling catheters who are reliant on carers for emptying catheter bags, the large volume of nocturnal urine can lead to problems if the bag is full before the carer's attendance in the morning. In addition, an excessively full catheter bag can potentially impair bladder emptying, which can cause autonomic dysreflexia or increase the risk of urinary sepsis.^{112, 121, 122}

Orthostatic intolerance in SCI

Orthostatic intolerance and orthostatic hypotension are another common feature of the autonomic derangement in SCI. Illman et al¹⁰⁵ demonstrated that orthostatic hypotension was present in all 14 patients with acute SCI who were being mobilised during physiotherapy, and in a series of 129 treatments on these patients, 73.6% were associated with orthostatic hypotension, and of these treatments, 58.9% were associated with symptoms. Orthostatic hypotension was deemed to interfere with treatment in 33.3% of the 129 treatments, with signs and symptoms in all of these. Signs and symptoms of orthostatic intolerance occurred without a fall in BP in a few cases. Thus, orthostatic symptoms delay rehabilitation and contribute to a prolonged hospital stay. People with higher levels of SCI were more likely to experience orthostatic intolerance.

Orthostatic intolerance and orthostatic hypotension are thought to improve with time after injury, but are still common in chronic SCI.^{106, 107, 248} This has physical, psychological and social implications for the person with SCI. Physically, a person confined to a wheel chair might fall and be injured in an event of syncope, and recovery may be delayed because they do not end up in a supine position which would allow restoration of cerebral perfusion, which of course, tends to be the result of a collapse in an able-bodied person. Even with sufficient warning, the motor impairments of SCI mean that a person in a manual wheelchair may be unable to independently elevate their legs or tilt their chair. Moreover, anecdotes exist wherein the provision by inexperienced bystanders of urgent assistance in tilting a manual wheelchair or commode backwards can produce accidental injury (personal observation, Min Yin Goh, 2013).

Management options for orthostatic intolerance include non-pharmacological and pharmacological strategies. Non pharmacological strategies that are commonly used are slow notching or a gradual change in posture, hydration prior to rising in the morning and the use of abdominal binders, although there is limited evidence for the effectiveness of these strategies.¹⁵⁴

Of available pharmacotherapy, which is used in other conditions with autonomic dysfunction, midodrine has the best, though still limited, evidence for effectiveness in SCI.¹⁵²⁻¹⁵⁴ It is a peripheral alpha agonist which elevates BP by causing vasoconstriction. It has been found to be relatively safe,^{152, 153} however people with high level SCI have the potential to experience autonomic dysreflexia, a condition in which the BP rises significantly in relation to an insult usually below the level of injury; if such an event occurs, one might expect the presence of midodrine to exacerbate this. There is limited evidence to suggest that fludrocortisone is not effective, and limited evidence to suggest that ephedrine, dihydroergotamine, L-DOPS (droxidopa) and L-NAME may be effective in SCI.¹⁵⁴

Given the impact of symptoms of orthostatic intolerance on the SCI population and potential risks of currently available treatment, I undertook this study which aimed to examine the effect of short acting nocturnal antihypertensive agents on orthostatic symptoms and nocturnal polyuria in people with chronic SCI. Although my assessment would include postural BP measurements, the aim of the study was to examine the effect of treatment on orthostatic symptoms, rather than orthostatic hypotension, because the symptoms affect the quality of life. Therefore screening questions were

directed at identifying potential participants with significant symptoms, regardless of postural BPs.

To reiterate, as discussed earlier in this chapter, previous studies on autonomic failure raise the possibility that nocturnal administration of antihypertensive agents to selectively reduce nocturnal BP and natriuresis (or diuresis in SCI) by reducing nocturnal renal perfusion and thus keeping the patient more fluid replete, could theoretically improve orthostatic tolerance in the day.⁶⁻⁸

I chose to use captopril for this purpose. One of the reasons for choosing captopril was its short duration of action²⁴⁹ which meant that very little residual effect would be predicted to remain on the morning following a night dose. This is important as the antihypertensive action is desired only overnight while supine, but not desired during the daytime when upright, as this is likely to exacerbate orthostatic intolerance instead.

Of the short acting antihypertensive agents available, captopril was chosen because of activation of the RAAS in SCI^{52, 250} – thus suggesting that interruption of this pathway would be likely to have a significant effect on BP, as observed with reduction in BP when captopril was administered to five people with tetraplegia.²⁵¹ Unlike in autonomic failure where renin is low, RAAS activity is increased in high SCI, with observations of elevated resting renin and a further renin rise in response to an orthostatic challenge.^{52, 205} Captopril, an angiotensin converting enzyme inhibitor, inhibits the conversion of angiotensin I to angiotensin II and thus acts against the downstream vasoconstrictor effects of renin through the RAAS, to lower BP.²⁴⁹ Another reason to think that

captopril might be effective is that it is effective in the treatment of autonomic dysreflexia in SCI;¹⁶⁶ whereas it is used to reduce BP during episodic elevation of BP in autonomic dysreflexia, I aim to use it to selectively reduce nocturnal BP and thereby nocturnal diuresis, as this is postulated to potentially reduce daytime orthostatic symptoms.⁶⁻⁸ The other reason for choosing captopril was based upon my personal experience wherein I have used it to treat patients with autonomic dysfunction and nocturnal hypertension (personal observation, Min Yin Goh). In such patients, I have found it safe and clearly effective at reducing night BP. In addition, angiotensin converting enzyme inhibitors are one of the first line agents recommended for management of elevated BP due to their benefit of reduction in cardiovascular events,²⁵²⁻²⁵⁵ which is of relevance to the SCI population in which there are increased rates of cardiovascular disease and risk factors including diabetes mellitus.^{138, 143, 144, 256}

In considering other short acting antihypertensive agents, the glyceryl trinitrate patch was unsuitable due to the potential interaction with phosphodiesterase-5 inhibitors²⁵⁷ which are commonly used in this population for sexual health, and because impaired hand function may preclude independent application and removal of the patch nightly. The use of immediate release nifedipine has been discouraged due to concerns about large falls in BP and other adverse effects, albeit in the setting of a hypertensive emergency in populations without SCI.^{258, 259} Prazosin has the potential adverse effects of significant first dose effect and postural hypotension,²⁶¹ hydralazine may be longer acting in some individuals due to being slow acetylators²⁶⁰ and methyldopa or beta blockers which work on the sympathetic nervous system²⁶¹ may be less effective due to the impaired sympathetic function in SCI.

6.2. Methods

This was conducted as a double-blind, placebo-controlled, crossover study with a 4-week titration phase and 4-week maintenance phase for each treatment arm, separated by a 2-week washout period. Eligible participants were those with SCI and were outpatients, with symptoms of orthostatic intolerance (regardless of presence of orthostatic hypotension), occurring at least weekly, that were deemed by themselves to require further management.

Study participants were recruited by advertisement as well as individually addressed letters and telephone calls. Advertisements were placed in the hospital, on general community websites and in websites and newsletters of SCI support associations as well as SCI research groups. The presence of the study was also made known to people and organisations who care for people with SCI, including a general practitioner who has a large SCI patient base, carer organisations who provide carers for people with SCI and a series of community gyms and physical trainers who were undertaking training as part of a concurrent research program on physical activity in SCI.

Potential participants were also identified from the records of the Austin Health's VSCS, which records data about patients treated. This list was refined to exclude patients without traumatic SCI, who were deceased or who had addresses interstate and overseas. Potential participants were sent a letter inviting participation, and this was followed by a telephone call. Because this study required participants to receive

multiple home visits, the order of recruitment was to begin with individuals who had addresses within metropolitan Melbourne.

At the time of the initial telephone call, potential study participants were surveyed about symptoms which were potentially indicative of prevalence and impact of orthostatic intolerance on the chronic SCI population. Potential study participants were questioned about the severity and frequency of symptoms, as well as being asked about capacity including time spent upright in a day and frequency of leaving the house (Table 6.1). The goal of the questionnaire was to identify potential participants who had symptoms of orthostatic intolerance (regardless of presence of orthostatic hypotension), and whose symptoms were of a sufficient severity that they might consider further investigation or intervention, to enter the treatment study. A secondary goal of the questionnaire was as a survey of the prevalence of such symptoms in the screened population from which the participants were recruited.

My questionnaire was developed based on the Orthostatic Hypotension Questionnaire²⁶² which has been validated in patients who have orthostatic symptoms secondary to autonomic disorders, but has not been validated in the SCI population. It is a questionnaire that requires ten responses to severity of symptoms and ability to remain upright, but my rudimentary questionnaire asked patients about some symptoms using the language used in some of the questions in the Orthostatic Hypotension Questionnaire. In developing the questionnaire, I also considered questions usually asked in a clinical setting to assess the impact of symptoms on daily function. Question 1 was designed to firstly determine the presence or absence of orthostatic symptoms

(answer (a) vs (b) or (c)). For those with symptoms, they were asked whether they felt symptoms were sufficiently severe to warrant further treatment, as (c) identifies potential participants for my study examining treatment of such symptoms. Question 2 obtains information about the course and nature of presyncope or syncope if present, in order to identify potential participants for the treatment study who have sufficiently frequent symptoms for an effect to be observed with treatment during the study. Questions 3 to 6 were included as a survey on basic indicators of how symptoms may impact on function, while Questions 7 to 9 obtain information about urine production to explore the possibility of nocturnal polyuria and nocturia (acknowledging limitations by patient history), as nocturnal polyuria was prevalent in the SCI populations in my previous studies.

Table 6.1 Questions asked during screening telephone interview for Study 4

- 1) Do you have any symptoms of low blood pressure?
(e.g. lightheadedness/dizziness, symptoms occurring while upright)
 - a) No, none at all
 - b) Yes, sometimes but it doesn't bother me enough to want treatment for it
 - c) Yes, I would like to explore treatment for this
- 2a) Have you ever fainted/blacked out?
- 2b) Have you ever felt faint/like you might blackout, but didn't? For each:
 - Never or Ever had an episode
 - Before or after the SCI?
 - Episode in the setting of illness/prolonged bed rest only
 - Episode in the acute period after SCI
 - Episode past acute period after SCI
 - Frequency: how many times a week/month/year?
 - Age at first episode & most recent episode
- 3) Comments/Triggers/ How does this (pre/syncope) affect your life?
- 4) How many hours do you spend upright in a day?
- 5) How many days a week would you leave your house?
- 6) Main mode of mobility:
 - Power chair / Manual chair / Both chairs / Walks / aids, e.g. frame, sticks
- 7) Continence aids
 - None / IMC / IDC / SPC / Condom drainage / Other
- 8) How many times do you need to wake up overnight to void?
- 9) Do you produce a larger volume of urine in the day or night?

Abbreviations: IMC, intermittent catheter; IDC, indwelling catheter; SPC, suprapubic catheter.

Interested participants were invited to attend the hospital for the initial assessment, which comprised a medical interview, 24-hour ambulatory BP and ECG monitoring, recording of urine production over 3 days and nights and completing questionnaires relating to orthostatic symptoms. Blood tests for renal function, a full blood count and a spot urine protein:creatinine and albumin creatinine ratio were also conducted. These assessments were conducted before and after each treatment arm, and subsequent assessments were conducted at the participants' homes. Ambulatory monitors were returned by courier to facilitate quick availability of results.

Eligibility for entry to the treatment phase of the study included:

- symptoms occurring at least weekly, to allow titration of treatment according to study protocol
- a loss of diurnal BP variation on 24-hour ABPM

If eligible for entry to the treatment phase, each participant was started on 25mg captopril nocte or a similar looking placebo, to which both investigator and participant were blinded. Weekly assessments were conducted to assess effectiveness and safety, and to titrate dosing. The dose could increase by 25mg each week in the first 4 weeks (titration phase), and the dose would be continued in the maintenance phase in weeks 5 to 8. A 2-week washout period followed, and the alternative treatment arm was entered.

The Pharmacy Department of Austin Health organised, stored and dispensed the captopril 25mg capsules and identical looking placebo capsules. Random block

assignment of placebo and active drug were conducted and maintained by the pharmacy department, and unblinding was to occur only after results were collected and finalised.

Assuming a total of 25 patients enter this two-treatment crossover study, the probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 10 mmHg. This is based on the assumption that the within-patient SD of the SBP is 12 mmHg.

Chi-square or Fisher tests were used to compare the categorical variables between groups in the results section of this chapter. Significance was set at $p < 0.05$.

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The protocol for this study was approved by the Human Research Ethics Committee of Austin Health.

6.3. Results

Only five responses to advertisements were received, and this included one interstate and one overseas enquiry. There was one referral from the SCI clinic. Of 2424 records of the VSCS that were examined, 885 were excluded for duplication, SCI not having a traumatic cause, death of the individual or overseas or interstate address; 311 were kept for consideration, being in regional Victoria. Of 342 letters posted and 182 calls attempted, 76 people undertook the telephone survey. This revealed 62 people who had no or minimal symptoms. Fourteen people had eligible symptoms. After 5 declined participation and 1 was lost to follow up, a total of 8 people attended for assessment. Of these, four were eligible and entered the treatment phase (Figure 6.1).

Of the 76 people who participated in the telephone survey, 27 reported no symptoms at all, while 32 reported mild symptoms they felt were of insufficient severity to warrant further management. This left 17 who reported significant symptoms and wished their symptoms could be improved upon or eliminated (3 had ineligible symptoms or known ineligible diurnal BP profile) however 6 declined participation in the study because they felt it was too involved, there were other personal or medical issues of greater current concern at the time, fear of the risk of adverse effects even though orthostatic symptoms were still classified as significant, or they felt they still needed to work on non-pharmacological measures such as keeping better hydration, of which they were aware but had not optimised.

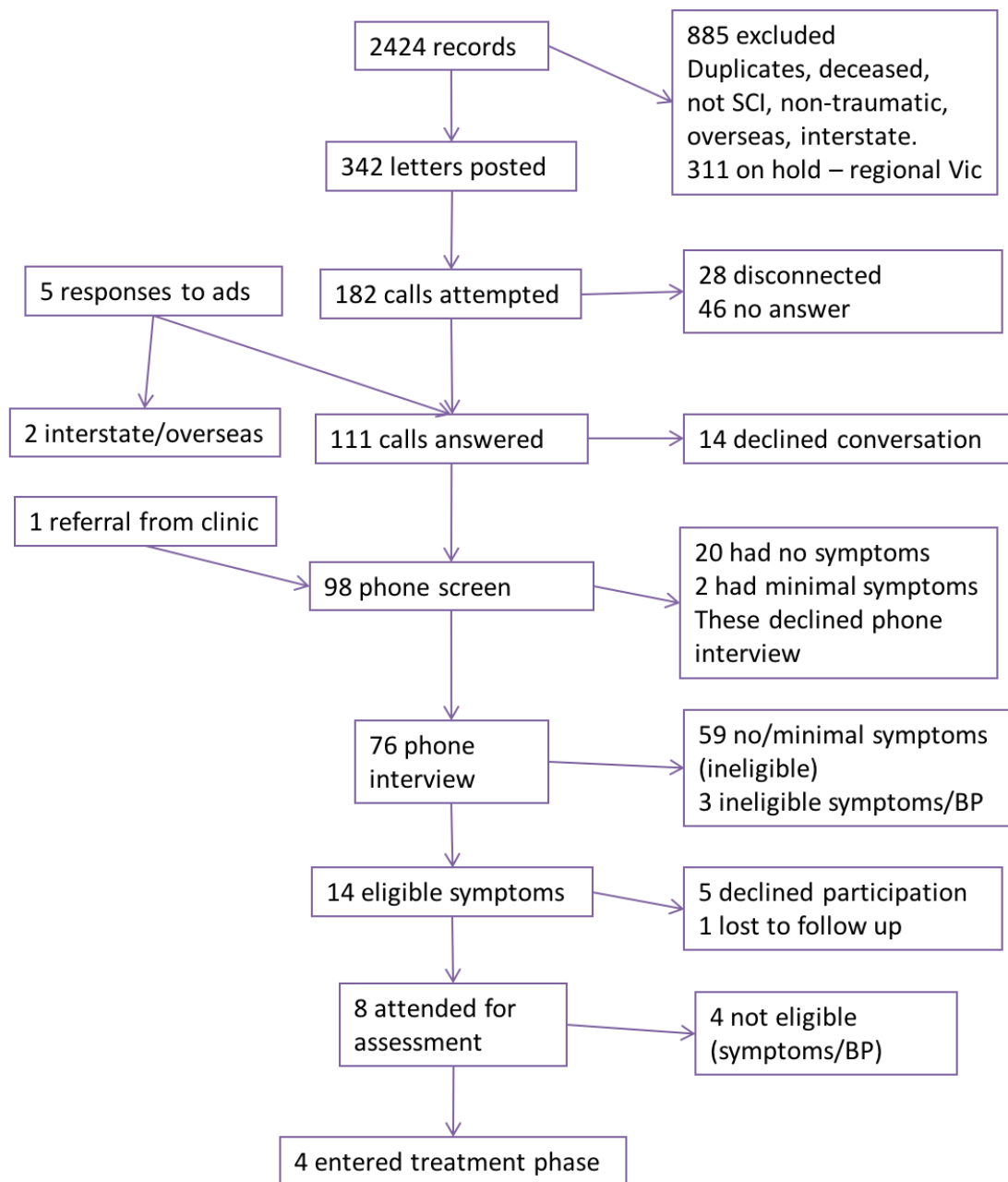


Figure 6.1 Flow diagram showing number of records screened and number of participants recruited.

Abbreviations: Vic, Victoria; ads, advertisements; BP, blood pressure.

Participants were divided into three groups, dependent on their answer to whether they had any orthostatic symptoms.

A) None at all (n=27, 36%)

B) Some but it doesn't bother them enough to want treatment for it (n=32, 42%)

C) Yes, and they would explore treatment options. (N=17, 22%)

There were 55 participants with tetraplegia (C1-C7) (21 complete, 34 incomplete) and 21 with paraplegia (T1-T12) (12 complete, 8 incomplete, 1 missing information) of mean age 48 (SD 13, range 19-70) and duration from SCI 13 years (SD 14, range 1-61 years). Of the people who answered (C), none had sought medical advice for their symptoms.

The proportion of people reporting presyncope or syncope before the SCI was not significantly different between groups with tetraplegia (35%) or paraplegia (19%) ($\chi^2=1.7$, $df=1$, $p=0.19$). This was not statistically different for complete or incomplete tetraplegia (29% vs 38%, $\chi^2=0.54$, $df=1$, $p=0.46$), and for complete vs incomplete paraplegia (17% vs 25%, $\chi^2=0.21$, $df=1$, $p=1$). A high proportion (75%) of people with tetraplegia reported presyncope and syncope in the acute period after the SCI. The corresponding figure in the people with paraplegia was 52%, a difference that failed to reach statistical significance ($\chi^2=3.5$, $df=1$, $p=0.063$). There was no difference in this history for those with complete vs incomplete tetraplegia (76% vs 74%, $\chi^2=0.05$, $df=1$, $p=0.83$), or those with complete vs incomplete paraplegia (67% vs 38%, $\chi^2=1.6$, $df=1$, $p=0.36$).

There was a significant difference in reports of presyncope or syncope before the SCI (15% (A) vs 28% (B) vs 53% (C), $\chi^2=7.4$, $df=2$, $p=0.025$). Pairwise comparisons showed a trend towards a difference between groups (A) and (C) ($p=0.055$) but no significant differences between each pair. The proportion of people in category (A), (B) and (C) reporting presyncope or syncope soon after SCI was 48%, 84% and 65% respectively ($\chi^2=8.8$, $df=2$, $p=0.013$), with a significant pairwise difference for groups (A) and (B) ($p=0.022$) but not the other pairs.

The median number of days per week that participants from groups (A), (B) and (C) left the house was 5.5 ± 2.2 , 5.0 ± 2.2 and 5.5 ± 2.6 respectively ($\chi^2=0.65$, $df=2$, $p=0.724$).

Regarding mobility in the community, there was no significant difference between the three groups for the use of a power wheelchair, manual wheelchair or walking with/without aids. In groups (A), (B) and (C), a power wheelchair was used by 11%, 44% and 41% respectively, a manual wheelchair in 52%, 31% and 35% and walking with or without aids was the mode of mobility in 37%, 25% and 24% of participants.

6.4. Discussion

The study was ended early, because it soon became obvious as shown in Figure 6.1 that the intended 25 participants would not be achievable at this single site, as only about 5% of those screened ended up entering the treatment phase. Although this study did not manage to achieve the aims, it illustrates several important points.

First, it reveals there is a high prevalence of mild orthostatic symptoms in chronic SCI, but for which further management is not felt necessary. However there remain a small proportion of patients who have significant symptoms that they wish to improve, but none of these patients had sought medical advice. Furthermore, despite the offer of both participation in the study as well as clinical follow up, only about half opted to do one of these. This suggests that amongst the multiple issues that these patients face, management of orthostatic symptoms is not of high priority, and some have managed to find methods of coping, or manage by putting up with the symptoms. It is notable that some people gave feedback that although they did have some troublesome orthostatic symptoms, they feared an attempt to address this might lead to more problems in their overall health. The suggestion arising from this finding is to actively ask about the presence of such symptoms in people with chronic SCI, as they may not be forthcoming with information. It is also possible that following the conversation with the study investigators, the patients sought medical advice elsewhere.

My studies also found that at a single site, there was only a small proportion of responders to an extensive recruitment effort who were eligible for study entry.

Therefore, if further assessment of this method of treatment is to be attempted, a multi-centre study would be required to achieve sufficient numbers to allow for withdrawals and to assess safety and efficacy. It is my assessment that such an approach would be feasible but it would require substantial co-ordination and training for the application of ambulatory BP monitors by an investigator at each site. To include participants in the rural and more remote areas, which was not feasible in this study, video-conferencing and transporting equipment, i.e. BP monitors by post or courier may be an option. The participant may require a carer to help with application of the monitor, and instructions may be relayed over a video call to ensure it is applied correctly. In this study, I employed the use of couriers to return the monitor after it was removed, and this facilitated the availability of the monitor as well as prompt results.

Given my observations from the previous chapters, it may be relevant to test this management in the acute setting, where symptoms tend to be worse and an improvement in symptoms could lead to improved rehabilitation outcomes and duration. However as there tends to be spontaneous improvement in symptoms for many in the first few weeks, it will be difficult to distinguish this from the effect of the drug, and it would hinder the crossover design, which is important because of the wide variation in the manifestation of symptoms, and BP profile, between individuals in this population.

This study provided insight about the significance and relation of orthostatic symptoms to daily function. It is apparent that the presence of orthostatic symptoms in the chronic phase of SCI is not easily predicted on the basis of symptoms prior to SCI or the

occurrence of symptoms in the immediate period after an SCI. I also found that the presence and severity of symptoms did not appear to be related to the function in this population.

The importance of a SCI specific database and collaboration with other SCI centres for investigation of symptoms affecting a smaller proportion of the population was also highlighted in this work. Although there was a current database for Australia at the time the studies were conducted, it only collected data from selective specialist units in Australia on incident adult SCI with no follow up data, and data input was not always complete. It is increasingly recognised that standardised registries including epidemiological data and long term follow up of the SCI population is beneficial for improving social and medical outcomes for patients, and for furthering research collaboration.^{125, 126, 128}

A limitation of these conclusions is that participant interpretations are subject to recall bias. To overcome this would require a prospective study of people which began even before they sustained an SCI. Another potential limitation is participation bias, in that only people with symptoms may have been more willing and interested to speak about their symptoms, and thus their experiences may have been over-represented in this trial. To minimise this, simple and brief questions were used, it was explained the intention was to interview anyone willing to give a brief history, and a call back at a more convenient time was offered. Furthermore, there was only a small proportion of responders and a relatively small number of responders, conducted from a single centre, therefore the results of my survey may not be generalisable to the SCI population.

Future Directions

Although I was unable to complete this attempt to develop a new therapy for treatment of orthostatic symptoms observed in patients with SCI, future investigators may still wish to examine this question. I therefore include a report on the difficulties and the limited progress that was made in my study.

Of the four people who entered the treatment phase, one person completed the study with no side effects and provided feedback that symptoms appeared to improve from the time of the washout period thus there was no clear benefit of either treatment arm (symptoms of postural lightheadedness were rated 4 and 2 before and after the first treatment arm, and 3 and 2 before and after the second treatment arm). One person withdrew for personal reasons during the second treatment arm, with no clear benefit or adverse effect with either arm. Another person withdrew during the first treatment arm for side effects of abdominal discomfort, constipation and fatigue, and one person stopped treatment early due to side effects during each treatment arm – increased spasms in the first arm and dry mouth and fatigue in the second arm.

None of the participants took up the offer for clinical follow up for alternative management options, although one made an appointment but did not keep it. As mentioned above, this again illustrates that despite the significance of orthostatic symptoms in these patients, there are barriers to accessing medical care. These participants did not provide reasons for not taking up clinical follow up, but it is possible that they sought medical advice elsewhere.

I was not able to obtain sufficient data from the treatment phase of my study for analysis due to the low numbers of participants, however this is a potential treatment option to examine in a multi-centre study.

6.5. Conclusions

I found a high prevalence of mild orthostatic symptoms in the chronic SCI population, and a small proportion with significant symptoms. However even those with significant symptoms tended not to seek medical advice, therefore it is important for health care workers to screen for symptoms, so as to explore management options if desired. A multi-centre study would be required for future studies on management options, in order to achieve sufficient numbers of participants to assess drug effects.

Chapter 7. General Discussion

SCI represents one of the most devastating chronic conditions, causing significant disability that impacts on independence, quality of life and psychological wellbeing. This results from a range of impairments including motor, sensory and autonomic disturbances.^{111, 112, 118}

Cardiovascular effects of the SCI such as orthostatic hypotension can lead to symptoms such as dizziness, while autonomic dysreflexia can manifest as headaches and sweating and be life threatening; these symptoms can slow rehabilitation, and restrict activity in the community. In the longer term, risk factors for cardiovascular disease, such as elevated BP, glucose intolerance, dyslipidaemia and reduced physical activity, have been observed to be prevalent in the SCI population,^{142-144, 177} and may be sub-optimally managed.¹⁷⁸ In addition, the increased variability of BP, loss of nocturnal dipping and elevated nocturnal pressures are potential contributors to the increasingly recognised cardiovascular disease in this population,¹³⁸⁻¹⁴⁰ and may be potential treatment targets.

This thesis builds on previous work in diurnal BP and urine production in SCI. Although past studies examined diurnal BP in SCI with various characteristics, the prevalence of such abnormalities in groups of people with SCI has only been described according to dipping status in one study.¹⁹⁰ Other prior studies considered the presence or absence of statistical differences between average day and night BPs in groups with or without SCI, whereas this thesis examined the dipping status of each participant and reported on the prevalence of abnormal dipping in each group. This is clinically relevant

because it is recognised in the general population that the individual's dipping status is associated with cardiovascular prognoses. Prior studies focused on data from participants with minimal cardiovascular disease or 'orthostatic dysregulation', and tended to investigate complete SCI, with the focus on the pathophysiology and loss of autonomic function arising from the SCI. Abnormalities in diurnal urine production and symptoms of orthostatic hypotension were also examined in the same population, as this triad has been observed to be present in autonomic failure, in which there is also disruption to the ANS.

The studies contained in this thesis aimed to definitively identify the relationship between diurnal BP, diurnal urine production and orthostatic symptoms and prove that these symptoms could be pharmacologically treated. To achieve these aims, participants in these studies were recruited with minimal exclusion criteria, to characterise the natural history of diurnal variation of BP in a relatively unselected population of people with SCI, and the chronic SCI population managed in the community. The presence of this triad presented a potential treatment option for orthostatic intolerance which this thesis aimed to explore, however was unsuccessful due to difficulties in recruitment.

The main findings were:

- 1) Compared to control groups, there was a high prevalence of abnormal diurnal variation of BP in participants with SCI. The abnormalities were most evident in participants with higher and earlier SCI. The abnormalities improved with time in participants with either a high or low paraplegia. These abnormalities could not be explained simply by the lack of activity or recumbency imposed by SCI.

- 2) Nocturnal hypertension occurred in the absence of day hypertension in SCI.
- 3) Paraplegia was characterised by increased pulse rates compared with controls and chronic tetraplegia.
- 4) There were greater abnormalities in diurnal urine production in SCI compared with controls, and these tended to mirror abnormalities in diurnal BP.
- 5) Orthostatic hypotension and orthostatic intolerance were more prevalent in SCI than controls
- 6) Mild orthostatic intolerance was common in chronic SCI, but relatively few people with significant symptoms had previously sought medical advice, thus questioning for orthostatic intolerance is important during a medical consult to identify significant symptoms, even though it may be the case that patients will not desire to have those symptoms treated.
- 7) Recruiting participants for a crossover drug trial for management of orthostatic intolerance at a single centre did not provide enough participants to complete the study, suggesting that a study of this type would need to be conducted at multiple sites.

7.1. Prevalence of abnormal diurnal variation in blood pressure

By taking together the findings of my studies, it is possible to draw new conclusions about the nature of the haemodynamic changes in SCI. These studies indicate that early SCI is characterised by a loss of diurnal variation in BP, with greater disruption occurring in higher levels of SCI. From the time after injury, abnormalities of diurnal BP remained prevalent in tetraplegia whereas there was an improvement in paraplegia, such that most people with chronic paraplegia had intact diurnal variation of BP. This is consistent with observations in rat models of mid-thoracic SCI where diurnal BP variation returned to normal after both complete and incomplete thoracic SCI.^{263, 264}

My studies also included a control group of patients who were immobilised, predominantly because of orthopaedic injuries. Compared with mobilising controls, immobilisation reduced nocturnal dipping such that the mean group night:day SBP was just within the non-dipper range, but this difference did not reach statistical significance. It should be noted that other factors that also affected the immobilised controls could have affected the changes in diurnal variation compared to the control subjects. These factors might include pain or the disruption inherent to residing in a busy hospital.

Immobilisation alone was insufficient to produce the marked loss of nocturnal dipping which was observed in SCI. Krum et al previously reported on the loss of nocturnal fall in BP in chronic tetraplegia compared with immobilised orthopaedic controls.¹⁸¹ My studies add to Krum's observations by using participants with paraplegia and mobilising

controls as comparators. Moreover, I also studied patients with acute SCI. Thus, I was able to conclude that the shared hospital experiences of immobility and pain were insufficient to explain the marked changes in BP that occur in acute tetraplegia.

7.2. Subgroup comparisons

Although it had previously been suggested that nocturnal dipping of BP was diminished in complete tetraplegia, it has previously been concluded that diurnal variation in BP was intact in incomplete tetraplegia or high paraplegia. My studies provide a new perspective to the latter.

1. Complete and Incomplete tetraplegia

Nitsche's and Curt's group^{161, 180} conducted the only studies of incomplete tetraplegia and concluded that diurnal variation in BP was intact, based on average night pressures being statistically lower than average day pressures for the group, or the individual's average night pressures not exceeding average day pressures. However, in those studies, the average group night:day SBP was 92%, which is in the non-dipper category and thus, the studies did not take into account a more subtle abnormality in diurnal variation. The recognition of the relation of dipping category to cardiovascular prognosis may just have been emerging at the time. Another consideration might be the use of 4 hour windows to represent the day and night. In my studies, the average night:day SBP was in the non-dipper or reverse dipper category for all groups of tetraplegia, including in early and chronic SCI. The data from three of my studies showed numerically higher night:day SBP (more abnormal) in complete than incomplete tetraplegia, although it should be noted that statistical difference was only observed in the retrospective referred population. In chronic SCI, prevalence of dipping in complete tetraplegia (15%) was about half that of incomplete injury (33%), whereas that of reverse dipping (60%) was about twice that of incomplete injury (33%). This

contrasts with much lower prevalence of intact diurnal BP variation in the acute tetraplegia group and in the referred population, where less than a tenth of the group had the normal diurnal variation. Therefore, I concluded that partial disruption of the sympathetic system at the cervical level is sufficient to cause a chronic disruption of diurnal variation. The clinical implication of these findings is that a contribution of abnormal diurnal BP to cardiovascular risk applies to both complete and incomplete tetraplegia.

2. High paraplegia compared with tetraplegia and low paraplegia

The only study of diurnal variation of BP in high paraplegia was conducted by Rosado-Rivera et al, who found the average night:day SBP was 94%, or in other words, was in the non-dipper category, which was reported as indicating the presence of nocturnal dipping.¹⁸³ For participants with high paraplegia, I found that in early SCI, the night:day SBP was not different from tetraplegia, but higher than in controls (Study 2), whereas in chronic SCI, I found the night:day SBP was lower compared with tetraplegia, but not different to controls in chronic SCI (Study 3). The prevalence of abnormal diurnal BP variation in high paraplegia was numerically between that of tetraplegia and low paraplegia in the early SCI, but was much closer to figures for low paraplegia in chronic SCI. Thus, there appears to be an improvement in control of diurnal BP in both high and low paraplegia following traumatic SCI, which is consistent with animal models.^{263, 264} West et al attribute the initial loss of diurnal BP to neurogenic shock, but still had expectations for a persistent loss of nocturnal dipping, given the complete transaction injury in their model causing significant disruption of sympathetic activity. It is unlikely that neurogenic shock explained the changes I observed in my studies of acute

paraplegia as none of the participants with paraplegia met a common definition of neurogenic shock, being $SBP \leq 100$ mmHg and pulse rate ≤ 80 bpm, at baseline. Other explanations for the improvement over time may be related to compensatory neuro-humoral mechanisms including overactivity of residual sympathetic nerve function over T1 to T6, and activation of the RAAS.^{205, 250, 263, 264}

7.3. Nocturnal hypertension

In the general population, night pressures are better predictors of cardiovascular prognosis - and that relationship is independent of 24-hour pressures.^{9, 11, 91} Also, isolated nocturnal hypertension is associated with poorer cardiovascular prognosis, even amongst individuals who are normotensive on ambulatory or clinic pressures.¹⁸⁹ Non-dipping in patients who are normotensive is also associated with worse cardiovascular prognosis.¹⁰

In my studies, I found that participants with SCI had a higher rate of nocturnal hypertension than day hypertension, especially in tetraplegia. It is often supposed that because people with SCI often have lower BPs than able-bodied individuals, they should have lower cardiovascular risk. However, hidden elevated nocturnal pressures and/or non-dipping of BP may be factors that contribute to the elevated cardiovascular risk that has been associated with SCI.^{138, 139, 141, 265} This may be an important topic that would be worth studying in the future.

Another implication of the high rate of reversed diurnal variation is that restricting measurement of BPs to the day will not provide an indication about the possibility that nocturnal pressure may be elevated. The greater prevalence of elevated pressures during the day in paraplegia than tetraplegia is consistent with Groah's observations of greater age adjusted risk of hypertension in paraplegia than tetraplegia.¹⁴¹

Sleep disordered breathing is known to be common in tetraplegia, and sleep apnoea is a contributor to the loss of diurnal variation in BP and elevation of nocturnal BP in the general population. However, in my studies, and within the limits of the data, I did not find an association between sleep disordered breathing and diurnal BP. In the 16 individuals with, and 5 individuals without, sleep apnoea, the average night:day SBP was in the reverse dipper category and was not statistically different. Similarly, in a retrospective review conducted with my colleagues and which included some patients who participated in my studies, it was found that amongst 42 individuals with SCI who underwent ABPM within 6 months of a diagnostic sleep study, there was no association between the diurnal BP abnormalities and severity of sleep disordered breathing.²⁶⁶ Increased sympathetic activity arising from apnoeic arousals are thought to cause elevation in nocturnal BP in the able-bodied population with sleep apnoea. However, sympathetic function is impaired in SCI and this may explain why there was no relationship between sleep apnoea and abnormal diurnal variation in SCI.

7.4. Pulse rate

Diurnal variation in pulse rate was observed for all groups, consistent with previous studies and the expectation that sympathetic, but not parasympathetic function, is affected in SCI. Compared with control participants, pulse rates were higher in both high and low paraplegia with early SCI, but were higher only in low paraplegia with chronic SCI. Pulse rates in chronic tetraplegia were lower than that of controls, but no different to that of controls in acute tetraplegia. These observations confirm the observations of other investigators who found higher clinic and ambulatory HR in paraplegia,^{148, 183, 216} and reduction in resting HR over time.¹⁴⁸

The elevated pulse rates are significant because in the general population, elevated HR has been associated with future hypertension, which is thought to be driven by increased sympathetic tone and arterial stiffness. Evidence for increased sympathetic activity and impaired vagal function,^{183, 217-220} along with arterial stiffness, has been observed in paraplegia.²¹²⁻²¹⁵ In my studies, I found that elevation of pulse rates in paraplegia began soon after SCI and persisted in chronic SCI. Other investigators who studied cardiovascular disease in SCI found hypertension to be more prevalent in paraplegia than tetraplegia.^{141, 177} Thus, this elevation in pulse rate beginning soon after SCI may be a contributing factor to the hypertension in paraplegia which is a risk factor in itself for cardiovascular disease, therefore it is a potential therapeutic target of interest.

7.5. Urine production

In my first study, I observed a loss of nocturnal fall in urine production in patients with SCI who had been referred for management of BP issues. This phenomenon affected all SCI groups. I observed the same phenomenon in my prospective examination of SCI, except in the group with chronic paraplegia. I noted that the loss of nocturnal fall in urine production persisted in the six participants in each of the tetraplegia and paraplegia groups that provided urine measurements at 1 year follow up. However, there was persistence of abnormalities in diurnal urine production in chronic tetraplegia but not chronic paraplegia in Study 3. This suggests that there may be further improvement in diurnal urine production over time from SCI, or it may be that the small numbers contributing to the figures for the one year follow up did not reflect the group characteristics.

There was a weak correlation between night:day SBP and night:day urine output rates in acute tetraplegia, but the same correlation was not observed in acute paraplegia or chronic SCI. However, as a group, those with a dipper BP pattern tended to have a significant fall in night time urine production, whereas those with a reverse dipper pattern tended to have a higher night urine production. (Chapter 5, Study 3, Figure 2) It may be related to imprecision in measurements, or that the extent of change in night and day BP is different from that of urine production leading to the lack of a strong correlation between the two parameters. That there tends to be disruption of diurnal variation of both BP and urine production in the same groups, and what appears to be improvement of both over time in paraplegia but not tetraplegia, consistent with animal

models of thoracic SCI, raises the possibility of common factors affecting both. This may be explained by compensatory neurohormonal mechanisms, fluid shifts and increased physical activity over time leading to changes in the diurnal patterns of both urine production and BP, as discussed above.²⁶⁷⁻²⁶⁹

7.6. Orthostatic hypotension and orthostatic intolerance

As expected, median scores for orthostatic symptoms were lowest in controls and highest in tetraplegia, with both acute and chronic SCI (Studies 2 and 3). Although symptoms improved with time from SCI, orthostatic symptoms are still prevalent in chronic SCI and a small number have significant symptoms. There was a weak correlation of these symptom scores with the diurnal variation of BP, which may be explained by the relatively simple method for assessing symptoms, but the lack of a strong relationship with BP measurements is also consistent with findings of Hubli et al that symptoms of hypotension were not correlated with episodes of hypotension on the ambulatory monitoring.¹⁹¹

The relation of the impaired diurnal variation in BP with urine production have previously been explained by posture dependent fluid shifts, which were thought to contribute to orthostatic BP changes.^{198, 199, 250} Thus, it is suggested that because SCI causes the loss of vascular tone and reduced muscle pump activity, upright posture results in gravity dependent pooling of venous blood. The resulting reduction in central circulating volume leads to activation of humoral systems including the RAAS and ADH to conserve volume while upright. Upon return to the supine position, redistribution of this sequestered fluid increases circulating volume and renal perfusion, thus triggering diuresis. Additionally, ADH secretion does not rise as much as in individuals with intact spinal cord function.¹⁹⁸⁻²⁰⁰ This triad of abnormal diurnal BP and urine production, and orthostatic hypotension is also observed in autonomic failure, albeit that the nocturnal rise in BP in tetraplegia is not as high as in autonomic failure.⁵⁻⁸

The work in this thesis does not definitively confirm the mechanisms for this process but observations of the concurrent abnormalities in diurnal BP and urine production which is most prominent in groups with the most marked symptoms provides support for this mechanism.

7.7. Treatment of orthostatic symptoms

In autonomic failure, the possibility of using short acting nocturnal antihypertensive agents to manage orthostatic intolerance and nocturnal hypertension, in the setting of loss of diurnal variation in BP and urine production, has been proposed and attempted with variable results.^{7, 8, 241, 246} Nocturnal hypertension was identified in 32% (n=17) of the referred subjects (Study 1), all but 2 of whom had tetraplegia, thus in these patients, night pressures were not too low for such treatment.

The drug treatment study was unsuccessful due to a low recruitment rate - only about 5% of those screened entered the treatment phase. Findings from the screening survey revealed:

- A high prevalence (42%) of mild orthostatic symptoms for which further management was not desired.
- A smaller proportion (22%) of participants with significant orthostatic symptoms for which management was desired, but none had sought medical advice about this, and only half chose to participate in the study or seek clinical follow up.
- Other more pressing medical and social factors were listed as reasons against attempting medical management of the orthostatic symptoms, while the level of involvement with assessments also dissuaded some from participating in the study.

Thus, the findings of my studies suggest that although people with SCI should be actively asked about orthostatic symptoms during the medical consult, this questioning is unlikely to lead to a substantial uptake of potential therapies. Moreover, to further

investigate this issue, my findings suggest that a multi-centre study would be required in order to recruit sufficient participants to provide a meaningful result.

7.8. Limitations

Like all clinical research, my studies have a number of limitations. The following are limitations of my studies and how these limitations have been addressed where possible.

- The referred population in Study 1 was retrospectively examined and lacked a control group for comparison of measured parameters. These limitations were addressed by conducting Study 2 and Study 3.
- Although in Study 2 I aimed to prospectively recruit patients who were consecutively admitted to our institution, I did not manage to achieve complete recruitment, thus participation bias could have affected the results of the study. However, those who declined participation did not differ significantly from the study group in age, gender or neurological category of SCI. (Table 7.1)
- Study 2 was subject to an attrition rate of participants of about 50% in each group at the 1 year follow up. An examination of the characteristics of the participants who returned for follow up compared with those who did not revealed a trend towards differences in gender in tetraplegia and symptom scores in paraplegia, but no significant differences in age, gender, neurological category of SCI or baseline BP, urine or symptom scores (Table 7.2). Median baseline symptom scores for those who did and did not complete the study were 3 and 3 for participants with tetraplegia ($p=0.892$), 1 and 3 for those with paraplegia ($p=0.089$), 1 and 3 for immobilised participants ($p=0.185$), and 1 and 0 for controls ($p=0.5753$).

Table 7.1 Comparison of eligible patients with SCI who did and did not consent for Study 2

(a) Age

	Consented		Not consented		p-value
	n	mean	n	mean	
Tetraplegia	47	40.0 ±17.3	19	40.6 ±16.1	0.890
Paraplegia	35	34.4 ±13.9	15	36.1 ±15.8	0.723

Values are mean±sd.

(b) Gender

		Consented	Not consented	p-value
Tetraplegia	Female	5	3	0.680
	Male	42	16	
Paraplegia	Female	7	1	0.407
	Male	28	14	

(c) Neurological category¹²⁹

		Consented	Not consented	p-value
Tetraplegia	AIS A	20	7	0.771
	AIS B	13	5	
	AIS C	7	5	
	AIS D	7	2	
Paraplegia	AIS A	25	11	1.000
	AIS B	4	2	
	AIS C	4	2	
	AIS D	2	0	
All SCI	C1-4, ABC	9	2	0.783
	C5-8, ABC	20	6	
	T1-6, ABC	20	11	
	T7-S5, ABC	13	5	
	Any D	20	10	

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; ABC, AIS A, B or C; Any D, AIS D.

Table 7.2 Comparison of participants who did and did not complete Study 2**(a) Age**

	Completed		Did not complete		p-value
	n	mean	n	mean	
Tetraplegia	19	39.7±17.2	28	40.1±17.7	1.000
Paraplegia	11	40.5±15.7	24	31.6±12.4	0.705
Immobilised	8	31.5±9.7	10	30.4±12.9	1.000
Control	27	35.6±15.3	17	29.0±8.9	0.822

Abbreviations: Immobilised, immobilised controls; Control, mobilising controls. Values are mean±sd.

(b) Gender

		Completed	Did not complete	p-value
Tetraplegia	Female	0	5	0.072
	Male	19	23	
Paraplegia	Female	4	3	0.171
	Male	7	21	
Immobilised	Female	3	1	0.275
	Male	5	9	
Control	Female	14	5	0.143
	Male	13	12	

Abbreviations: Immobilised, immobilised controls; Control, mobilising controls.

(c) Neurological category¹²⁹

		Completed	Did not Complete	p-value
Tetraplegia	AIS A	9	11	0.857
	AIS B	4	9	
	AIS C	3	4	
	AIS D	3	4	
Paraplegia	AIS A	8	17	0.839
	AIS B	1	3	
	AIS C	2	2	
	AIS D	0	2	
All SCI	C1-4, ABC	6	14	0.731
	C5-8, ABC	10	10	
	T1-6, ABC	4	9	
	T7-S5, ABC	7	13	
	Any D	3	6	

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; ABC, AIS A, B or C; Any D, AIS D.

(d) Blood pressure and pulse rates

		Tetraplegia	Paraplegia	Immobilised	Controls
n	Completed	13	10	6	26
	Did not complete	20	16	9	17
<i>Systolic BP (mmHg)</i>					
24h	Completed	110 ±2.4	116 ±2.3	126 ±7.9	116 ±1.9
	Did not complete	113 ±2.7	117 ±1.8	127 ±1.7	119 ±1.7
	p-value	0.998	1.000	1.000	0.990
Day	Completed	109 ±2.6	119 ±3.0	129 ±8.7	122 ±2.1
	Did not complete	112 ±3.2	120 ±2.2	133 ±2.1	125 ±1.9
	p-value	0.981	1.000	0.997	0.992
Night	Completed	112 ±2.5	110 ±2.4	120 ±7.4	105 ±1.8
	Did not complete	112 ±2.9	113 ±2.1	119 ±1.7	107 ±2.2
	p-value	1.000	0.997	1.000	0.987
Night:Day (%)	Completed	103 ±2.1	93 ±2.3	94 ±3.2	86 ±0.9
	Did not complete	100 ±2.1	94 ±2.1	89 ±1.4	86 ±1.2
	p-value	0.937	1.000	0.943	1.000
<i>Diastolic BP (mmHg)</i>					
24h	Completed	60 ±1.6	67 ±2.3	74 ±2.7	68 ±1.3
	Did not complete	64 ±1.4	66 ±1.2	72 ±2.6	70 ±2.1
	p-value	0.796	1.000	1.000	0.978
Day	Completed	60 ±1.5	69 ±2.6	75 ±3.8	73 ±1.4
	Did not complete	65 ±1.6	71 ±1.8	75 ±2.9	76 ±2.2
	p-value	0.672	1.000	1.000	0.905
Night	Completed	59 ±1.7	62 ±2.6	71 ±2.4	58 ±1.3
	Did not complete	62 ±1.5	61 ±1.2	68 ±2.6	58 ±2.4
	p-value	0.917	1.000	0.995	1.000
<i>Pulse rates (bpm)</i>					
24h	Completed	67 ±3.7	84 ±4.2	72 ±6.0	71 ±1.7
	Did not complete	69 ±2.2	83 ±2.4	67 ±2.1	71 ±2.0
	p-value	0.997	1.000	0.989	1.000
Day	Completed	69 ±3.4	88 ±4.1	75 ±6.0	75 ±1.9
	Did not complete	72 ±2.3	89 ±2.7	71 ±1.9	74 ±2.0
	p-value	0.993	1.000	0.996	1.000
Night	Completed	61 ±4.2	75 ±4.7	67 ±7.0	61 ±1.9
	Did not complete	66 ±2.2	74 ±2.5	61 ±1.9	63 ±2.8
	p-value	0.969	1.000	0.976	1.000

Abbreviations: Immobilised, immobilised controls; Controls, mobilising controls. BP, blood pressure; bpm, beats per minute. Values are mean±sem. P-values for comparison of those who did and did not complete the final assessment within each subgroup, using Tukey's Honestly Significant Difference tests for pairwise comparisons and ANOVA.

(e) Urine measures

		Tetraplegia	Paraplegia	Immobilised	Controls
n	Completed	10	9	4	25
	Did not complete	15	19	3	11
<i>Urine production (ml/min)</i>					
Day	Completed	1.2 $\pm$ 0.2	2.1 $\pm$ 0.4	1.6 $\pm$ 0.4	1.5 $\pm$ 0.1
	Did not complete	1.7 $\pm$ 0.2	1.5 $\pm$ 0.2	1.2 $\pm$ 0.0	1.2 $\pm$ 0.1
	p-value	0.623	0.264	0.994	0.959
Night	Completed	1.8 $\pm$ 0.2	1.8 $\pm$ 0.4	1.2 $\pm$ 0.1	0.9 $\pm$ 0.1
	Did not complete	1.8 $\pm$ 0.2	1.7 $\pm$ 0.1	1.3 $\pm$ 0.3	0.9 $\pm$ 0.1
	p-value	1.000	1.000	1.000	1.000

Abbreviations: Immobilised, immobilised controls; Controls, mobilising controls. Values are mean $\pm$ sem. P-values for comparison of those who did and did not complete the final assessment within each subgroup, using Tukey's Honestly Significant Difference tests for pairwise comparisons and ANOVA.

- To provide an indication of the effect of time on studied parameters, I made comparisons between the acute and chronic SCI cohorts. However different sampling methods were used to recruit participants in each study and this may have led to biases.
- The study examined a sample of convenience so my observations may not be representative of the general SCI population. It was conducted through a single centre; however, this is the specialist SCI centre for the state so patients approached were likely representative of the traumatic SCI population in this state. Advertisements were put out to SCI support organisations which allowed a wider range of people with SCI to be reached. There may be a volunteer bias in the SCI or control groups as those with BP abnormalities may be more likely to be interested in participation. Conversely, especially with the SCI groups, it is plausible that those with the worst impact of disordered BP may be too ill to volunteer.
- The symptom score used to assess orthostatic intolerance was rudimentary and served as a simple measure of the presence of symptoms. Regrettably, at the time these studies were planned there was no validated questionnaires for orthostatic hypotension for the SCI population. Validating the symptom score was beyond the scope of my studies.
- It would have been ideal to have the current sleep indices for the SCI population to determine the contribution of sleep apnoea to the diurnal BP, however the demands of clinical care meant that this was not within the scope of the studies for every participant to have a current sleep study.

Chapter 8. Conclusions

The work in this thesis characterises the diurnal BP and urine production in a population referred for BP disorders, and in early and chronic SCI. Diurnal BP was most disrupted and prevalent in patients with clinically significant BP disorders, and in those with acute and higher SCI. Abnormalities persisted in tetraplegia but improved in paraplegia, being no different from controls in the chronic phase. No differences between complete and incomplete tetraplegia were observed. Nocturnal hypertension occurred in tetraplegia in the absence of day hypertension, while elevated pulse rates were observed in paraplegia.

Abnormalities in diurnal urine production mirrored that of diurnal BP, being most disrupted in tetraplegia and in reverse dippers, and least disrupted in chronic paraplegia and dippers, lending support to the idea that these changes are a consequence of postural fluid shifts and humoral compensatory mechanisms (this has not been the case for all previous studies¹⁹²). The apparent improvement in diurnal BP and urine production over time in paraplegia is consistent with observations from animal models of traumatic SCI at the thoracic level. Mild orthostatic intolerance is common in chronic SCI but as a rule, most patients did not have a severe disorder. A single centre study to investigate a drug treatment of orthostatic intolerance was unsuccessful due to low recruitment rates.

Given that cardiovascular disease is recognised to be elevated in the SCI population, and that non-dipping, isolated nocturnal hypertension and elevated HR are individually associated with poorer cardiovascular outcomes in the general population, these are also

potential contributors to cardiovascular disease in SCI, therefore future studies should examine their role in SCI, and whether they are potential therapeutic targets. ABPM in larger populations of SCI with longer follow up for cardiovascular disease would help to determine this, and access to a well maintained national SCI registry with long term follow up data will facilitate such investigations.

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