

The Clinical Relevance of Autonomic Dysfunction, Cerebral Hemodynamics and Sleep Interactions in Individuals Living with SCI

Ji, Wenjie; Nightingale, Tom E.; Zhao, Fei; Fritz, Nora E.; Phillips, Aaron A.; Sisto, Sue Ann; Nash, Mark S.; Badr, M.Safwan; Wecht, Jill M.; Mateika, Jason H.; Panza, Gino S.

DOI:

[10.1016/j.apmr.2023.08.006](https://doi.org/10.1016/j.apmr.2023.08.006)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Ji, W, Nightingale, TE, Zhao, F, Fritz, NE, Phillips, AA, Sisto, SA, Nash, MS, Badr, MS, Wecht, JM, Mateika, JH & Panza, GS 2023, 'The Clinical Relevance of Autonomic Dysfunction, Cerebral Hemodynamics and Sleep Interactions in Individuals Living with SCI', *Archives of Physical Medicine and Rehabilitation*.
<https://doi.org/10.1016/j.apmr.2023.08.006>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Journal Pre-proof

The Clinical Relevance of Autonomic Dysfunction, Cerebral Hemodynamics and Sleep Interactions in Individuals Living with SCI

Wenjie Ji , Tom E. Nightingale PhD , Fei Zhao MPT PhD ,
Nora E. Fritz DPT, PhD , Aaron A. Phillips PhD ,
Sue Ann Sisto PT PhD , Mark S. Nash PhD , M.Safwan Badr MD ,
Jill M. Wecht EdD , Jason H. Mateika PhD , Gino S. Panza PhD ,
On behalf of the American Congress of Rehabilitation Medicine,
Interdisciplinary Special Interest Group, Spinal Cord Injury Physical
Function and Wellness Task Force



PII: S0003-9993(23)00474-4
DOI: <https://doi.org/10.1016/j.apmr.2023.08.006>
Reference: YAPMR 58900

To appear in: *Archives of Physical Medicine and Rehabilitation*

Received date: 31 May 2023
Revised date: 25 July 2023
Accepted date: 6 August 2023

Please cite this article as: Wenjie Ji , Tom E. Nightingale PhD , Fei Zhao MPT PhD , Nora E. Fritz DPT, PhD , Aaron A. Phillips PhD , Sue Ann Sisto PT PhD , Mark S. Nash PhD , M.Safwan Badr MD , Jill M. Wecht EdD , Jason H. Mateika PhD , Gino S. Panza PhD , On behalf of the American Congress of Rehabilitation Medicine, Interdisciplinary Special Interest Group, Spinal Cord Injury Physical Function and Wellness Task Force, The Clinical Relevance of Autonomic Dysfunction, Cerebral Hemodynamics and Sleep Interactions in Individuals Living with SCI, *Archives of Physical Medicine and Rehabilitation* (2023), doi: <https://doi.org/10.1016/j.apmr.2023.08.006>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Inc. on behalf of the American Congress of Rehabilitation Medicine

SPECIAL COMMUNICATION**Clinical Relevance of Autonomic Dysfunction, Cerebral Hemodynamics and Sleep****Interactions in Individuals with Spinal Cord Injury**

Running Title: Autonomic and Cerebral Function in SCI

Wenjie Ji¹, Tom E. Nightingale^{2,3} PhD, Fei Zhao^{4,5} MPT PhD, Nora E. Fritz^{6,7} DPT, PhD,
Aaron A. Phillips^{8,9} PhD, Sue Ann Sisto¹ PT PhD, Mark S. Nash^{10,11} PhD, M.Safwan
Badr^{5,12} MD, Jill M. Wecht^{13,14} EdD, Jason H. Mateika^{5,12,14} PhD, Gino S. Panza^{4,5} PhD

Wenjie Ji: ¹Department of Rehabilitation Science, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY

Tom E. Nightingale: ²School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK. Centre for Trauma Science Research, University of Birmingham, United Kingdom. ³International Collaboration on Repair Discoveries (ICORD), University of British Columbia, Vancouver, British Columbia, Canada.

Fei Zhao: ⁴Department of Health Care Sciences, Program of Occupational Therapy, Wayne State University; ⁵John D. Dingell VA Medical Center, Research and Development

Nora E. Fritz: ⁶Department of Health Care Sciences, Program of Physical Therapy; ⁷Department of Neurology, Wayne State University

Aaron A. Phillips: ⁸Department of Physiology and Pharmacology, Cardiac Sciences, Clinical Neurosciences, Biomedical Engineering, Libin Cardiovascular institute,

Hotchkiss Brain Institute, Cumming School of Medicine, ⁹RESTORE.network, University of Calgary

Sue Ann Sisto: ¹Department of Rehabilitation Science, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY

Mark S. Nash: ¹⁰Department of Neurological Surgery, Physical Medicine & Rehabilitation Physical Therapy; ¹¹Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, FL, USA, 33136

M.Safwan Badr: ¹²Department of Internal Medicine, Wayne State University; ⁵John D. Dingell VA Medical Center, Research and Development

Jill M. Wecht: ¹³James J Peters VA Medical Center Department of Spinal Cord Injury Research; ¹⁴Icahn School of Medicine Mount Sinai, Departments of Rehabilitation and Human Performance, and Medicine Performance, and Medicine

Jason H. Mateika: ⁵John D. Dingell VA Medical Center, Research and Development; ¹⁴Departments of Physiology and ¹²Internal Medicine, Wayne State University, Detroit, MI.

Gino S. Panza: ⁴Department of Health Care Sciences, Program of Occupational Therapy, Wayne State University; ⁵John D. Dingell VA Medical Center, Research and Development

On behalf of the American Congress of Rehabilitation Medicine, Interdisciplinary Special Interest Group, Spinal Cord Injury Physical Function and Wellness Task Force

Disclosure: none

Address for correspondence:

Gino S. Panza, PhD

Wayne State University

Eugene Applebaum College of Pharmacy and Health Sciences

259 Mack Ave

Room 2259

Detroit, MI, 48201

Phone: 313.576.3107

E-mail: fg5726@wayne.edu

ABSTRACT:

A myriad of physiological impairments is seen in individuals following a spinal cord injury (SCI). These include altered autonomic function, cerebral hemodynamics, and sleep. These physiological systems are interconnected and likely insidiously interact leading to secondary complications. These impairments negatively influence quality of life. A comprehensive review of these systems, and their interplay, may improve clinical treatment and the rehabilitation plan of individuals living with SCI. Thus, these physiological measures should receive more clinical consideration. This special communication introduces the under investigated autonomic dysfunction, cerebral hemodynamics, and sleep disorders in people with SCI to stakeholders involved in SCI rehabilitation. We also discuss the linkage between autonomic dysfunction, cerebral

hemodynamics, and sleep disorders and some secondary outcomes are discussed. Recent evidence is synthesized to make clinical recommendations on the assessment and potential management of important autonomic, cerebral hemodynamics, and sleep-related dysfunction in people with SCI. Finally, a few recommendations for clinicians and researchers are provided.

Keywords

Spinal Cord Injuries, Autonomic Nervous System, Cerebrovascular, Cognition, Sleep Apnea Syndromes, Rehabilitation

INTRODUCTION

Individuals who have sustained a spinal cord injury (SCI) suffer from a multitude of impairments. The sequelae of impairments includes autonomic nervous system (ANS) dysfunction, which contributes to a host of disorders, including adverse changes in cardiovascular stability, cerebral hemodynamics, sleep, and cognitive function.¹⁻⁷ These impairments are interconnected and negatively impact physical rehabilitation⁸ detracting from community engagement and quality of life among individuals living with a SCI (Figure 1).^{9,10} Disrupted cardiovascular ANS control can impair oxygen delivery to exercising muscles (i.e., exertional hypotension¹¹) resulting in decreased performance during activities of daily living and potentially limit physical rehabilitation for these individuals.¹² It is important to note that ANS impairments that limit physical rehabilitation are not isolated to the disruption of cardiovascular function, but also impact bladder function¹³ which has shown to detract from participation,⁸ independence

with daily activities,¹⁴ and quality of life in individuals living with a SCI¹⁵ due in part to catheterization considerations, and frequent urinary tract infections.¹⁶

Mounting evidence links sleep disordered breathing (SDB) to ANS dysfunction, cardiovascular instability, and poor adherence to physical rehabilitation in the general and SCI populations.¹⁷ The prevalence of SDB in individuals with a SCI is greater than the prevalence in those without a SCI, especially among individuals with tetraplegia where prevalence may exceed 90%.^{18–20} Recently, it has been suggested undiagnosed and untreated SDB may be confounding rehabilitation research in individuals living with a SCI,¹⁷ due to the known negative impact on autonomic, cardiovascular, cognitive and motor function in uninjured individuals. Although the indicators of autonomic cardiovascular dysfunction differ between those with and without a SCI (i.e., transient episodes of autonomic dysreflexia [AD] vs chronic hypertension), it is contended that SDB negatively impacts autonomic and cerebrovascular function in individuals living with a SCI in a manner similar to that identified in patients with intact spinal cords (See Figure 1).

Thus, following the International Classification of Functioning framework, these impairments to the body structures and functions negatively impact activity and participation in life. Likewise, albeit outside of the scope of this review, promotion of a healthy lifestyle (i.e. smoking cessation, nutrition, alcohol consumption, physical activity), as well as improving social support, may improve autonomic function and facilitate a reduction in disability. Despite the prevalence and impact of ANS dysfunction, the implementation of this knowledge into SCI rehabilitation remains low, perhaps due to a lack of standardized recommendations and screening assessments.

Therefore, the purpose of this special communication is to provide: 1) a brief review of cardiovascular autonomic, cerebrovascular, and sleep dysfunction in individuals with a SCI, 2) explanations on what these impairments may mean for clinicians and researchers, 3) recommendations on how SCI clinicians and researchers can address these concomitant impairments in practice and future studies.

Figure 1: Theoretical Model Overview:

CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Impaired cardiovascular ANS control is prevalent in individuals with SCI at or above the 6th thoracic level ($\geq T6$). This includes AD and orthostatic hypotension (OH). Autonomic dysreflexia is characterized as a sudden rise in blood pressure (BP) due to a sustained spinal sympathetic reflex initiated from afferent signaling below the injury that persists due to the loss of descending inhibitory control.²¹ Orthostatic hypotension, the drop in BP during position change, is often concomitant with persistent hypotension, creating a highly unstable BP profile⁵, which is the clinical expression of impaired descending sympathetic vasomotor control.²²

Prevalence rates for both AD and OH are highly variable because many individuals remain asymptomatic.^{2,23} In a retrospective review of the medical records in 277 Veterans with a SCI, the diagnosis of AD and OH were less than 7%, regardless of the level of the injury.²⁴ However, in individuals with an injury higher than T6, AD has been reported in 48-100% of cases,^{21,25,26} while OH was reported in 36% of individuals with a chronic SCI (C4-T11).²⁷ Additionally, it has been found that 32 of 46 (70%) individuals with a chronic SCI (C2-T12) met OH criteria.²⁸ . Overall, autonomic

dysfunction and BP instability have been shown to negatively impact activities of daily living,²⁹ participation in rehabilitation,^{30,31} length of hospital stays,³² stroke risk^{33,34} and cognitive function.^{2,35} Moreover, given that OH has been identified as a significant predictor of ischemic stroke in the general population,³⁶ the increased prevalence of OH in individuals living with SCI may contribute to the increased prevalence of stroke compared to individuals without a SCI.^{33,34}

Two potential mechanisms that have been suggested³⁷ for the increased stroke risk^{33,34} are 1) the inability to adequately control arterial BP, and 2) impaired cerebral hemodynamics. Although each mechanism is linked physiologically to the other, it is important to distinguish between these two mechanisms in the clinical management of the elevated stroke risk in the SCI population.^{5,38-40} Evidence in humans has linked surges in BP during AD with increases in middle cerebral artery blood flow velocity,⁴¹ increased arterial stiffness,⁴¹⁻⁴⁴ and loss of baroreflex sensitivity⁴⁵ leading to cerebral hypo- and hyper-perfusion.⁴¹ Concomitantly, animal studies report that uncontrolled BP results in increases in arterial stiffness, altered vascular reactivity,⁴⁶ and reduced cardiac contractility.⁷ However, the level of injury does not always correlate strongly with autonomic dysfunction^{27,47,48} and a gold standard for measuring autonomic function remains elusive.⁴⁹ Nevertheless, it is becoming increasingly clear that autonomic dysfunction impacts cerebral hemodynamics,³⁷ and activities related to physical function and rehabilitation.² Albeit evidence is scant, it has been reported that cerebral hemodynamics may play a significant role in the adaptation to OH in individuals with SCI,⁵⁰ suggesting that the relationship between cardiovascular ANS dysfunction and cerebrovascular function may be bidirectional (Figure 1).

CEREBRAL HEMODYNAMICS

Studies investigating cerebrovascular function in individuals living with a SCI have primarily used transcranial Doppler, thus measures of cerebral blood flow velocity (CBFv) are typically reported. With this consideration, the terminology recently suggested by Skow et al. (2022) will be used.⁵¹ Effective regulation of cerebral blood flow is required for appropriate cerebral perfusion, and is accomplished by three primary mechanisms:⁵²

1. cerebral autoregulation (CA); Δ CBF / Δ BP, which can include measurements made during steady-state (sCA) or transient fluctuations in arterial BP (dynamic [dCA]).
2. cerebrovascular reactivity to changes in arterial carbon dioxide; Δ CBF / Δ arterial gas concentration.
3. neurovascular coupling (NVC); Δ CBF / Δ metabolic demand.

There is controversial evidence regarding CBFv in the SCI population with some reporting a decrease or no difference in CBFv compared to individuals without a SCI.^{35,52–55} Evidence shows that an increase in BP induced by the administration of pharmacological agents,^{56,57} or AD⁴¹, all increased resting CBFv in individuals living with a chronic SCI, which may be independent of resting BP.⁵⁶ However, in older individuals without a SCI, hypertension has been shown to reduce CBFv.⁵⁸ The distinct findings across populations may point out a common characteristic shared by individuals with a SCI and the elderly without a SCI, which is that they may all demonstrate impaired CA, and highlight the importance of NVC (See “Cerebral Hemodynamics and Cognition” below).

Conversely, lower BP may not have the same relationship with CBFv. Despite heterogenous evidence, in individuals with a SCI, chronic hypotension has been shown to decrease cerebral perfusion and NVC.^{59,60} The reduced CBFv and cognitive decline may be a result of reduced cerebral oxygenation.⁶¹ This finding is important considering relationships have been found between OH severity and cognitive function⁶² and arterial stiffness⁴⁴ in individuals living with a SCI which is congruent with findings from older adults without a SCI.⁶³ In animal models of SCI, episodes of AD resulted in cerebrovascular endothelial dysfunction and fibrosis⁴¹ and cognitive decline.⁴² However, reduced CBFv may not be the sole factor responsible for impaired cognitive function following SCI for two reasons. First, pharmacological interventions are shown to increase systemic BP and CBFv but fail to improve cognitive performance in hypotensive individuals with a chronic SCI.^{56,57} Second, the administration of pharmacological intervention improves cognitive function, but does not increase CBFv in individuals with a subacute and a chronic SCI with hypotension.³ Furthermore, the relationship between systemic BP and CBFv may be limited to those living with a chronic SCI, given no significant correlations were found between systolic BP changes and CBFv during a sit-up test in newly injured individuals.⁶⁴

These discrepant findings may be due to the heterogeneity of the participants studied in previous experiments as some included individuals with hypotension and chronic injuries⁵⁷ while Phillips et al. conducted their studies with individuals with subacute or chronic injuries.³ Other factors, such as SDB,⁶⁵⁻⁶⁷ psychological distress,⁶⁸ and physical activity⁶⁹ may explain the difference as they may moderate the baseline cardiovascular ANS function, thus influencing cognitive function jointly with the

cerebrovascular system. Methodologically, it is important to highlight that inter-day cerebral blood flow measurements appear to be reliable in those with and without SCI⁷⁰ and that the dose of pharmaceuticals (i.e., midodrine) prior to assessment are important to consider in these studies.⁷¹

The use of other techniques may improve our understanding of the relationship among cardiovascular ANS control, cerebral hemodynamics, and cognition. One such technique is the use of near-infrared spectroscopy (NIRS, or functional NIRS [fNIRS]), a real-time, non-invasive measurement capable of measuring cerebral perfusion, oxygenation, and activation.⁷² The use of NIRS is robust and includes measures of skeletal muscle oxidative capacity in healthy populations as well as those with chronic pathologies,⁷³ including in individuals with SCI.⁷⁴ Likewise, NIRS has been used to evaluate cortical oxygenation during transcranial magnetic stimulation,⁷⁵ visual stimulation,⁷⁶ motor cortex activation,⁷⁷ and lower-body negative pressure.⁶¹ However, the available evidence of brain oxygenation with NIRS remains limited in the SCI population, providing an intriguing area of investigation regarding cardiovascular ANS control, cerebral hemodynamics, and cognition in individuals with a SCI. Ultimately, several mechanisms likely impair cerebral hemodynamics in individuals living with a SCI, which may partially mediate the reduction in cognitive function in this population.

SLEEP

Interest in sleep physiology has grown over the decades. More recently, interest in SDB in individuals living with a SCI^{1,17,19,78–80} has increased exponentially. The prevalence of SDB in individuals with a SCI is greater than those without a SCI,

especially in persons with tetraplegia.^{18–20} The increased prevalence of SDB in individuals with a SCI may be due to a reduction in excitability of brainstem motoneurons that innervate upper airway muscles, leading to narrowing and/or closure of the upper airway that occurs concomitantly with a spinal injury.⁸¹ This modification may be exacerbated by the direct impact of the spinal lesion on breathing function.^{82–86} Sleep disordered breathing, in addition to other sleep disorders (i.e., insomnia, restless leg syndrome, sleep apnea), impact several important outcome measures in the SCI population, including but not limited to diminished quality of life,⁸⁷ increases in pressure injuries and impaired healing,⁸⁸ neurogenic obesity and metabolic syndrome.⁸⁹ Even with the growing interest and understanding of sleep disorders in the SCI population, diagnosis and treatment remain poor.^{90–92}

Sleep and Autonomic Function in Individuals with and without SCI

Sleep disturbances in individuals without a SCI are associated with altered autonomic function⁹³ and impaired vascular function⁹⁴ (in addition to impaired cognition and reduced physical performance^{95,96}). Alterations in autonomic function in individuals with an intact spinal cord and SDB was recently reviewed by Dissanayake et al.⁹³ The authors evaluated 71 studies that examined heart rate variability, BP variability, baroreceptor sensitivity, catecholamine levels, and muscle sympathetic nerve recordings. The evaluation showed that 81% of the published studies reported altered autonomic function in patients with SDB compared to healthy controls and 77% showed a relationship with SDB severity. Collectively, the primary conclusion reached from the evaluation was that SDB leads to increased sympathetic activity and low heart rate variability with less evidence supporting a reduction in parasympathetic activity.

Notwithstanding the limitations of heart rate variability and spontaneous cardio-vagal baroreflex sensitivity for understanding the ANS,⁹⁷⁻⁹⁹ the authors also noted that the evidence may be biased by additional comorbidities associated with SDB.⁹³

The evidence linking sleep and altered autonomic activity in individuals living with a SCI remains scant. However, when individuals with a SCI and SDB are treated, and adhere to continuous positive airway pressure treatment, fewer individuals experience symptoms of AD and orthostatic dizziness.¹⁰⁰ The treatment with continuous positive airway pressure reduces or eliminates the nocturnal hypoxic and hypercapnic episodes, and sleep fragmentation. This is an important finding considering the known negative impact of SDB on vascular function in humans without a SCI⁹⁴ and the known impact of SCI on vascular physiology.⁴⁷ Future studies are needed to confirm findings describing the beneficial effects of continuous positive airway pressure on sleep quality in individuals with a SCI compared to a control group.

Recently, Fang et al. (2018) reported highly variable BP control in a heterogeneous group of individuals with acute and a chronic SCI.¹⁰¹ The authors grouped the participants based on BP responses (or lack thereof) during sleep. The groups included “dippers” (a nocturnal BP dipping more than 10% of daytime value), “non-dippers” (a nocturnal BP dipping from 10% to 0% of daytime value), and “reverse dippers” (a higher night than daytime BP). Participants were also divided based on disease severity (apnea/hypopnea index [events/hour]; mild [5-15], moderate [15-30], severe [> 30]). When the data was analyzed based on the “dipper”, “non-dipper”, and “reverse dipper” categories, differences in nocturnal BP were evident as expected but no differences in heart rate variability were apparent.¹⁰¹ When stratified for severity of

SDB, no differences in BP or heart rate variability were found between groups.

However, when the data were stratified for acute vs chronic SCI, “reverse dippers” with acute injuries were found to have a lower apnea/hypopnea index, and the opposite was found in individuals with chronic SCI, which suggests that chronic SDB may negatively impact autonomic control BP during sleep in individuals with SCI.¹⁰¹

Sleep and Cerebral Hemodynamics in Individuals with and without SCI

Sleep apnea is associated with altered cerebral hemodynamics in individuals with and without a SCI. In uninjured individuals with SDB, lower carotid artery blood flow and increased carotid artery resistance was evident during hyperventilation and carbon dioxide rebreathing trials compared to uninjured individuals without SDB.¹⁰² The degree to which the severity of SDB impacts cerebrovascular reactivity remains equivocal.

Some investigators have reported that disease severity does not impact cerebrovascular reactivity,⁶⁵ while others have reported a linear relationship between vessel stiffness (i.e., mean middle cerebral artery pulsatility index) and total volume of white matter.⁶⁶ In addition, regression analysis showed a significant relationship between age and disease severity with cerebrovascular compliance,⁶⁶ highlighting that the duration and severity of SDB are likely important variables to consider when investigating the impact of SDB on cerebral hemodynamics. Additionally, sleep fragmentation and disease severity were negatively correlated with age- and body-mass-index- adjusted CBFv.⁶⁶ Cognitive function was also assessed and there was no relationship between CBFv and cognitive processes of attention and executive function in people with SDB, but a positive relationship between those two in individuals without

SDB.⁶⁷ This further supports the notion that the chronicity of SDB negatively impacts cerebral hemodynamics and cognitive function in individuals without SCI.

There is a paucity of studies investigating cerebral hemodynamics and sleep in individuals with SCI. The Phillips Lab has studied impaired cerebral hemodynamics in SCI,^{3,103,104} and recently reported impaired cerebrovascular reactivity is associated with SDB in individuals with SCI using many variables as part of a principle component analysis.¹⁰⁵ Specifically, number of oxygen desaturations, amplitude of oxygen desaturations, number of apneic events, and apnea/hypopnea index were strongly correlated to impaired cerebrovascular reactivity. This is important as cerebrovascular reactivity is associated with BP variability, cognitive decline, and white matter hyperintensities.^{106–108} It was concluded that examining SDB in participants with SCI should be considered as part of routine clinical care, which we have also suggested.¹⁷

CLINICAL CONSIDERATIONS

Mitigating the Deleterious Impact of Autonomic Control on the Cardiovascular System in Patients with SCI

Body position and exercise should be considered when modifications in autonomic control of the heart, splanchnic and peripheral vasculature are addressed in individuals with SCI. When individuals suddenly change position (from supine to sitting or standing), there is an insufficient sympathetic response¹⁰⁹ resulting in a rapid pooling of blood in the splanchnic area and the legs.¹¹⁰ This pooling results in a reduction of venous return thereby lowering systemic BP. Symptoms of “light headedness” ensue and if the original position cannot be quickly restored, the person may experience syncope.² This orthostatic intolerance can be mitigated by the use of an abdominal

binder and elastic stockings¹¹¹ and may be combined with medications such as Midodrine,² though this recommendation is limited.¹¹² There is emerging evidence suggesting that spinal cord electrical stimulation may improve OH following SCI,^{113–115} and improve cognitive function.¹¹⁶ Transcutaneous spinal cord stimulation may also improve CBFv and stabilize BP in individuals living with a SCI.¹¹⁴ Likewise, functional electrical stimulation for whole-body exercise was shown to significantly improve NVC in individuals living with a SCI above T4.¹¹⁷ However, more information regarding modality of exercise (e.g., aerobic and resistance exercise) and the impact of exercise intensity is required. These data present several clinically applicable interventions to facilitate appropriate management of BP instability in individuals living with a SCI.

The sequence of events following the positional change and sympathetic failure have important clinical consequences. Although many individuals living with OH remain asymptomatic, it has been reported that OH is associated with prolonged recovery which is coupled with increases in the time spent in physical rehabilitation^{30,31} hospitals.³² In addition, OH is linked to diminished physical, social, and emotional health,²⁹ as well as increased reporting of anxiety and depression.¹¹⁸ Likewise, AD poses several unique challenges, and treatment modalities for AD have remained unchanged since 1997¹¹⁹ with antihypertensive medications as the primary management recommendation. Unfortunately, these medications may exacerbate OH.¹²⁰

Exercise may be an option for the treatment of autonomic dysfunction in individuals with a SCI. Activity-based therapy options include body-weight-supported or robotic-aided locomotor training with or without electrical stimulation, or respiratory

muscle training.¹²¹⁻¹²⁸ However, for those with severe OH, exercise may result in “exertional hypotension”^{11,129} further impeding physical training. Interestingly, a case study reported that modulating BP via epidural spinal cord stimulation in individuals with a SCI had a beneficial impact on exercise performance, further demonstrating the adverse impact of OH on physical performance and thus rehabilitation.¹²⁹ Unfortunately, exercise studies in individuals with a SCI are typically of poor quality for a variety of reasons.^{112,130} Regardless of the available literature, there are several important factors to consider when initiating physical rehabilitation or training, including body position¹³¹ and exercise intensity.¹³² Exercises performed while seated (i.e., upper-body ergometry, wheelchair propulsion), can be used to facilitate, or circumvent, specific signs of autonomic dysfunction. Likewise, standing exercises, such as using a standing table with arm ergometry may be useful to acclimate orthostatic BP control,^{69,133} while supine upper extremity exercise may be useful to increase CBFv.¹³⁴

In general, higher intensity exercise should be employed when possible.¹³⁵ Other clinical approaches to improve physical function during exercise could include medications² and compression garments^{111,136} to prevent hypotension or aquatic training to facilitate venous return.¹³⁷ Exercise intensity is often determined using heart rate expressed as a percentage of maximum. However, this form of standardization is not recommended for individuals with cervical and upper-thoracic SCI due to disrupted cardiac sympathetic control and the usage of antihypertensive medications in this population may attenuate heart rate responses during exercises.¹³⁸ These individuals may want to consider using ratings of perceived exertion (RPE) to regulate relative

exercise intensity.¹³⁹ However, limitations with the use of RPE in individuals with a SCI has been noted in the literature.¹⁴⁰

Cerebral Hemodynamics and Cognition

The effects of cerebral hemodynamics on cognitive function have been studied extensively in those without a SCI.¹⁴¹ However, like autonomic function,¹⁴² recovery- and health-related outcomes of cerebral hemodynamics after SCI have not received adequate attention compared to recovery- and related-comorbidities associated with motor and sensory function. It is reported that up to 60% of individuals with SCI experience some degree of cognitive impairment after injury,⁶ and it may be an under investigated barrier to education, sustainable employment, and independent living for these individuals.^{143,144} However, the prevalence rate of cognitive dysfunction remains uncertain,⁶ and this may be due to the heterogeneity of the injury characteristics and various domains of cognitive function that can be tested.

The relationship between CBFv and cognitive function is complex, likely bidirectional, and not fully understood.¹⁴⁵ A community-based population study indicates that higher CBFv is correlated with better executive function,¹⁴⁵ which may be moderated by other factors. For example, reductions in CBFv (i.e., 20-30%) elicited by caffeine leads to improved executive function.^{146,147} It may be that appropriate temporal and spatial delivery of CBFv, achieved through dynamic control pathways, is necessary for optimal cognitive functioning. Some studies in uninjured individuals report links between NVC,^{148,149} cerebrovascular reactivity,¹⁵⁰ and dCA¹⁵¹ and cognitive function. Reports indicate altered dCA^{35,152} and NVC^{55,153} in people with SCI, but to the authors' knowledge, only NVC has been linked to cognitive dysfunction.^{55,153} More work

is needed to understand if cognitive function is related to dynamic CBFv regulation or cerebrovascular reactivity after SCI. Therefore, the use of standardized and clinically-feasible assessment tools for cognitive function in SCI is warranted. Furthermore, impaired CA during physiological stimuli^{64,152} and cognitive testing³ is reported in individuals with both subacute and chronic SCI. Those with more severe autonomic dysfunction demonstrated a larger extent of impairment in cerebral autoregulation.^{55,64,152} Cognitive performance is also correlated with cerebral hemodynamics following SCI.^{3,4} However to date, there is no valid biomarker of cerebral hemodynamics that can evaluate cognitive function in people with SCI. Evidence in people without a SCI shows that cognition is associated with cerebral vessel contractility and dilation¹⁵⁴ and increased cerebral oxygenation is correlated to improved cognitive performance.¹⁵⁵ Therefore, cerebrovascular reactivity and cerebral oxygenation may be promising biomarkers of cognitive for evaluation during clinical practice.

Sleep

Disruptions in sleep can negatively affect several measures of physical function in uninjured individuals, which impact decision making regarding physical rehabilitation. Decreases in physical activity and self-selected exercise intensity,¹⁵⁶ reductions in peak torque and power during exercise,^{157,158} reduced maximal work and heart rate independent of aerobic capacity,¹⁵⁹ and an increased prevalence of fatigue compared to sleepiness^{160,161} have been reported in individuals with SDB. Importantly, treating SDB with continuous positive airway pressure in these individuals improves self-reported physical activity,¹⁶² peak aerobic capacity,^{163,164} and decrease symptoms of anxiety and

depression.¹⁶⁵ However, much of the literature involved with sleep and SCI has not focused on the potential impact of SDB on physical function. A preliminary framework on how sleep disruptions may negatively impact physical function and health in SCI has previously been published.¹⁷ Although the impact of SDB on autonomic function in individuals with and without an injury is not the same (hypertension vs AD and OH), the impact of SDB on autonomic function is still present. Thus, by logical extension, SDB would impact autonomic function in individuals living with a SCI. Thus, it is contended that SDB is a moderating variable, and not causative. Thus, it is likely that chronic SDB worsens autonomic dysfunction over time in these individuals, potentially confounding the current SCI literature.¹⁷

RECOMMENDATIONS

In summary, these findings underscore the importance of the multidisciplinary team for managing care in persons with acute and chronic SCI. Here it is suggested that additional members need to be added to the team, and that assessments of SDB¹⁷ and cognitive function should become standard practice to improve evaluation and treatment of autonomic dysfunction and mitigate adverse cardiovascular and cognitive function, and impaired sleep. The literature surrounding differences in autonomic dysfunction between those with acute and chronic SCI and those with higher and lower-level lesions is not robust; thus, recommendations are provided that span both the chronicity and severity of SCI.

Recommendation 1. Improved education for health care providers.

Knowledge regarding mechanisms of autonomic dysfunction and downstream effects (Figure 1) is low among nursing and physiotherapy students^{166,167} and likely low among other healthcare professionals, including medical, and physiotherapy and occupational therapy students. Despite the relevance, oral maxillofacial surgeons were also deficient in knowledge about obstructive sleep apnea.¹⁶⁸ This suggests that despite dealings with many healthcare professionals, persons with SCI are not receiving appropriate education about the consequences and potential treatments for autonomic dysfunction. To combat this, it is suggested that providers working with individuals with SCI pursue the following resources:

- (i) Become proficient in the assessments recommended by the ISAFSCI (International Standards to Document Autonomic Function following SCI)⁴⁹
- (ii) Gain an understanding the Apnea-Hypopnea Index (AHI)¹⁶⁹ and treatment options for SDB¹⁷⁰
- (iii) Acquire knowledge regarding the technical and methodological recommendations for measuring and interpreting CBFv¹⁷¹
- (iv) Become familiar with the preliminary framework on how untreated SDB may be confounding rehabilitation research.¹⁷

However, please note that some of these are preliminary recommendations which require additional research to establish a better understanding of what variables are clinically important based on the duration and severity of the lesion as well as other comorbidities.

Recommendation 2. Comprehensive assessment of sleep and cognition should complement motor and sensory assessments.

To establish a baseline, and to determine the interplay of SCI and autonomic dysfunction on everyday life, all persons with a SCI should receive a standard evaluation of sleep from a sleep professional, and cognitive functioning, from a neuropsychologist. Although speech language pathologist or occupational therapist may provide an abbreviated cognitive exam, systematic assessment involving multiple cognitive domains is needed to provide a better understanding of the prevalence of cognitive dysfunction following SCI, and establish patterns in cognitive deficits affected by SCI. Critically, motor-free cognitive function tests have been shown to be reliable when used in individuals with SCI.¹⁷² The data from these evaluations can be used immediately by the rest of the team to challenge cognitive functioning during rehabilitation (physical / occupational therapy) or to develop strategies to manage cognitive dysfunction (speech language pathology). Data from the sleep study can characterize disturbances in sleep, including restless leg syndrome, insomnia, and sleep apnea, which can be used to inform treatment decisions (i.e., prescribe positive airway pressure treatment or other therapies). Regular re-assessment of sleep and cognitive functioning over time is also recommended to determine changes over time and in response to treatment. Further, it is also relevant to evaluate the impact of CBFv, pharmacological agents, and SDB on cognitive function, as they may contribute to a reversible dysfunction.

Recommendation 3. Assessment of Cerebral Hemodynamics.

At present, the assessment of cerebral hemodynamics is not a routine part of the clinical evaluation of persons with SCI. It is critical that technicians are trained in

assessment techniques, such as TCD and fNIRS, and that these are considered for regular clinical care. Due to the cost of such items, an affiliation with research laboratories or hospitals may be beneficial for the research team and clinician alike. For a thorough measurement, and the most clinically realistic approach, one would use TCD with validated beat-to-beat BP monitoring for accurate assessment of CBFv.⁵² The addition of these measurements, and during positional changes in those with SCI, would provide a more comprehensive assessment to improve decision making regarding optimal interventions to facilitate the rehabilitation.

Recommendation 4. Assessment of Autonomic Dysfunction.

Both OH and AD may be under-reported as many individuals remain asymptomatic,^{2,23,26} as such, standardized assessment is warranted. While many sites use tilt-tables to examine OH, recent work suggests that the sit-up test is equally effective, reliable,¹⁷³ and does not require any specialized equipment.¹⁷⁴ However, if objective measures are not possible, there are item banks¹⁷⁵ and questionnaires⁴⁰ available. Appropriate recognition and treatment of AD is critically important to prevent complications such as stroke, seizures, or cardiac arrest.¹⁷⁶ Despite the critical nature of AD, many healthcare providers report low levels of knowledge regarding AD.^{166,167,177,178} Consistent monitoring of BP is critical during the acute and subacute stages of recovery to establish a baseline BP and it improves AD diagnosis.

Healthcare professionals working with individuals with a SCI should be well-versed in acute management of AD, which includes repositioning the person into an upright position, and removing potential triggers, such as tight clothing (i.e., abdominal

binders), blocked catheters, and impacted bowels. If BP does not return to baseline within 5-10 minutes after addressing triggers, pharmacological management should begin.¹¹⁹ This management is in contrast to acute management for OH, which includes repositioning the individual with SCI into a supine position with the feet elevated. In conjunction with standardized assessment, standardized education for persons with SCI and their family members/caregivers is needed to improve carryover from inpatient settings to home settings. This includes education not only on the importance of BP management, but also the elevated risk for stroke. Rehabilitation professionals play an important part of the healthcare team managing persons with SCI; in addition to advocating for standardized assessment and monitoring of autonomic dysfunction, providing education (e.g., stroke prevention, BP management, AD prevention and management, sleep hygiene) to patients and caregivers is critical. Further, rehabilitation professionals should prescribe therapeutic exercise to improve cardiovascular function, cognitive functioning, and sleep quality.

CONCLUSIONS

In this special communication article, up-to-date evidence on cardiovascular autonomic function, cerebral hemodynamics, and sleep in individuals with a SCI is reviewed. Extensive knowledge gaps in the currently available literature was found and provide a working framework on how these variables may be related (Figure 1). Finally, we provide recommendations on how these variables can be incorporated into the clinical assessment of individuals living with a SCI.

The gaps in our current knowledge, scientifically and clinically, highlight the need for improving communication between researchers and clinicians for improving physiological and psychological outcomes following SCI. The combination of rigorous scientific studies, and reports of effective treatment strategies from the clinics, will ultimately lead to improved clinical treatment and research studies aimed at promoting health, and quality of life, and reducing disability in these individuals. The clinical considerations and recommendations on patient assessments and management for potentially existing autonomic cardiovascular, cerebral hemodynamics, and sleep impairments in this article are meant to be the impetus that begins to fill the knowledge gaps surrounding research and clinical treatment for individuals living with SCI. By discussing comprehensive perspectives on these topics, it is hoped to improve the foundational knowledge and communication surrounding these topics, and direct future work for stakeholders involved in SCI rehabilitation.

FIGURE LEGENDS

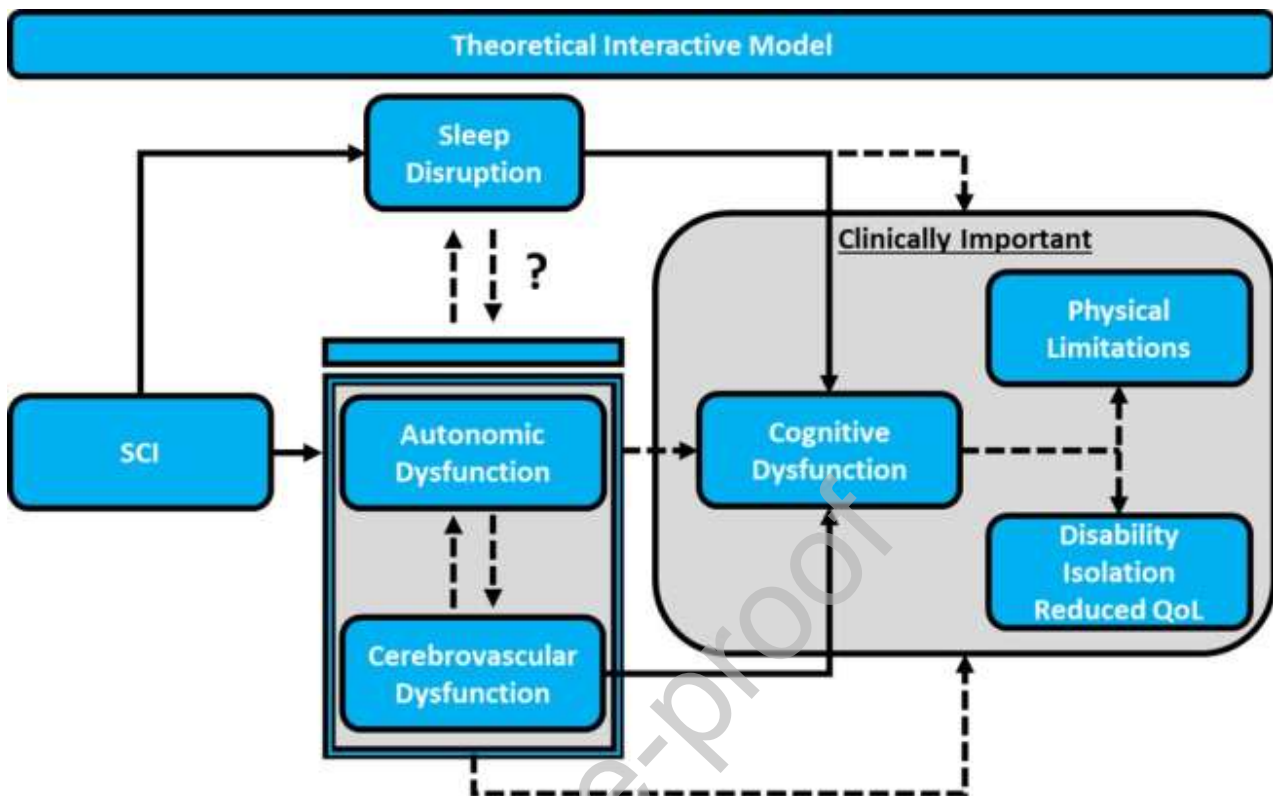


Figure 1: Theoretical interactive model showing the more established relationships (solid lines), and the less established relationships (dashed lines), in the SCI literature. The bidirectional arrows between autonomic and cerebrovascular dysfunction are dashed due to the heterogeneity of the literature between these two variables (see text for full details). However, these two variables in totality are known to have an impact on cognitive function, physical limitations, disability, isolation and changes in quality of life thus indicated by a dashed line to the surrounding gray box. Similarly, sleep has been shown to impact these variables in individuals without a SCI thus also represented by a dashed line to represent the limited evidence in the SCI population. More known relationships exist that reflect the influence of cerebrovascular and sleep disruption on cognitive function, thus represented by solid lines directly to cognitive dysfunction. For clarity, no solid line is drawn to represent the known association between SCI and

physical limitations, disability, isolation, or quality of life. Gray shading implies interrelated variables. SCI = Spinal Cord Injury, QoL = Quality of Life

REFERENCES

- 1 Sankari A, Vaughan S, Bascom A, Martin JL, Badr MS. Sleep-Disordered Breathing and Spinal Cord Injury: A State-of-the-Art Review. *Chest* 2019; **155**: 438–445.
- 2 Wecht JM, Bauman WA. Implication of altered autonomic control for orthostatic tolerance in SCI. *Autonomic Neuroscience* 2018; **209**: 51–58.
- 3 Phillips AA, Warburton DE, Ainslie PN, Krassioukov AV. Regional neurovascular coupling and cognitive performance in those with low blood pressure secondary to high-level spinal cord injury: improved by alpha-1 agonist midodrine hydrochloride. *Journal of Cerebral Blood Flow & Metab* 2014; **34**: 794–801.
- 4 Wecht JM, Weir JP, Katzelnick CG, Wylie G, Eraifej M, Nguyen N *et al.* Systemic and Cerebral Hemodynamic Contribution to Cognitive Performance in Spinal Cord Injury. *Journal of Neurotrauma* 2018; **35**: 2957–2964.
- 5 Sachdeva R, Nightingale TE, Krassioukov AV. The Blood Pressure Pendulum following Spinal Cord Injury: Implications for Vascular Cognitive Impairment. *International Journal of Molecular Science* 2019; **20**. doi:10.3390/ijms20102464.
- 6 Sachdeva R, Gao F, Chan CCH, Krassioukov AV. Cognitive function after spinal cord injury: A systematic review. *Neurology* 2018; **91**: 611–621.
- 7 Squair JW, DeVeau KM, Harman KA, Poormasjedi-Meibod M-S, Hayes B, Liu J *et al.* Spinal Cord Injury Causes Systolic Dysfunction and Cardiomyocyte Atrophy. *Journal of Neurotrauma* 2018; **35**: 424–434.
- 8 Stampas A, Dominick E, Zhu L. Evaluation of functional outcomes in traumatic spinal cord injury with rehabilitation-acquired urinary tract infections: A retrospective study. *The Journal of Spinal Cord Medicine* 2019; **42**: 579–585.
- 9 Wilson CS, DeDios-Stern S, Bocage C, Gray AA, Crudup BM, Russell HF. A systematic review of how spinal cord injury impacts families. *Rehabilitation Psychology* 2022; **67**: 273–303.
- 10 Newman SD, Li C, Krause JS. Social isolation after spinal cord injury: Indicators from the Longitudinal Aging Study. *Rehabilitation Psychology* 2016; **61**: 408–416.
- 11 King ML, Lichtman SW, Pellicone JT, Close RJ, Lisanti P. Exertional hypotension in spinal cord injury. *Chest* 1994; **106**: 1166–1171.

- 12 Nas K, Yazmalar L, Şah V, Aydın A, Öneş K. Rehabilitation of spinal cord injuries. *World Journal of Orthopedics* 2015; **6**: 8–16.
- 13 Hou S, Rabchevsky AG. Autonomic consequences of spinal cord injury. *Comprehensive Physiology* 2014; **4**: 1419–1453.
- 14 Phillips AA, Krassioukov AV. Contemporary Cardiovascular Concerns after Spinal Cord Injury: Mechanisms, Maladaptations, and Management. *Journal of Neurotrauma* 2015; **32**: 1927–1942.
- 15 Theisen KM, Mann R, Roth JD, Pariser JJ, Stoffel JT, Lenherr SM *et al.* Frequency of patient-reported UTIs is associated with poor quality of life after spinal cord injury: a prospective observational study. *Spinal Cord* 2020; **58**: 1274–1281.
- 16 Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC *et al.* Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2010; **50**: 625–663.
- 17 Panza GS, Sutor T, Gee CM, Graco M, McCully K, Chiodo A *et al.* Is Sleep Disordered Breathing Confounding Rehabilitation Outcomes in Spinal Cord Injury Research? *Archives of Physical Medicine and Rehabilitation* 2021; **0**. doi:10.1016/j.apmr.2021.08.015.
- 18 Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC *et al.* Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews* 2017; **34**: 70–81.
- 19 Graco M, McDonald L, Green SE, Jackson ML, Berlowitz DJ. Prevalence of sleep-disordered breathing in people with tetraplegia-a systematic review and meta-analysis. *Spinal Cord* 2021. doi:10.1038/s41393-020-00595-0.
- 20 Sankari A, Bascom A, Oomman S, Badr MS. Sleep disordered breathing in chronic spinal cord injury. *Journal of Clinical Sleep Medicine* 2014; **10**: 65–72.
- 21 Eldahan KC, Rabchevsky AG. Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience* 2018; **209**: 59–70.
- 22 Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. *Circulation* 2009; **119**: 139–146.
- 23 Faaborg PM, Christensen P, Krassioukov A, Laurberg S, Frandsen E, Krogh K. Autonomic dysreflexia during bowel evacuation procedures and bladder filling in subjects with spinal cord injury. *Spinal Cord* 2014; **52**: 494–498.
- 24 Zhu C, Galea M, Livote E, Signor D, Wecht JM. A retrospective chart review of heart rate and blood pressure abnormalities in veterans with spinal cord injury. *The Journal of Spinal Cord Medicine* 2013; **36**: 463–475.
- 25 Krassioukov A, Claydon VE. The clinical problems in cardiovascular control following spinal cord injury: an overview. *Progress in brain research* 2006; **152**: 223–229.

- 26 Kirshblum SC, House JG, O'connor KC. Silent autonomic dysreflexia during a routine bowel program in persons with traumatic spinal cord injury: a preliminary study. *Archives of Physical Medicine and Rehabilitation* 2002; **83**: 1774–1776.
- 27 Claydon VE, Krassioukov AV. Orthostatic Hypotension and Autonomic Pathways after Spinal Cord Injury. *Journal of Neurotrauma*. 2006 Dec;23(12):1713-25. doi: 10.1089/neu.2006.23.1713. PMID: 17184183.
- 28 Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I *et al*. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clinical Autonomic Research* 2011; **21**: 69–72.
- 29 Carlozzi NE, Fyffe D, Morin KG, Byrne R, Tulsy DS, Victorson D *et al*. Impact of blood pressure dysregulation on health-related quality of life in persons with spinal cord injury: development of a conceptual model. *Archives of Physical Medicine and Rehabilitation* 2013; **94**: 1721–1730.
- 30 Barber DB, Rogers SJ, Fredrickson MD, Able AC. Midodrine hydrochloride and the treatment of orthostatic hypotension in tetraplegia: two cases and a review of the literature. *Spinal Cord* 2000; **38**: 109–111.
- 31 Illman A, Stiller K, Williams M. The prevalence of orthostatic hypotension during physiotherapy treatment in patients with an acute spinal cord injury. *Spinal Cord* 2000; **38**: 741–747.
- 32 Blackmer J. Orthostatic hypotension in spinal cord injured patients. *The Journal of Spinal Cord Medicine* 1997; **20**: 212–217.
- 33 Wu J-C, Chen Y-C, Liu L, Chen T-J, Huang W-C, Cheng H *et al*. Increased risk of stroke after spinal cord injury: a nationwide 4-year follow-up cohort study. *Neurology* 2012; **78**: 1051–1057.
- 34 Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury. *Neurology* 2013; **81**: 723–728.
- 35 Saleem S, Vucina D, Sarafis Z, Lee AHX, Squair JW, Barak OF *et al*. Wavelet decomposition analysis is a clinically relevant strategy to evaluate cerebrovascular buffering of blood pressure after spinal cord injury. *American Journal of Physiology-Heart and Circulatory Physiology* 2018; **314**: H1108–H1114.
- 36 Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study... 1987-1996. *Stroke* 2000; **31**: 2307–2313.
- 37 Kim D-I, Tan CO. Alterations in autonomic cerebrovascular control after spinal cord injury. *Autonomic Neuroscience* 2018; **209**: 43–50.
- 38 Wecht JM, Zhu C, Weir JP, Yen C, Renzi C, Galea M. A prospective report on the prevalence of heart rate and blood pressure abnormalities in veterans with spinal cord injuries. *The Journal of Spinal Cord Medicine* 2013; **36**: 454–462.

- 39 Gee CM, Tsang A, Bélanger LM, Ritchie L, Ailon T, Paquette S *et al.* All over the MAP: describing pressure variability in acute spinal cord injury. *Spinal Cord* 2022. doi:10.1038/s41393-022-00802-0.
- 40 Hubli M, Gee CM, Krassioukov AV. Refined assessment of blood pressure instability after spinal cord injury. *American Journal of Hypertension* 2015; **28**: 173–181.
- 41 Phillips AA, Matin N, Jia M, Squair JW, Monga A, Zheng MMZ *et al.* Transient Hypertension after Spinal Cord Injury Leads to Cerebrovascular Endothelial Dysfunction and Fibrosis. *Journal of Neurotrauma* 2018; **35**: 573–581.
- 42 Sachdeva R, Jia M, Wang S, Yung A, Zheng MMZ, Lee AHX *et al.* Vascular-Cognitive Impairment following High-Thoracic Spinal Cord Injury Is Associated with Structural and Functional Maladaptations in Cerebrovasculature. *Journal of Neurotrauma* 2020; **37**: 1963–1970.
- 43 Katzelnick CG, Weir JP, Pinto Zipp G, LaFontaine MF, Bauman WA, Dyson-Hudson TA *et al.* Increased pulse wave velocity in persons with spinal cord injury: the effect of the renin-angiotensin-aldosterone system. *American Journal of Physiology Heart Circulation Physiology* 2021; **320**: H272–H280.
- 44 Currie KD, Hubli M, MacDonald MJ, Krassioukov AV. Associations between arterial stiffness and blood pressure fluctuations after spinal cord injury. *Spinal Cord* 2019; **57**: 1057–1063.
- 45 Draghici AE, Taylor JA. Baroreflex autonomic control in human spinal cord injury: Physiology, measurement, and potential alterations. *Autonomic Neuroscience* 2018; **209**: 37–42.
- 46 Alan N, Ramer LM, Inskip JA, Golbidi S, Ramer MS, Laher I *et al.* Recurrent autonomic dysreflexia exacerbates vascular dysfunction after spinal cord injury. *Spine J* 2010; **10**: 1108–1117.
- 47 West CR, Bellantoni A, Krassioukov AV. Cardiovascular Function in Individuals with Incomplete Spinal Cord Injury: A Systematic Review. *Topics in Spinal Cord Injury Rehabilitation* 2013; **19**: 267–278.
- 48 Wang S, Wecht JM, Legg Ditterline B, Ugiliweneza B, Maher MT, Lombard AT *et al.* Heart rate and blood pressure response improve the prediction of orthostatic cardiovascular dysregulation in persons with chronic spinal cord injury. *Physiological Reports* 2020; **8**: e14617.
- 49 Round AM, Park SE, Walden K, Noonan VK, Townson AF, Krassioukov AV. An evaluation of the International Standards to Document Remaining Autonomic Function after Spinal Cord Injury: input from the international community. *Spinal Cord* 2017; **55**: 198–203.
- 50 Gonzalez F, Chang JY, Banovac K, Messina D, Martinez-Arizala A, Kelley RE. Autoregulation of cerebral blood flow in patients with orthostatic hypotension after spinal cord injury. *Paraplegia* 1991; **29**: 1–7.
- 51 Skow RJ, Brothers RM, Claassen JAHR, Day TA, Rickards CA, Smirl JD *et al.* On the use and misuse of cerebral hemodynamics terminology using transcranial Doppler ultrasound: a call for standardization. *American Journal of Physiology-Heart and Circulatory Physiology* 2022; **323**: H350–H357.

- 52 Phillips AA, Ainslie PN, Krassioukov AV, Warburton DER. Regulation of cerebral blood flow after spinal cord injury. *Journal of Neurotrauma* 2013; **30**: 1551–1563.
- 53 Coombs GB, Vucina D, Caldwell HG, Barak OF, Mijacika T, Lee AHX *et al.* Cerebrovascular function is preserved during mild hyperthermia in cervical spinal cord injury. *Spinal Cord* 2019; **57**: 979–984.
- 54 Saleem S, Sarafis ZK, Lee AHX, Squair JW, Barak OF, Sober-Williams E *et al.* Spinal Cord Disruption Is Associated with a Loss of Cushing-Like Blood Pressure Interactions. *Journal of Neurotrauma* 2019; **36**: 1487–1490.
- 55 Phillips AA, Squair JR, Currie KD, Tzeng Y-C, Ainslie PN, Krassioukov AV. 2015 ParaPan American Games: Autonomic Function, But Not Physical Activity, Is Associated with Vascular-Cognitive Impairment in Spinal Cord Injury. *Journal of Neurotrauma* 2017; **34**: 1283–1288.
- 56 Wecht JM, Weir JP, Katzelnick CG, Chiaravalloti ND, Kirshblum SC, Dyson-Hudson TA *et al.* Double-blinded, placebo-controlled crossover trial to determine the effects of midodrine on blood pressure during cognitive testing in persons with SCI. *Spinal Cord* 2020; **58**: 959–969.
- 57 Wecht JM, Weir JP, Radulovic M, Bauman WA. Effects of midodrine and L-NAME on systemic and cerebral hemodynamics during cognitive activation in spinal cord injury and intact controls. *Physiological Reports* 2016; **4**: e12683.
- 58 Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke* 2007; **38**: 1766–1773.
- 59 Duschek S, Meinhardt J, Schandry R. Reduced cortical activity due to chronic low blood pressure: an EEG study. *Biological Psychology* 2006; **72**: 241–250.
- 60 Duschek S, Schandry R. Cognitive performance and cerebral blood flow in essential hypotension. *Psychophysiology* 2004; **41**: 905–913.
- 61 Houtman S, Serrador JM, Colier WN, Strijbos DW, Shoemaker K, Hopman MT. Changes in cerebral oxygenation and blood flow during LBNP in spinal cord-injured individuals. *Journal of Applied Physiology (1985)* 2001; **91**: 2199–2204.
- 62 Nightingale TE, Zheng MMZ, Sachdeva R, Phillips AA, Krassioukov AV. Diverse cognitive impairment after spinal cord injury is associated with orthostatic hypotension symptom burden. *Physiology & Behavior* 2020; **213**: 112742.
- 63 Bailey TG, Klein T, Meneses AL, Stefanidis KB, Ruediger S, Green DJ *et al.* Cerebrovascular function and its association with systemic artery function and stiffness in older adults with and without mild cognitive impairment. *European Journal of Applied Physiology* 2022; **122**: 1843–1856.
- 64 Vaccaro DH, Weir JP, Noonavath M, Bryce TN, Escalon MX, Huang V *et al.* Orthostatic systemic and cerebral hemodynamics in newly injured patients with spinal cord injury. *Auton Neurosci* 2022; **240**: 102973.

- 65 Ryan CM, Battisti-Charbonney A, Sobczyk O, Mikulis DJ, Duffin J, Fisher JA *et al.* Evaluation of Cerebrovascular Reactivity in Subjects with and without Obstructive Sleep Apnea. *J Stroke Cerebrovasc Dis* 2018; **27**: 162–168.
- 66 Lee W-J, Jung K-H, Nam H-W, Lee Y-S. Effect of obstructive sleep apnea on cerebrovascular compliance and cerebral small vessel disease. *PLoS One* 2021; **16**: e0259469.
- 67 Yan L, Park HR, Kezirian EJ, Yook S, Kim J-H, Joo EY *et al.* Altered regional cerebral blood flow in obstructive sleep apnea is associated with sleep fragmentation and oxygen desaturation. *Journal of Cerebral Blood Flow & Metabolism* 2021; **41**: 2712–2724.
- 68 Wecht JM, Bauman WA. Decentralized cardiovascular autonomic control and cognitive deficits in persons with spinal cord injury. *The Journal of Spinal Cord Medicine* 2013; **36**: 74–81.
- 69 Kyriakides A, Poulidakos D, Galata A, Konstantinou D, Panagiotopoulos E, Chroni E. The effect of level of injury and physical activity on heart rate variability following spinal cord injury. *The Journal of Spinal Cord Medicine* 2019; **42**: 212–219.
- 70 Wecht JM, Weir JP, Bauman WA. Inter-day reliability of blood pressure and cerebral blood flow velocities in persons with spinal cord injury and intact controls. *The Journal of Spinal Cord Medicine* 2017; **40**: 159–169.
- 71 Wecht JM, Rosado-Rivera D, Handrakis JP, Radulovic M, Bauman WA. Effects of Midodrine Hydrochloride on Blood Pressure and Cerebral Blood Flow During Orthostasis in Persons With Chronic Tetraplegia. *Archives of Physical Medicine and Rehabilitation* 2010; **91**: 1429–1435.
- 72 Rashnavadi T, Macnab A, Cheung A, Shadgan A, Kwon BK, Shadgan B. Monitoring spinal cord hemodynamics and tissue oxygenation: a review of the literature with special focus on the near-infrared spectroscopy technique. *Spinal Cord* 2019; **57**: 617–625.
- 73 Hamaoka T, McCully KK, Quaresima V, Yamamoto K, Chance B. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. *Journal of Biomedical Optics* 2007; **12**: 062105.
- 74 Erickson ML, Ryan TE, Young H-J, McCully KK. Near-infrared assessments of skeletal muscle oxidative capacity in persons with spinal cord injury. *European Journal of Applied Physiology* 2013; **113**: 2275–2283.
- 75 Sun X, Long H, Zhao C, Duan Q, Zhu H, Chen C *et al.* Analgesia-enhancing effects of repetitive transcranial magnetic stimulation on neuropathic pain after spinal cord injury: An fNIRS study. *Restorative Neurology and Neuroscience* 2019; **37**: 497–507.
- 76 Ochiai H, Song C, Ikei H, Imai M, Miyazaki Y. Effects of Visual Stimulation with Bonsai Trees on Adult Male Patients with Spinal Cord Injury. *International Journal of Environmental Research and Public Health* 2017; **14**: E1017.
- 77 Koenraadt KLM, Duysens J, Rijken H, van Nes IJW, Keijsers NLW. Preserved foot motor cortex in patients with complete spinal cord injury: a functional near-infrared spectroscopic study. *Neurorehabilitation and Neural Repair* 2014; **28**: 179–187.

- 78 Sankari A, Martin JL, Badr MS. Sleep Disordered Breathing and Spinal Cord Injury: Challenges and Opportunities. *Current Sleep Medicine Reports* 2017; **3**: 272–278.
- 79 Chiodo AE, Sitrin RG, Bauman KA. Sleep disordered breathing in spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine* 2016; **39**: 374–382.
- 80 Berlowitz DJ, Brown DJ, Campbell DA, Pierce RJ. A Longitudinal Evaluation of Sleep and Breathing in the First Year After Cervical Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation* 2005; **86**: 1193–1199.
- 81 Morrell MJ, Badr MS. Effects of NREM sleep on dynamic within-breath changes in upper airway patency in humans. *Journal of Applied Physiology* 1998; **84**: 190–199.
- 82 Golder FJ, Reier PJ, Bolser DC. Altered respiratory motor drive after spinal cord injury: supraspinal and bilateral effects of a unilateral lesion. *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience* 2001; **21**: 8680–8689.
- 83 Manning HL, Brown R, Scharf SM, Leith DE, Weiss JW, Weinberger SE *et al.* Ventilatory and P0.1 response to hypercapnia in quadriplegia. *Respiration Physiology* 1992; **89**: 97–112.
- 84 Bascom AT, Sankari A, Goshgarian HG, Badr MS. Sleep onset hypoventilation in chronic spinal cord injury. *Physiological Reports* 2015; **3**. doi:10.14814/phy2.12490.
- 85 Wijesuriya NS, Gainche L, Jordan AS, Berlowitz DJ, LeGuen M, Rochford PD *et al.* Genioglossus reflex responses to negative upper airway pressure are altered in people with tetraplegia and obstructive sleep apnoea. *Journal of Physiology* 2018; **596**: 2853–2864.
- 86 Schilero GJ, Spungen AM, Bauman WA, Radulovic M, Lesser M. Pulmonary function and spinal cord injury. *Respiratory Physiology & Neurobiology* 2009; **166**: 129–141.
- 87 Shafazand S, Anderson KD, Nash MS. Sleep Complaints and Sleep Quality in Spinal Cord Injury: A Web-Based Survey. *Journal of Clinical Sleep Medicine* 2019; **15**: 719–724.
- 88 Weintraub SJ, Chen SX. A potential widespread and important role for sleep-disordered breathing in pressure injury development and delayed healing among those with spinal cord injury. *Spinal Cord* 2020; **58**: 626–629.
- 89 Kryger MA, Chehata VJ. Relationship Between Sleep-Disordered Breathing and Neurogenic Obesity in Adults With Spinal Cord Injury. *Topics in Spinal Cord Injury Rehabilitation* 2021; **27**: 84–91.
- 90 Sankari A, Martin JL, Badr M. A retrospective review of sleep-disordered breathing, hypertension and cardiovascular diseases in spinal cord injury patients. *Spinal Cord* 2015; **53**: 496–497.
- 91 Burns SP, Kapur V, Yin KS, Buhner R. Factors associated with sleep apnea in men with spinal cord injury: a population-based case-control study. *Spinal Cord* 2001; **39**: 15–22.
- 92 Graco M, Berlowitz DJ, Green SE. Understanding the clinical management of obstructive sleep apnoea in tetraplegia: a qualitative study using the theoretical domains framework. *BMC Health Services Research* 2019; **19**: 405.

- 93 Dissanayake HU, Bin YS, Ucak S, de Chazal P, Sutherland K, Cistulli PA. Association between autonomic function and obstructive sleep apnea: A systematic review. *Sleep Medicine Reviews* 2021; **57**: 101470.
- 94 Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nature Reviews Cardiology* 2010; **7**: 677–685.
- 95 Vitacca M, Paneroni M, Braghiroli A, Balbi B, Aliani M, Guido P *et al.* Exercise capacity and comorbidities in patients with obstructive sleep apnea. *Journal of Clinical Sleep Medicine* 2020; **16**: 531–538.
- 96 Chennaoui M, Arnal PJ, Sauvet F, Léger D. Sleep and exercise: a reciprocal issue? *Sleep Medicine Reviews* 2015; **20**: 59–72.
- 97 Hayano J, Yuda E. Pitfalls of assessment of autonomic function by heart rate variability. *Journal of Physiological Anthropology* 2019; **38**: 3.
- 98 Heathers JAJ. Everything Hertz: methodological issues in short-term frequency-domain HRV. *Frontiers in Physiology* 2014 May 7;5:177. doi: 10.3389/fphys.2014.00177. PMID: 24847279; PMCID: PMC4019878.
- 99 Lipman RD, Salisbury JK, Taylor JA. Spontaneous indices are inconsistent with arterial baroreflex gain. *Hypertension* 2003; **42**: 481–487.
- 100 Brown JP, Bauman KA, Kurili A, Rodriguez GM, Chiodo AE, Sitrin RG *et al.* Positive airway pressure therapy for sleep-disordered breathing confers short-term benefits to patients with spinal cord injury despite widely ranging patterns of use. *Spinal Cord* 2018; **56**: 777–789.
- 101 Fang X, Goh MY, O’Callaghan C, Berlowitz D. Relationship between autonomic cardiovascular control and obstructive sleep apnoea in persons with spinal cord injury: a retrospective study. *Spinal Cord Series and Cases* 2018; **4**: 29.
- 102 Loeppky JA, Miranda FG, Eldridge MW. Abnormal cerebrovascular responses to CO₂ in sleep apnea patients. *Sleep* 1984; **7**: 97–109.
- 103 Phillips AA, Krassioukov AV, Ainslie PN, Cote AT, Warburton DER. Increased central arterial stiffness explains baroreflex dysfunction in spinal cord injury. *Journal of Neurotrauma* 2014; **31**: 1122–1128.
- 104 Phillips AA, Krassioukov AV, Ainslie PN, Warburton DER. Perturbed and spontaneous regional cerebral blood flow responses to changes in blood pressure after high-level spinal cord injury: the effect of midodrine. *Journal of Applied Physiology (1985)* 2014; **116**: 645–653.
- 105 Squair JW, Lee AHX, Sarafis ZK, Coombs G, Barak O, Cragg JJ *et al.* Sleep-disordered breathing is associated with brain vascular reactivity in spinal cord injury. *Neurology* 2019; **93**: e2181–e2191.
- 106 Kim D, Hughes TM, Lipford ME, Craft S, Baker LD, Lockhart SN *et al.* Corrigendum: Relationship between cerebrovascular reactivity and cognition among people with risk of cognitive decline. *Frontiers in Physiology* 2022; **13**: 1020999.

- 107 Ni L, Zhang B, Yang D, Qin R, Xu H, Ma J *et al.* Lower Cerebrovascular Reactivity Contributed to White Matter Hyperintensity-Related Cognitive Impairment: A Resting-State Functional MRI Study. *Journal of Magnetic Resonance Imaging* 2021; **53**: 703–711.
- 108 Sible IJ, Jang JY, Dutt S, Yew B, Alitin JPM, Li Y *et al.* Older Adults With Higher Blood Pressure Variability Exhibit Cerebrovascular Reactivity Deficits. *American Journal of Hypertension* 2023; **36**: 63–68.
- 109 Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *The American Journal of Medicine* 2007; **120**: 841–847.
- 110 Chao CYL, Cheing GLY. Orthostatic Hypotension for People with Spinal Cord Injuries. *Hong Kong Physiotherapy Journal* 2008; **26**: 51–58.
- 111 Vallbona C, Spencer WA, Cardus D, Dale JW. Control of orthostatic hypotension of quadriplegic patients with a pressure suite. *Archives of Physical Medicine and Rehabilitation* 1963; **44**: 7–18.
- 112 Krassioukov A, Eng JJ, Warburton DE, Teasell R, Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of the management of orthostatic hypotension after spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 2009; **90**: 876–885.
- 113 West CR, Phillips AA, Squair JW, Williams AM, Walter M, Lam T *et al.* Association of Epidural Stimulation With Cardiovascular Function in an Individual With Spinal Cord Injury. *JAMA Neurology* 2018; **75**: 630–632.
- 114 Phillips AA, Squair JW, Sayenko DG, Edgerton VR, Gerasimenko Y, Krassioukov AV. An Autonomic Neuroprosthesis: Noninvasive Electrical Spinal Cord Stimulation Restores Autonomic Cardiovascular Function in Individuals with Spinal Cord Injury. *Journal of Neurotrauma* 2018; **35**: 446–451.
- 115 Squair JW, Gautier M, Mahe L, Soriano JE, Rowald A, Bichat A *et al.* Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury. *Nature* 2021; **590**: 308–314.
- 116 Darrow D, Balsler D, Netoff TI, Krassioukov A, Phillips A, Parr A *et al.* Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury. *Journal of Neurotrauma* 2019; **36**: 2325–2336.
- 117 Ozturk ED, Lapointe MS, Kim D-I, Hamner JW, Tan CO. Effect of 6-Month Exercise Training on Neurovascular Function in Spinal Cord Injury. *Medicine & Science in Sports & Exercise* 2021; **53**: 38–46.
- 118 Craig A, Guest R, Tran Y, Middleton J. Cognitive Impairment and Mood States after Spinal Cord Injury. *Journal of Neurotrauma* 2017; **34**: 1156–1163.
- 119 Consortium for Spinal Cord Medicine. Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities. *The Journal of Spinal Cord Medicine* 2002; **25 Suppl 1**: S67-88.

- 120 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
- 121 Schilero GJ, Bauman WA, Radulovic M. Traumatic Spinal Cord Injury: Pulmonary Physiologic Principles and Management. *Clinics in Chest Medicine* 2018; **39**: 411–425.
- 122 Field-Fote EC, Roach KE. Influence of a Locomotor Training Approach on Walking Speed and Distance in People With Chronic Spinal Cord Injury: A Randomized Clinical Trial. *Physical Therapy* 2011; **91**: 48–60.
- 123 Fritz SL, Merlo-Rains AM, Rivers ED, Peters DM, Goodman A, Watson ET *et al.* An intensive intervention for improving gait, balance, and mobility in individuals with chronic incomplete spinal cord injury: a pilot study of activity tolerance and benefits. *Archives of Physical Medicine and Rehabilitation* 2011; **92**: 1776–1784.
- 124 Harkema SJ, Schmidt-Read M, Lorenz DJ, Edgerton VR, Behrman AL. Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using locomotor training-based rehabilitation. *Archives Of Physical Medicine And Rehabilitation* 2012; **93**: 1508–1517.
- 125 Jones ML, Harness E, Denison P, Tefertiller C, Evans N, Larson CA. Activity-based Therapies in Spinal Cord Injury:: Clinical Focus and Empirical Evidence in Three Independent Programs. *Topics in Spinal Cord Injury Rehabilitation* 2012; **18**: 34–42.
- 126 Yang JF, Musselman KE, Livingstone D, Brunton K, Hendricks G, Hill D *et al.* Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. *Neurorehabilitation and Neural Repair* 2014; **28**: 314–324.
- 127 Hornby TG, Reisman DS, Ward IG, Scheets PL, Miller A, Haddad D *et al.* Clinical Practice Guideline to Improve Locomotor Function Following Chronic Stroke, Incomplete Spinal Cord Injury, and Brain Injury. *Journal of Neurologic Physical Therapy*. 2020 Jan;44(1):49-100. doi: 10.1097/NPT.0000000000000303. PMID: 31834165.
- 128 Gollie JM, Guccione AA, Keyser RE, Chin LMK, Panza GS, Herrick JE. Walking endurance, muscle oxygen extraction, and perceived fatigability after overground locomotor training in incomplete spinal cord injury: A pilot study. *The Journal of Spinal Cord Medicine* 2020; **0**: 1–9.
- 129 Nightingale TE, Walter M, Williams AMM, Lam T, Krassioukov AV. Ergogenic effects of an epidural neuroprosthesis in one individual with spinal cord injury. *Neurology* 2019; **92**: 338–340.
- 130 van der Scheer JW, Martin Ginis KA, Ditor DS, Goosey-Tolfrey VL, Hicks AL, West CR *et al.* Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology* 2017; **89**: 736–745.
- 131 Baydur A, Adkins RH, Milic-Emili J. Lung mechanics in individuals with spinal cord injury: effects of injury level and posture. *Journal Of Applied Physiology* 2001; **90**: 405–411.

- 132 Solinsky R, Draghici A, Hamner JW, Goldstein R, Taylor JA. High-intensity, whole-body exercise improves blood pressure control in individuals with spinal cord injury: A prospective randomized controlled trial. *PLOS ONE* 2021; **16**: e0247576.
- 133 Lee YH, Lee JH, Kim SH, Yi D, Oh KJ, Kim JH *et al.* Hemodynamic Adaptations to Regular Exercise in People With Spinal Cord Injury. *Annals of Rehabilitation Medicine* 2017; **41**: 25–33.
- 134 Inskip JA, Ravensbergen HRJC, Sahota IS, Zawadzki C, McPhail LT, Borisoff JF *et al.* Dynamic wheelchair seating positions impact cardiovascular function after spinal cord injury. *PLoS One* 2017; **12**: e0180195.
- 135 Vivodtzev I, Taylor JA. Cardiac, Autonomic, and Cardiometabolic Impact of Exercise Training in Spinal Cord Injury: A QUALITATIVE REVIEW. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2021; **41**: 6–12.
- 136 Hart N, Laffont I, de la Sota AP, Lejaille M, Macadou G, Polkey MI *et al.* Respiratory effects of combined truncal and abdominal support in patients with spinal cord injury. *Archives Of Physical Medicine And Rehabilitation* 2005; **86**: 1447–1451.
- 137 Thomaz S, Beraldo P, Mateus S, Horan T, Leal JC. Effects of partial isothermic immersion on the spirometry parameters of tetraplegic patients. *Chest* 2005; **128**: 184–189.
- 138 Forton K, Lamotte M, Gillet A, Chaumont M, van de Borne P, Faoro V. Beta-Adrenergic Receptor Blockade Effects on Cardio-Pulmonary Exercise Testing in Healthy Young Adults: A Randomized, Placebo-Controlled Trial. *Sports Medicine Open* 2022; **8**: 150.
- 139 Hutchinson MJ, Paulson TAW, Leicht CA, Bennett H, Eston R, Goosey-Tolfrey VL. Oxygen uptake and heart rate responses to 4 weeks of RPE-guided handcycle training. *European Journal of Applied Physiology* 2023. doi:10.1007/s00421-023-05210-7.
- 140 Hutchinson MJ, Goosey-Tolfrey VL. Rethinking aerobic exercise intensity prescription in adults with spinal cord injury: time to end the use of ‘moderate to vigorous’ intensity? *Spinal Cord* 2022; **60**: 484–490.
- 141 Stroobant N, Vingerhoets G. Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review. *Neuropsychology Review* 2000; **10**: 213–231.
- 142 Alexander M. It’s time to focus on autonomic function after spinal cord injury. *Spinal Cord Series and Cases* 2017; **3**: 17082.
- 143 Rossignol S, Schwab M, Schwartz M, Fehlings MG. Spinal cord injury: time to move? *Journal of Neuroscience* 2007; **27**: 11782–11792.
- 144 Wong AWK, Chen C, Baum MC, Heaton RK, Goodman B, Heinemann AW. Cognitive, Emotional, and Physical Functioning as Predictors of Paid Employment in People With Stroke, Traumatic Brain Injury, and Spinal Cord Injury. *The American Journal of Occupational Therapy* 2019; **73**: 7302205010p1-7302205010p15.

- 145 Leeuwis AE, Smith LA, Melbourne A, Hughes AD, Richards M, Prins ND *et al.* Cerebral Blood Flow and Cognitive Functioning in a Community-Based, Multi-Ethnic Cohort: The SABRE Study. *Frontiers in Aging Neuroscience* 2018; **10**: 279.
- 146 Kim H, Kang SH, Kim SH, Kim SH, Hwang J, Kim J-G *et al.* Drinking coffee enhances neurocognitive function by reorganizing brain functional connectivity. *Scientific Reports* 2021; **11**: 14381.
- 147 Addicott MA, Yang LL, Peiffer AM, Burnett LR, Burdette JH, Chen MY *et al.* The effect of daily caffeine use on cerebral blood flow: How much caffeine can we tolerate? *Human Brain Mapping* 2009; **30**: 3102–3114.
- 148 Li W, Qu G, Huo C, Hu X, Xu G, Li H *et al.* Identifying Cognitive Impairment in Elderly Using Coupling Functions Between Cerebral Oxyhemoglobin and Arterial Blood Pressure. *Frontiers in Aging Neuroscience* 2022; **14**: 904108.
- 149 Ni M-H, Li Z-Y, Sun Q, Yu Y, Yang Y, Hu B *et al.* Neurovascular decoupling measured with quantitative susceptibility mapping is associated with cognitive decline in patients with type 2 diabetes. *Cerebral Cortex* 2022; bhac422.
- 150 Chen W-T, Chi N-F, Cheng H-M, Ko Y-T, Chuang S-Y, Pan W-H *et al.* Associations Between Cerebral Vasoreactivity and Cognitive Function in the Middle-Aged Non-Demented Population. *Journal of Alzheimer's Disease* 2022; **86**: 679–690.
- 151 S M, M S, S S, K Y, Jm H, Dm L-J *et al.* Vascular health across young adulthood and midlife cerebral autoregulation, gait, and cognition. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2021; **17**. doi:10.1002/alz.12246.
- 152 Sahota IS, Ravensbergen HRJC, McGrath MS, Claydon VE. Cerebrovascular responses to orthostatic stress after spinal cord injury. *Journal of Neurotrauma* 2012; **29**: 2446–2456.
- 153 Squair JW, Lee AH, Sarafis ZK, Chan F, Barak OF, Dujic Z *et al.* Network analysis identifies consensus physiological measures of neurovascular coupling in humans. *Journal of Cerebral Blood Flow & Metabolism* 2020; **40**: 656–666.
- 154 Catchlove SJ, Parrish TB, Chen Y, Macpherson H, Hughes ME, Pipingas A. Regional Cerebrovascular Reactivity and Cognitive Performance in Healthy Aging. *Journal of Neurology & Experimental Neuroscience* 2018; **12**: 1179069518785151.
- 155 Mekari S, Fraser S, Bosquet L, Bonn ery C, Labelle V, Pouliot P *et al.* The relationship between exercise intensity, cerebral oxygenation and cognitive performance in young adults. *European Journal of Applied Physiology* 2015; **115**: 2189–2197.
- 156 Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Benedict C, Lehnert H *et al.* Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. *The American Journal Of Clinical Nutrition* 2009; **90**: 1476–1482.

- 157 Bulbulian R, Heaney JH, Leake CN, Sucec AA, Sjöholm NT. The effect of sleep deprivation and exercise load on isokinetic leg strength and endurance. *European Journal Of Applied Physiology And Occupational Physiology* 1996; **73**: 273–277.
- 158 Legg SJ, Patton JF. Effects of sustained manual work and partial sleep deprivation on muscular strength and endurance. *European Journal Of Applied Physiology And Occupational Physiology* 1987; **56**: 64–68.
- 159 Antunes BM, Campos EZ, Parmezani SS, Santos RV, Franchini E, Lira FS. Sleep quality and duration are associated with performance in maximal incremental test. *Physiology & Behavior* 2017; **177**: 252–256.
- 160 Bailes S, Libman E, Baltzan M, Grad R, Kassissia I, Creti L *et al.* Fatigue: The forgotten symptom of sleep apnea. *J Journal of Psychosomatic Research* 2011; **70**: 346–354.
- 161 Puri S, Herrick JE, Collins JP, Aldhahi M, Baattaiah B. Physical functioning and risk for sleep disorders in US adults: results from the National Health and Nutrition Examination Survey 2005-2014. *Public Health* 2017; **152**: 123–128.
- 162 Stevens D, Loffler KA, Buman MP, Dunstan DW, Luo Y, Lorenzi-Filho G *et al.* CPAP increases physical activity in obstructive sleep apnea with cardiovascular disease. *Journal of Clinical Sleep Medicine* 2020. doi:10.5664/jcsm.8792.
- 163 Fletcher HV, Pan Cho PS, Lee Loong S, Estrada-Petrocelli L, Patel AS, Birring SS *et al.* Effect of continuous positive airway pressure on maximal exercise capacity in patients with obstructive sleep apnea: a systematic review and meta-analysis. *Journal of Clinical Sleep Medicine* 2020. doi:10.5664/jcsm.8686.
- 164 Zota IM, Stătescu C, Sascău RA, Roca M, Gavril RS, Vasilcu TF *et al.* CPAP Effect on Cardiopulmonary Exercise Testing Performance in Patients with Moderate-Severe OSA and Cardiometabolic Comorbidities. *Medicina (Kaunas)* 2020; **56**. doi:10.3390/medicina56020080.
- 165 Lundetræ RS, Saxvig IW, Lehmann S, Bjorvatn B. Effect of continuous positive airway pressure on symptoms of anxiety and depression in patients with obstructive sleep apnea. *Sleep and Breathing* 2021; **25**: 1277–1283.
- 166 Strčić N, Markić D. The knowledge about autonomic dysreflexia among nursing and physiotherapy students. *The Journal of Spinal Cord Medicine* 2019; **42**: 791–796.
- 167 Tederko P, Ugniewski K, Bobecka-Wesołowska K, Tarnacka B. What do physiotherapists and physiotherapy students know about autonomic dysreflexia? *The Journal of Spinal Cord Medicine* 2021; **44**: 418–424.
- 168 Chadha S, Inglehart MR, Shelgikar A, Stanley JJ, Aronovich S. OMS residents' obstructive sleep apnea-related education, knowledge, and professional behavior: A national survey. *Journal of Dental Education*; 2023 Apr;87(4):441-453. doi: 10.1002/jdd.13146. Epub 2022 Nov 30. PMID: 36449210.

- 169 Understanding the Apnea-Hypopnea Index (AHI). Sleep Foundation. 2021. <https://www.sleepfoundation.org/sleep-apnea/ahi> (accessed 9 May2023).
- 170 Pavwoski P, Shelgikar AV. Treatment options for obstructive sleep apnea. *Neurology: Clinical Practice* 2017; **7**: 77–85.
- 171 Phillips AA, Chan FH, Zheng MMZ, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. *Journal of Cerebral Blood Flow & Metabolism* 2016; **36**: 647–664.
- 172 Nightingale TE, Lim CAR, Sachdeva R, Zheng MMZ, Phillips AA, Krassioukov A. Reliability of Cognitive Measures in Individuals With a Chronic Spinal Cord Injury. *PM R* 2019; **11**: 1278–1286.
- 173 Currie KD, Wong SC, Warburton DE, Krassioukov AV. Reliability of the sit-up test in individuals with spinal cord injury. *The Journal of Spinal Cord Medicine* 2015; **38**: 563–566.
- 174 Oyake K, Murayama J, Tateishi T, Mochida A, Matsumoto M, Tsujikawa M *et al.* Comparison of the sit-up test and head-up tilt test for assessing blood pressure and hemodynamic responses in healthy young individuals. *Blood Pressure Monitoring* 2022; **27**: 79–86.
- 175 Carlozzi NE, Kallen MA, Morin KG, Fyffe DC, Wecht JM. Item Banks for Measuring the Impact of Blood Pressure Dysregulation on Health-Related Quality of Life in Persons with Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation* 2023; : S0003-9993(23)00288–5.
- 176 Cowan H, Lakra C, Desai M. Autonomic dysreflexia in spinal cord injury. *BMJ* 2020; **371**: m3596.
- 177 Kaydok E. Nurses and physiotherapists' knowledge levels on autonomic dysreflexia in a rehabilitation hospital. *The Journal of Spinal Cord Medicine* 2021; : 1–5.
- 178 Jackson CR, Acland R. Knowledge of autonomic dysreflexia in the emergency department. *Emergency Medicine Journal* 2011; **28**: 866–869.