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DOI:
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

Journal Pre-proof

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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

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

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Disclosure: none

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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 rehabilitation[8] 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 hypotension[11]) 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 function[13] which has shown to detract from participation,[8] independence

with daily activities,[14] and quality of life in individuals living with a SCI[15] 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 (≥ 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 profile[5], 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 suggested[37] 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 sensitivity[45] 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 AD[41], 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 function[62] and arterial stiffness[44] 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 fibrosis[41] 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 injuries[57] 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 activity[69] 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 SCI[70] 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 function[93] and impaired vascular function[94] (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 theANS,[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 SCI[94] 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 heterogenous 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 response[109] 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 stockings[111] 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 1997[119] 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 position[131] 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 medications[2] and compression garments[111,136] to prevent hypotension or aquatics 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 dCA[151] 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 testing[3] 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 dilation[154] 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 SDB[17] 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 SDB[170]

(iii) Acquire knowledge regarding the technical and methodological recommendations for measuring and interpreting CBFv[171]

(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 facilitation 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 banks[175] and questionnaires[40] 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

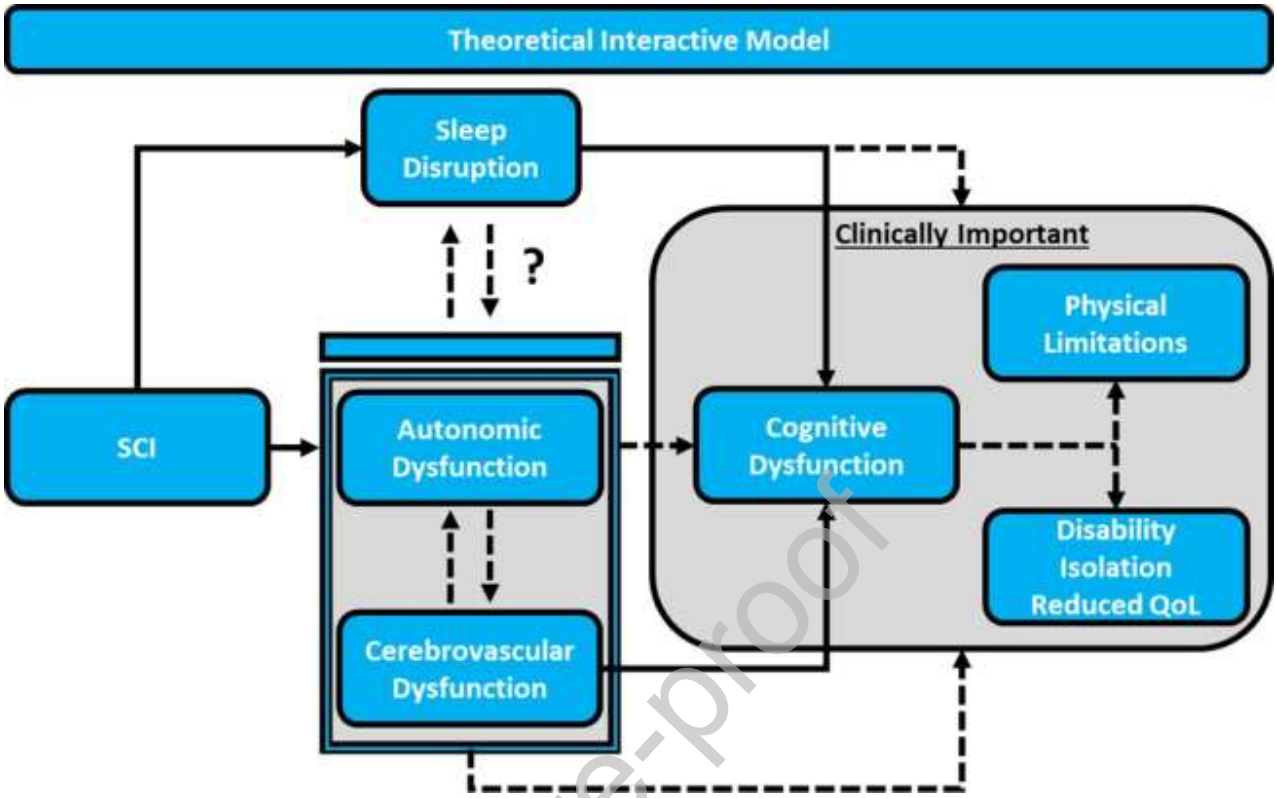

Figure 1: Theoretical interactive model showing the more established relationships (solid lines), and the less established relationships (dashed lines), in the SCI literature. The bidirectional arrows between autonomic and cerebrovascular dysfunction are dashed due to the heterogeneity of the literature 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

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