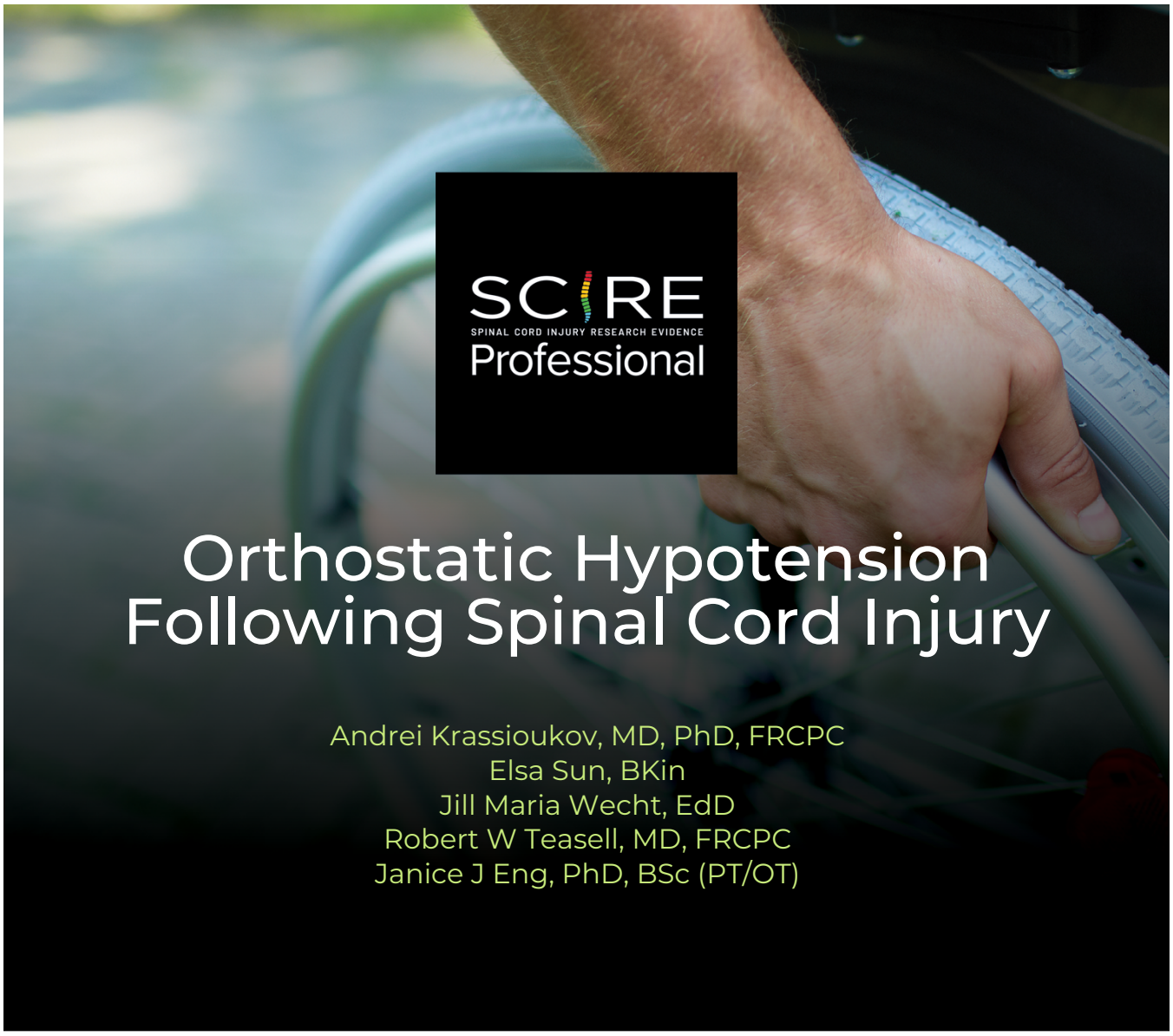

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Orthostatic Hypotension Following Spinal Cord Injury

Andrei Krassioukov, MD, PhD, FRCPC
Elsa Sun, BKin
Jill Maria Wecht, EdD
Robert W Teasell, MD, FRCPC
Janice J Eng, PhD, BSc (PT/OT)

Our Partners:

icord · LAWSON HEALTH RESEARCH INSTITUTE · PRAXIS Spinal Cord Institute · St. Joseph's Health Care · Vancouver Coastal Health Research Institute · Western · UBC

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Key Points

Individuals with SCI may experience orthostatic hypotension, characterized by drops in sBP of 20mmHg or greater and drops in dBP of 10mmHg or greater with accompanying increases in HR upon the assumption of an upright position.

Orthostatic hypotension symptoms include:

- Light-headedness
- Dizziness
- Fatigue
- Blurry vision
- Muscle weakness
- Fainting/ temporary loss of consciousness

In the management protocol of OH in individuals with spinal cord injury the following recommendations can be made:

Midodrine hydrochloride should be included

- There is limited evidence that fludrocortisone is effective
- There is limited evidence that ergotamine is effective.
- There is little evidence that ephedrine is effective.
- There is limited evidence that droxidopa is effective
- There is limited evidence that L-NAME is effective.
- There is emerging evidence that spinal cord epidural stimulation is effective.

The benefits of sodium/salt loading have not been sufficiently proven effective in individuals with SCI.

There is insufficient evidence that elastic stockings or abdominal binders have any effect on cardiovascular responses to orthostasis in SCI.

The use of FES is an effective adjunct treatment to minimize cardiovascular changes during changes in position.

Exercise training is a powerful tool to improve cardiorespiratory fitness in people with spinal cord injury.

The benefits of body-weight supported treadmill training, arm crank exercise, and active stand training for management of OH have not been sufficiently proven in SCI.

Table of Contents

1 Executive Summary

What is orthostatic hypotension?

Orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure (sBP) of at least 20mmHg, or a reduction in diastolic blood pressure (dBP) of at least 10mmHg, upon the change in body position from a supine (lying) to an upright position regardless of the presence of symptoms (Ringer et al. 2025). Normally, the nervous system automatically constricts or dilates the blood vessels to balance blood pressure. However, this ability may become compromised after a SCI, and OH may be experienced.

Several studies have documented the presence of OH following SCI, particularly during the acute period of injury, but it can persist for many years (Chelvarajah et al. 2009; Cariga et al. 2002; Faghri et al. 2001; Mathias, 1995; Sidorov et al. 2008; Claydon et al. 2006; Frisbie & Steele 1997). Sitting or standing in physiotherapy is reported to trigger blood pressure decreases that are diagnostic of OH in 74% of people with SCI, and cause symptoms of OH (such as light-headedness or dizziness) in 59% of people with SCI (Illman et al. 2000). Thus, this may discourage people with SCI from participating in rehabilitation, creating the need for management methods.

What are the risk factors of orthostatic hypotension?

Many factors can contribute to OH. The low level of efferent sympathetic nervous activity and the loss of the vasoconstriction reflex following SCI are two major causes of OH. Decreases in blood pressure (BP) following the change to an upright position in individuals with SCI may be related to excessive pooling of blood in the abdominal viscera and lower extremities (Mathias, 1995; Claydon et al. 2006; Krassioukov & Claydon 2006). Additionally, regular movement of muscles pushes against blood vessels which help guide blood back to the heart. Hence, loss of muscle function in the lower extremities can cause blood to accumulate there. These mechanisms lead to a reduction of blood flow back to the heart and the rest of the body and present as OH.

Other causes of OH include low blood volume, low sodium levels in the blood, and deconditioning of the heart and blood vessels from extended bedrest (Mathias, 1995; Claydon et al. 2006; Illman et al. 2000). Those with a traumatic SCI may also be at a greater risk than those with a non-traumatic SCI (McKinley et al. 1999). The prevalence of OH is greater in patients with higher spinal cord lesions, and thus it is more common in people with tetraplegia (Claydon et al. 2006; Frisbie & Steele 1997; Mathias, 2006). Some evidence show that people with SCI produce more nitric oxide, a chemical that widens the blood vessels, which can result in a further decrease in blood pressure (Vaziri, 2003).

What are the signs and symptoms of OH?

OH may occur with or without the presence of symptoms. Common signs and symptoms include:

- Light-headedness
- Dizziness
- Fatigue
- Blurry vision
- Muscle weakness
- Fainting/ temporary loss of consciousness

How do I manage my patients with OH?

Management of OH consists of pharmacological and non-pharmacological interventions. Although a wide array of physical and pharmacological measures are recommended for the general management of OH (Kaufmann et al. 2006), very few have been evaluated for use in SCI. The general approach to managing OH is to implement therapeutic interventions incrementally, depending on the severity of symptoms (Kaufman et al. 2006). Non-pharmacologic measures alone are often insufficient to prevent symptoms of OH. Thus, pharmacological interventions are needed, particularly in SCI patients with moderate to severe OH symptoms.

Pharmacological Options

Only Midodrine (a drug that constricts the blood vessels to increase blood pressure) has some evidence supporting its use. There is evidence that Midodrine can elevate blood pressure and improve exercise performance (Nieshoff et al. 2004. Even so, the use of Midrodrine should be monitored carefully as 2 males reported urinary bladder dysreflexia with its use (Vaidyanathan et al. 2007).

Non-Pharmacological Options

Functional Electrical Stimulation (FES) is a non-pharmacological treatment option for individuals with SCI. During FES, electrical impulses are sent to weak or paralyzed muscles, usually within the legs, which causes muscles to contract and helps move blood back to the heart and around the body. FES has been shown to be effective and can be used to supplement other forms of therapy, often exercise (Chi et al. 2008; Davis et al. 1990; Raymond et al. 2001). Studies have demonstrated that leg muscle contraction by FES allowed people with tetraplegia and OH to stand more often and for longer periods of time (Elokda et al. 2000; Sampson et al. 2000).

Non-pharmacological options also include fluid and salt intake, pressure binders or stockings, whole-body vibration, electrical stimulation, and physical activities. However, studies looking at non-pharmacological options in isolation remain limited (Frisbie & Steele 1997).

2 Introduction

Blood pressure instability, including orthostatic hypotension (OH), is common in people with spinal cord injuries (SCI). OH is defined by The Consensus Committee of the American Autonomic Society and the American Academy of Neurology (CCAAS & AAN 1996) as a decrease in systolic blood pressure of at least 20mmHg, or a reduction in diastolic blood pressure of at least 10mmHg occurring within 3 minutes upon the assumption of an upright position from supine (i.e., laying down), regardless of the presence of symptoms (Krassioukov et al. 2012). OH occurs during the acute period of SCI and persists in many individuals for several years (Sidorov et al. 2008; Claydon et al. 2006; Frisbie & Steele 1997).

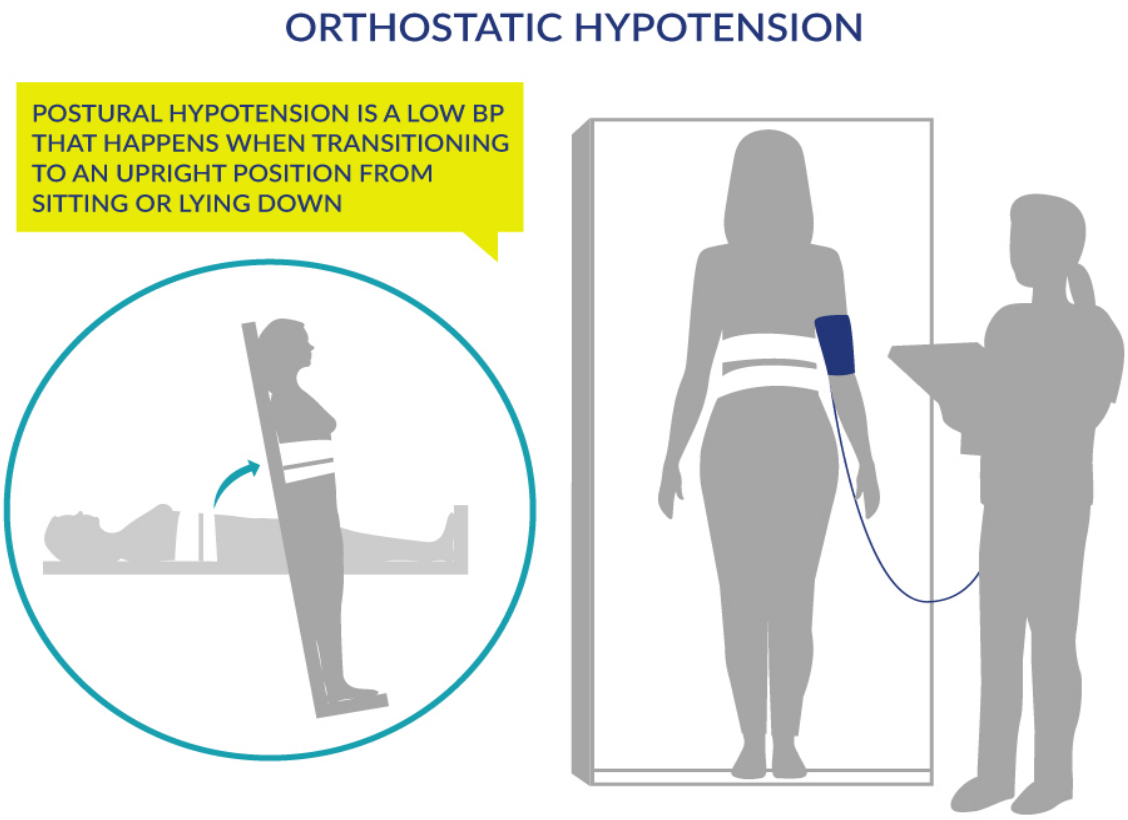


Figure 1 – Orthostatic Hypotension as generated by Postural Changes

Normally, the nervous system automatically constricts or dilates the blood vessels to balance blood pressure during postural changes; however, this ability may be compromised after an SCI, particularly for people with injuries at or above T6, resulting in OH. During an episode of OH, symptoms including dizziness, blurred vision, and fainting, may or may not occur.

Table 1. Signs and Symptoms of OH

- Light-headedness
- Dizziness
- Blurred vision
- Fatigue
- Muscle weakness
- Fainting

Studies have shown that delayed BP recovery and OH are associated with future risk of falls, fractures, fainting, stroke, cardiovascular disease, and even earlier death (10-year mortality rate of 50-64%). Further, standard mobilization treatment during physiotherapy (e.g., sitting or standing) is reported to trigger BP decreases that are diagnostic of OH in 74% of people with SCI and cause symptoms in 59% (Illman et al. 2000). Therefore, simple activities like sitting up or eating may trigger BP drops and cause symptoms of OH, discouraging people with SCI from participating in rehabilitation, exercise, or completing activities of daily living; thus creating the need for other management methods.

3 Characteristics/ Predictors of OH

Two major causes of OH can be attributed to the low level of efferent sympathetic nervous activity and the loss of the vasoconstriction reflex following SCI. Additionally, decreases in BP following the change to an upright position in individuals with SCI may be related to excessive pooling of blood in the abdominal viscera and lower extremities (Krassioukov & Claydon 2006; Claydon et al. 2006; Mathias, 1995). This decrease in BP is compounded by the loss of lower extremity muscle function post-SCI that is known to be important in counteracting venous pooling in the upright position. Excessive venous pooling in the lower extremities coupled with reduced intrathoracic blood volume lowers ventricular end-diastolic filling pressure and volume, therby reducing left ventricular stroke volume (Ten Harkel et al. 1994). Ultimately, this decreases cardiac output and arterial pressure, triggering arterial baroreceptor unloading which induces a reflexive reduction in cardiac parasympathetic (vagal) activity. As a result, HR increases but is often insufficient to compensate for the decreased stroke volume. Moreover, continued pooling of blood in the lower extremities may further reduce cerebral flow, causing symptoms of cerebral hypoperfusion such as dizziness, blurred vision, light-headedness, and fainting.

Several other factors may predispose individuals with SCI to OH, including low plasma volume, hyponatremia, and cardiovascular deconditioning due to prolonged bed-rest (Claydon et al. 2006; Illman et al. 2000; Mathias, 1995). The prevalence of OH is greater in individuals with higher spinal cord lesions, and thus it is more common in people with tetraplegia (Claydon et al. 2006; Mathias, 2006; Frisbie & Steele 1997). Furthermore, individuals with cervical SCI also experience greater posture-related decreases in blood pressure than those with paraplegia (Claydon et al. 2006; Mathias, 1995). There is also an increased risk of OH in individuals who

sustain a traumatic SCI versus a non-traumatic injury such as spinal stenosis (McKinley et al. 1999).

In addition to central causes of OH following SCI, there is also evidence that suggests peripheral mechanisms could contribute to orthostatic intolerance following SCI. For example, up-regulation of the potent vasodilator, nitric oxide (NO), could potentially contribute to the orthostatic intolerance in people with SCI (Vaziri, 2003). In animal studies, it has been shown that NO synthase expression is dysregulated following SCI (Zhao et al. 2007). Moreover, Wecht et al. (2007) found that intravenous infusion of a relatively low dose of the NO synthase inhibitor, L-arginine-N-methyl-ester (L-NAME), normalized blood pressure in individuals with SCI.

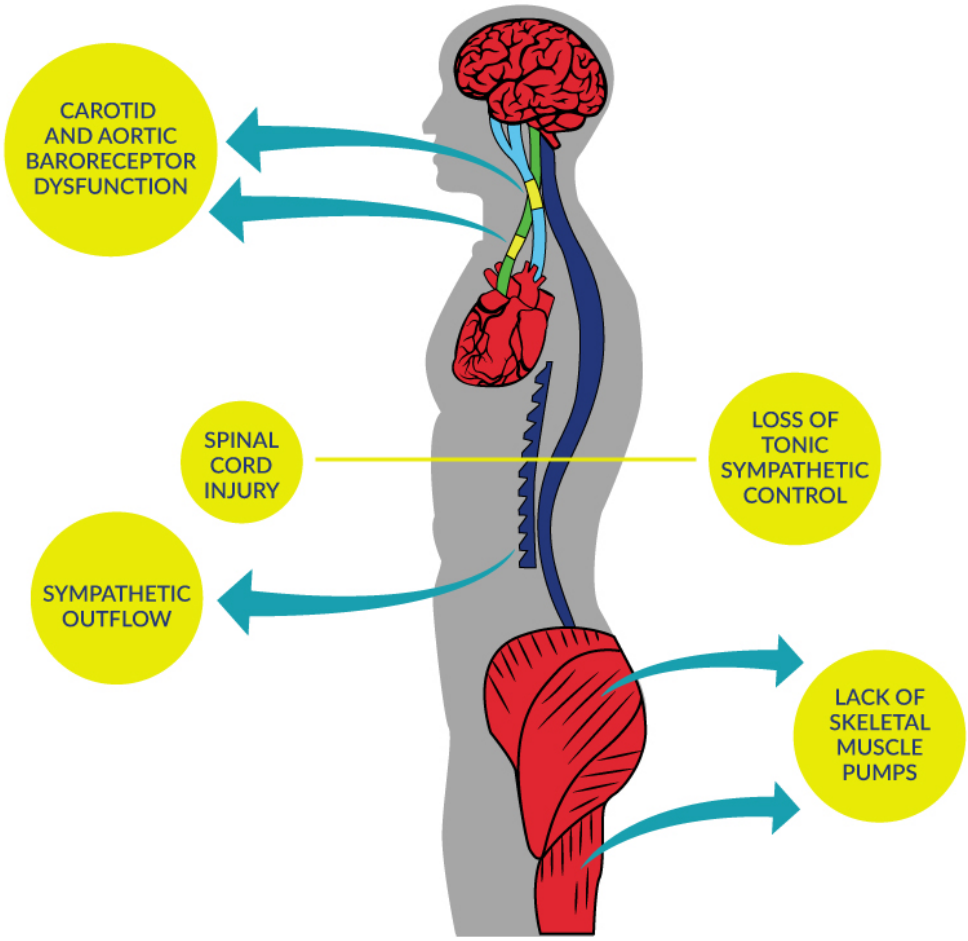


Figure 2 – Blood Pressure Dysfunction due to SCI

Table 2. Factors Contributing to OH Following SCI

Loss of tonic sympathetic control	Houtman et al. 2000; Wallin & Stjernberg 1984
Altered baroreceptor sensitivity	Wecht et al. 2003; Munakata et al. 1997
Lack of skeletal muscle pumps	Faghri & Yount 2002; Raymond et al. 2002; Ten Harkel et al. 1994
Cardiovascular deconditioning	Hopman et al. 2002; Vaziri, 2003
Altered salt and water balance	Frisbie, 2004
Multifactorial	Claydon et al. 2006

Table 3. Characteristics/ Predictors of OH

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Wang et al. 2020 USA Prospective controlled trial Level 2 N=207	**Population:** N=207, 159 with SCI and 48 non-injured controls **Treatment:** Participants lay in supine position and 5 min of resting data were recorded. Participants were then passively moved into the seated position. Beat-to-beat blood pressure and heart rate were recorded continuously during the transition and throughout the seated position lasting for 4 min or 15 min. **Outcome measures:** BP, HR, ECG	1. Dramatic increases in heart rate that accompanied decreases in systolic and diastolic blood pressure after moving the participant to an upright position were evident within each level and severity of injury. 2. Individuals with SCI that did not meet the criteria for orthostatic hypotension still had a drop in SBP between 10 and 20 mmHg and/or a drop in DBP between 5 and 10 mmHg and still experienced an increase in HR (>10 BPM). 3. Those individuals with SCI that did meet the criteria for having orthostatic hypotension also experienced profound increases in HR.
Wang et al. 2022	**Population:** N=55, 33 with SCI and 22 non-injured participants	1. SBP, DBP, and HR did not show a nocturnal dip in participants with SCI compared to the ambulatory non-

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
USA Prospective controlled trial Level 2 N=55	**Treatment:** BP was measured every 10, 15, or 20 min while awake and every 30 min while asleep. HR was measured continuously. All participants were to keep a diary of activities that affect their BP and the presence of symptoms without a related event. **Outcome measures:** BP and HR	injured and wheelchair non-injured group. 2. SBP was significantly increased while awake compared to asleep in the ambulatory non-injured group but not the wheelchair non-injured group or SCI group (awake, 122 [108–133]; asleep, 103 [91–113]; p < 0.01). 3. HR was significantly elevated while awake compared with asleep in ambulatory non-injured group (awake, 73 [63–89]; asleep, 63 [53–73]; p < 0.01) and wheelchair non-injured group (awake, 76 [66–84]; asleep, 60 [54–66]; p < 0.05), but not the SCI group. 4. Among participants with SCI, SBP, DBP, and HR decreased while awake compared to asleep (reversed nocturnal dip).
Park et al. 2024 Korea Prospective controlled trial Level 2 N=27	**Population:** N=27 **Treatment:** Participants remain still in a supine position for 6 min, then were tilted to a 60-degree position using a tilt table and remained in that position for another 6min. Measurement of R-R intervals and BP were conducted. Difference in HRV between people with OH and those without OH, as well as between people with symptoms of OH and those without symptoms of OH were analysed. **Outcome measures:** R-R intervals and BP	1. Comparison between without OH and with OH: Among participants with OH, the mean RR interval was lower (878.78 ms compared to 970.80 bpm, p<0.109), and the mean HR was higher during the 60-degree tilt-up test compared to the participants without OH (69.95bpm compared to 62.92bpm, p<0.106), however these results were non-significant. 2. Comparison between symptomatic and asymptomatic OH: The mean HR was significantly lower in the symptomatic OH group than in the asymptomatic OH group, in both the supine position (62.61bpm compared to 76.48bpm, p<0.007) and the 60-degree tilt-up position (66.78bpm compared to 84.27bpm, p<0.001). The mean R-R intervals were significantly higher in the symptomatic OH group for both the supine position and the postural

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		challenge (970.57ms compared to 797.18ms, p<0.005, and 906.75ms compared to 719.95ms, p<0.000, respectively). 3. In the 60-degree tilt up position, the mean values of lowest diastolic and systolic BP were lower in the symptomatic group compared to the asymptomatic group (46.88 compared to 47.50, and 72.22 compared to 78.50, respectively), although there was no significant statistical difference.
Stampas et al. 2019 USA Prospective controlled trial Level 2 N=18	**Population:** N=18 SCI, 10 people with tetraplegia, 8 with paraplegia; N=6 controls **Treatment:** BP was recorded while seated in wheelchairs after waiting 5 mins. Participants were then transferred to the exam table in supine position for 10 mins and BP and HRV were measured. Finally, participants were transferred to a seated position with immediate BP and HRV recordings. **Outcome measures:** BP and HRV	1. In the resting seated position, there were no differences in HRV measures when people with SCI were grouped by presence of OH. However, those with OH had lower SBP compared to those without OH [106 mmHg (16) v 136 mmHg (27), p = 0.049] and controls [132 mmHg (10), p = 0.024]. 2. The expected BP changes seen with postural challenge when grouping by OH were observed, but significant differences were only detected by DBP. In those with OH, DBP was lower in OH [59.8 mmHg (9.5]) compared to controls [78.7 mmHg (12.3), p = 0.033] and SCI without OH [78.6 mmHg (11.1), p = 0.017]. 3. Mean HR was significantly increased (109.8 bpm (45.5)) and mean RR was decreased (612.6 ms (174.3)) in OH compared to controls (68.6 bpm (9.8), 891 ms (123.5), respectively).
Hansen et al. 2021 Denmark Case series Level 4	**Population:** N=158, 109 males, 49 females , 449 meals Tetraplegia: 94; Paraplegia: 64; Non-traumatic SCI: 85; Diabetes: 16; Other neurological diseases: 20	1. Median sBP was 120 mmHg before breakfast, 125 mmHg before lunch, 125 mmHg before dinner, and 118 mmHg during the night. 2. A total of 114 (25.3%) episodes of decrease in SBP within two hours after a meal met the criteria of PPH in 78 (49.4%) participants. In seven

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
N=158	**Treatment:** Each participant was to keep a diary of activities, including time of meals, including snacks and nutrition through percutaneous endoscopic gastrostomy tube (PEG-tube), and symptoms of hypo- and hypertension (e.g., dizziness, headache, sweating). Physical activity including physical therapy appointments and transfers were noted in the diary as well. Postprandial hypotension (PPH) is defined as a decrease of ≥20 mmHg in SBP or a SBP of <90 mmHg after having been >100 mmHg before the meal within two hours after a meal. **Outcome measures:** sBP	(4.4%) participants, the decrease in SBP was associated with symptoms of hypotension. 3. The median time from ingestion of the meal until PPH was registered was 60 min (min 15, max 120 min). The median change in SBP during PPH was −28 mmHg (min: −87; max: −15 mmHg). 4. 20 of 114 (17%) episodes interpreted as PPH occurred simultaneously with transfers noted in the diary, while 26 (23%) occurred simultaneously with physical activity e.g., physical exercise, physiotherapy, and occupational therapy. 5. PPH and age had an odds ratio of 1.039 (p = 0.001); PPH and level of injury had an odds ratio of 1.512 (p = 0.023); PPH and injury completeness had an odds ratio of 9.482 (p = 0.000).
Katzelnick et al. 2019 USA Case Series Level 4 N=113	**Population:** N=113, 85% male, 64% cervical **Treatment:** Participants recorded their blood pressure using an ambulatory blood pressure monitor and heart rate at least three times a day for 30 days **Outcome measures:** Blood pressure, heart rate	1. Average 30-day SBP (114 ± 17 mm Hg), DBP (71 ± 9 mm Hg) and HR (73 ± 9 bpm) were within normal range (p < 0.05) 2. Average SBP, DBP, and HR were significantly lower in the tetraplegic group compared with the low thoracic group, and SBP and HR were significantly lower compared with the high thoracic group (p < 0.05).
Kee et al. 2021 Korea Case series Level 4 N=100	**Population:** N=100, tetraplegia **Treatment:** None. Authors reviewed the medical records of 100 patients with a cervical SCI who underwent carotid duplex ultrasonography (CDU). The differences between the systolic blood pressure, diastolic blood pressure, and CBF volume in the	1. 40 participants complained of presyncopal symptoms during the tilt. Presyncopal symptoms occurred when the CBFV decrease was more than 21% after tilt (p < 0.05).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	supine posture and after 5 min at 50° tilt were evaluated. **Outcome measures:** Blood flow velocity, peak systolic velocity, end diastolic velocity, mean velocity, vessel diameter, vessel area Determined correlation of CBF change with presyncopal symptoms, and factors affecting cerebral autoregulation.	
Vaccaro et al. 2022 USA Pre-post Level 4 N=53	**Population:** N=53 with traumatic SCI **Treatment:** While the participants rested quietly, 10-min of supine data collection was initiated prior to passive repositioning of the participants and a 10-min seated data collection period. **Outcome measures:** Beat-to-beat ECG and TCD signals, HR, and CBFv	1. The magnitude of change in SBP during the sit-up test was not significantly associated with NLI (slope (b) = −0.39 mm Hg/segment, 95% CI for b = −0.89 to 0.11 mm Hg/segment) 2. The effect of postural change on SBP conformed to the parameters of sensorimotor impairment as assessed on the ISNCSCI exam. 3. The sit-up test did not induce a systematic change in SBP among study participants, (range in SBP change = −53.8 to +18.9 mm Hg, 95% CI of the mean difference = −4.1 to 1.3 mm Hg, d = −0.16).

Discussion

Literature in SCI and OH is consistent in their findings, but there is some variability across studies. Consistently, studies (Park et al. 2024; Stampas et al. 2019) suggest decreases in sBP and dBP accompanied by increases in HR upon assumption of an upright position from supine, often meeting the criteria for OH. However, Vaccaro et al. (2022) did not find a change in sBP upon sitting in individuals with SCI.

Wang et al. (2020) found that some people without OH criteria still experienced drops in sBP of 10-20 mmHg, drops in dBP of 5-10 mmHg, and increase in HR of greater than 10 BPM. Wang et al.'s (2020) cluster analysis of hemodynamic responses to a seated position identified eight patterns of interaction between BP and HR during orthostatic stress, indicating varied

autonomic responses (e.g., Cluster 1: large decreases in sBP and dBP; moderate rise in HR; Cluster 3: large decreases in sBP and dBP; large rise in HR). This suggests that BP instability cannot be wholly predicted by level and completeness of SCI, and the consensus statement definition of OH is insufficient to characterize the variability of BP and HR responses during orthostatic stress (Wang et al. 2020).

In people without SCI, sBP, dBP, and HR decreases while asleep (nocturnal dip) and increases when awake, while individuals with SCI and OH will not show a nocturnal dip (Wang et al. 2022). However, participants with SCI in a study by Wang et al. (2022) demonstrated a reversed nocturnal dip, and sBP, dBP, and HR decreased while awake compared to asleep.

Post-prandial hypotension is another symptom commonly experienced by people with SCI. Post-prandial hypotension is defined as a decrease of ≥20 mmHg in SBP or a SBP of <90 mmHg after having been >100 mmHg before the meal within two hours after a meal (Hansen et al. 2021). A study by Hansen et al. (2021) found that 49.4% of their participants met the criteria for post-prandial hypotension, and in 4.4% of participants, the drop in sBP was accompanied by symptoms of hypotension. Moreover, 17% of post-prandial hypotension episodes occurred simultaneously with transfers, while 23% of episodes occurred with physical activity (physical exercise, physiotherapy, and occupational therapy (Hansen et al. 2021). Level of completeness of SCI also affects an individual's likelihood of getting PPH; one study shows people with complete injuries have a 9x higher risk of PPH than people with incomplete injuries (odds ratio: 9.482, p=0.000) (Hansen et al. 2021).

Conclusion

There is level 2 evidence (from one prospective controlled trial) (Park et al. 2024) that mean HR is lower in individuals with symptomatic OH compared to asymptomatic OH.

There is level 2 evidence (from one prospective controlled trial) (Stampas et al. 2019) that individuals with SCI and OH have lower BP and higher HR compared to individuals with SCI without OH and controls.

There is level 2 evidence (from one prospective controlled trial) (Wang et al. 2022) that individuals with SCI do not show a nocturnal dip in sBP, dBP, and HR like individuals without SCI, but rather show an increase in sBP, dBP, and HR during sleep (reversed nocturnal dip).

There is level 2 evidence (from one prospective controlled trial) (Wang et al. 2020) that individuals with SCI present drops in sBP and dBP accompanied by increases in HR upon the assumption of an upright position.

There is level 4 evidence (from one cohort study) (Hansen et al. 2021) that post-prandial hypotension was experienced by 49.4% of participants.

There is level 4 evidence (from one case series) (Kee et al. 2021) that presyncopal symptoms occur when the CBFV decrease is more than 21% after a 50 degree tilt.

There is level 4 evidence (from one pre-post) (Vaccaro et al. 2022) that a sit-up test did not induce changes in sBP in individuals with SCI.

There is level 5 evidence (from one observational study) (Katzelnick et al. 2019) that average sBP, dBP, and HR is significantly lower in individuals with tetraplegia compared to individuals with low thoracic SCI.

Key Points

Individuals with SCI experience drops in sBP and dBP and increases in HR upon the assumption of an upright position.

Individuals with SCI and OH have lower BP and higher HR compared to individuals with SCI but without OH, and those without SCI.

4 Pharmacological Management of OH in SCI

The majority of our knowledge in managing OH has been obtained from people with neurological causes other than SCI, such as diabetic neuropathy, heart disease, multiple system atrophy, pure autonomic failure, Parkinson's disease, and dysautonomia. Numerous medications, including midodrine hydrochloride, fludrocortisone, and ephedrine, have been successful in managing OH in these chronic conditions. However, as the mechanisms underlying the development of OH in the SCI population differ from those in these non-SCI populations, it is important to assess the effectiveness of these medications specifically in people with SCI.

Table 4. Pharmacological Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Krassioukov et al. 2009 Canada Reviewed published articles from 1950 to July 2008 N=26 n=251 **Level of evidence:**	**Methods:** Key word literature search for (original) articles, previous practice guidelines, and review articles was conducted to identify literature evaluating the effectiveness of any treatment or therapy for OH in the SCI population. **Databases:** PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO.	1. There is evidence that OH can be improved with the use of fludrocortisones, ergotamine, ephedrine, L-DOPS, and salt supplementation (level 4 or 5), and salt and fluid regulation, in combination with other pharmacologic interventions (level 5). 2. Cardiovascular responses during orthostatic challenges may be improved with FES (level 2), simultaneous upper extremity

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
PEDRo Scale - RCTs (9–10: excellent; 6–8: good; 4–5: fair; 0-4: poor) Modified Downs & Black scale - non RCTs (0 to 28) **Type of study:** 2 case reports, 1 case series, 2 observational, 1 pre-post, 1 RCT AMSTAR: 6		exercise with paraplegia, but not tetraplegia (level 2), but not 6 months of bodyweight support treadmill training. 3. Cardiovascular responses during exercise may be improved with midodrine (level 2) and elastic stockings and abdominal binders (level 2).
Wecht et al. 2020 US RCT Level 1 PEDro = 11 N=41	**Population:** N=41 individuals with SCI ≥ 1 year post-injury and hypotension **Treatment:** Seated sBP, CBFv, and cognitive performance were monitored before and after administration of Midodrine (10mg) or placebo **Outcome Measures:** HR, BP, cerebral blood flow velocity	1. Midodrine increased sBP 18±24 mmHg while the placebo increased sBP 4±13 mmHg ($p < 0.05$). 2. Responses varied widely with midodrine (-15.7 to +68.6 mmHg), suggesting careful clinical monitoring should accompany midodrine administration.
Wecht et al. 2023 US RCT Level 1 PEDro = 9 N=10	**Population:** N=10 with hypotension or OH **Treatment:** Participants were randomly assigned to received midodrine/placebo or placebo/midodrine, with a 2-week washout period in between, and both the participants and investigators were blinded to randomization order. Study medication was taken 2 or 3 times/day, and BP, and any related symptoms were recorded	1. Midodrine significantly increased average 30-day SBP (mean increase ~12.6 mmHg, $p < 0.0001$) and DBP (mean increase = 7.7 mmHg, $p < 0.0001$) compared to placebo. 2. The counts of BP recordings that remained below the target range were significantly reduced with midodrine for both SBP (~1.7 times lower, $p = 0.001$) and DBP (~1.5 times lower, $p < 0.001$) compared to placebo.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	before and 1 h after each dosage and periodically throughout the day. **Outcome Measures:** BP, symptoms of AD and OH including headache, pounding in the ears, tingling or itching of the scalp, goosebumps, chills, blurry vision, and dizziness, and adverse effects of midodrine including constipation, muscle spasms, urinary urge or increased lower abdominal pressure.	3. The target ranges were SBP: males: 110–129 mmHg; females: 101–129 mmHg and DBP: 70–89 mmHg. 4. The counts of BP recordings within the pre-defined target range were significantly increased with midodrine for both SBP (~2-times higher, P < 0.001) and DBP (~1.5-times higher, P < 0.001) compared to placebo. 5. The counts of BP recordings above the target range were significantly increased with midodrine for SBP (~2 times higher, P = 0.005) and DBP (~3.4 times higher, P < 0.001) compared to placebo.
Nieshoff et al. 2004 USA RCT Level 2 PEDro=6 N=4	**Population:** Chronic motor complete tetraplegia **Treatment:** Midodrine 5mg, 10 mg, or placebo (unmarked capsule), double blind, placebo-controlled cross-over design. **Outcome Measures:** Measure of cardiovascular parameters during wheelchair ergometer test.	1. Midodrine, 10 mg elevated systolic blood pressure during exercise in 3 participants. Peak systolic BPs ranged from 90 to 126 mmHg under baseline and placebo conditions, 114-148 after 5 mg of midodrine, and 104 to 200 mmHg after 10 mg. 2. Two participants showed reduced perceived exertion and increased VO_2 following midodrine 10 mg. 3. No adverse effects of midodrine were noted.
La Fountaine et al. 2013 USA Prospective controlled trial Level 2 N=27	**Population:** Study 1: 7 individuals with tetraplegia (38±10 years; 2 complete AIS A injury), 6 age-matched neurologically intact controls (32±8 years). Study 2: 7 individuals with tetraplegia (41±9 years; 1 complete AIS A injury), 7 age-matched	1. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change heart rate, PQ, QT or QTC (heart-corrected QT) intervals at rest or during head-up tilt in participants with tetraplegia or controls. 2. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change resting heart

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	neurologically intact controls (33±9). **Treatment:** Study 1: open-label trial with intravenous administration of L-NAME at specific doses (0, 1, 2, or 4 mg·kg^{-1}) in the supine position. Study 2: orthostatic challenge (head-up tilt) with or without L-NAME (0, 1, or 2 mg·kg^{-1}), controls completed a single visit (0 mg·kg^{-1}). **Outcomes Measures**: Study 1: Digital ECGs obtained at baseline, immediately after infusion (60 min) and 1-hour post-infusion (120 min). Study 2: Digital ECGs obtained at baseline, 60 min, and at 2 10 min post-infusion time points after head-up tilt.	rate, PQ, QT or QTC intervals in those with tetraplegia or controls. 3. L-NAME administration does not appear to affect cardiac rate or conduction.
Phillips et al. 2014a Canada Prospective controlled trial Level 2 N=16	**Population:** 8 persons with SCI (1 female) and 8 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 30 (11) years DOI: 7 participants <1 year post injury, 1 participant >1 year post injury All motor complete cervical spinal cord injuries AIS grade A: 6; AIS grade B: 2 **Treatment:** Participants tested supine and during upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine.	1. Systolic BP was lower in SCI while supine vs. AB; BP, CCA diameter and diameter difference were reduced in SCI while upright vs. AB; β-stiffness index was elevated in SCI when upright (+12%) and relative decrease in baroreflex sensitivity (BRS) was greater in SCI vs. non-SCI. 2. Negative relationship between BRS and β-stiffness in SCI; no relationship in people without SCI 3. Midodrine led to increased BP and decreased HR in both supine and upright positions; no change in BRS or CCA parameters 4. Reduced BRS is closely related to increased arterial stiffness in the SCI population

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Beat-by-beat BP and HR, common carotid artery (CCA) diameter. Calculated arterial distensibility and arterial stiffness (β-stiffness index)	
Phillips et al. 2014b Canada Prospective controlled trial Level 2 N=20	**Population:** 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 29 (10) years DOI: 8 participants <1 year post injury, 2 participants >1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** participants tested supine and during progressive upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine. **Outcome Measures:** beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	1. Coherence increased in SCI between BP-MCAv and BP-PCAv by 35% and 22% respectively compared to AB. 2. SCI BP-PCAv gain was reduced 30% compared to AB. 3. The acute (0–30 s after tilt) MCAv and PCAv responses were similar between groups. 4. In SCI, midodrine led to improved PCAv responses 30 – 60 s following tilt (10+/- 3% vs. 4+/- 2% decline). 5. In SCI, midodrine led to a 59% improvement in orthostatic tolerance.
Phillips et al. 2014c Canada Prospective controlled trial Level 2 N=20	**Population:** 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 29 (10) years DOI: 8 participants <1 year post injury, 2 participants >1 year post injury	1. At rest: mean BP was lower in SCI (70±10 versus 92±14 mm Hg); PCAv conductance was higher in SCI (0.56±0.13 versus 0.39±0.15 cm/second/mm Hg). 2. AB had a 20% increase in PCAv during cognition while this response was absent in SCI. 3. With midodrine, NVC was improved by 70% in SCI, and

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** Visual and verbal fluency task to assess neurovascular coupling (NVC). SCI group had 2 sessions, one with midodrine and one without. AB group had one session without midodrine. **Outcome Measures:** beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	cognitive function improved by 13%. 4. Improvements in BP were related to improvements in cognitive function in those with SCI.
Wecht et al. 2008 USA Prospective controlled trial Level 2 N=14	**Population**: 7 individuals with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years. **Treatment:** Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg). **Outcome Measures:** Supine heart rate (HR), mean arterial blood pressure (MAP) and plasma norepinephrine (NE) concentrations.	1. There was a heightened MAP response to escalating dose of L-NAME in people with tetraplegia compared to the controls. 2. HR was reduced in a dose dependent manner, and this response did not differ comparing those with tetraplegia to the controls. 3. Plasma NE was significantly at baseline in individuals with tetraplegia compared to the controls. 4. Following L-NAME infusion, plasma NE was reduced in a dose dependent manner in the controls, whereas plasma NE levels were un-changed following L-NAME infusion in people with tetraplegia.
Wecht et al. 2007 USA Prospective controlled trial	**Population**: 7 individuals with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years.	1. Supine MAP was significantly reduced in individuals with tetraplegia compared to controls at baseline. 2. Supine HR did not differ between the groups at baseline.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Level 2 N=14	**Treatment:** Placebo versus L-NAME (1.0 mg/kg). **Outcome Measures:** Supine heart rate (HR), and mean arterial blood pressure (MAP).	3. MAP was significantly reduced in people with tetraplegia compared to the controls following placebo infusion. 4. Differences in MAP between participants with tetraplegia and controls were no longer evident following L-NAME infusion.
Wecht et al. 2009 USA Prospective controlled trial Level 2 N=12	**Population:** 5 individuals with chronic tetraplegia (1 AIS A and 4 AIS B); 7 age-, height-, and weight matched controls without SCI. All participants were between 19 and 53 years old. **Treatment:** Individuals with SCI underwent treatment of 1.0 mg/kg of L-NAME, as well as placebo control at supine rest and during head-up tilt (HUT); the control group received only placebo. **Outcome Measures:** Heart rate (continuously monitored by ECG), mean arterial blood pressure (MAP); active plasma renin and serum aldosterone concentrations.	1. Supine systolic, diastolic, and mean arterial blood pressure were significantly higher in people with SCI after L-NAME infusion compared to placebo. 2. Orthostatic (45° HUT) MAP was significantly reduced after placebo infusion in SCI compared to controls (66±13 vs. 88±10 mmHg). 3. MAP during HUT was comparable to controls (88±10 mmHg) following L-NAME infusion in participants with SCI (83±3 mmHg). 4. Serum aldosterone levels were reduced during HUT after L-NAME infusion (120±45 pg/mL) compared to placebo (259±69 pg/mL; $p<0.05$) in individuals with SCI.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Wecht et al. 2013 USA Prospective controlled trial Level 2 N=10	**Population:** 10 hypotensive individuals with SCI (8M; 2F); 8 tetraplegic, 1 high thoracic (T4) and 1 low thoracic (T10); age: 44±10 years; duration of injury 15±13 years. **Treatment:** Escalating dose of L-Threo-3, 4-dihydroxyphenylserine (droxidopa) (100mg, 200mg, 400mg) given over four lab visits with placebo on first visit. Each visit involved 30 min seated baseline, 30- to 60 min supine, and a 4-hour seated post-drug observation. **Outcome measures:** Blood pressure and heart rate changes from baseline to the post-drug period; orthostatic heart rate and blood pressure responses; reporting of subjective adverse effects.	1. Seated blood pressure was significantly elevated with 400mg droxidopa compared with placebo and 100mg droxidopa for 3 hours, and was elevated for 2 hours compared with 200mg droxidopa. 2. Increase in supine blood pressure was not worsened following droxidopa. 3. Expected fall in blood pressure when transferred from the supine to the seated position was prevented with droxidopa 200mg and 400mg. 4. Peak seated blood pressure reached the hypertensive range in 3 study participants following the 400-mg dose of droxidopa (156/100, 150/94, 149/93 mmHg). These episodes occurred 100 minutes after administration of droxidopa and were resolved within 30 minutes.
Wecht et al. 2010 USA Prospective controlled trial Level 2 N=10	**Population:** 8 males, 2 females; 43±9 years; duration of injury 22±11 years; SCI C4-C7; AIS A or B **Treatment:** Midodrine (no drug, 5 mg or 10 mg) over 3 testing days. **Outcome Measures:** Blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) and middle cerebral artery mean blood flow velocity (MCA MFV) during supine and head-up tilt (HUT) of 45 min at 45°.	1. 10 mg midodrine increased supine diastolic BP and MAP, and increased systolic BP and MAP after tilt test compared to control. 2. The significant increase in systolic BP during HUT was due to an augmented response in 2 participants with little to no change in the 8 other individuals.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Wecht et al. 2011 USA Prospective controlled trial Level 2 N=7	**Population:** 5 male and 2 female healthy participants (26-54 years old, level of injury C4-C7, duration of injury 8-37 years). **Treatment:** Participants were studied during 3 laboratory visits: no drug, midodrine (10mg; administered orally 30 min before HUT), and L-NAME (1.0 mg/kg; infused over a 60-min period). **Outcome measures:** Heart rate, blood pressure (systolic and diastolic), mean arterial pressure (MAP), cerebral blood flow (CBF), and markers of the renin-angiotensin- aldosterone system (RAAS, plasma renin and serum aldosterone) were measured in the supine position at baseline (BL) and during a 45° HUT manoeuver.	1. L-NAME and midodrine reduced OH symptoms compared to the no-drug trial. 2. L-NAME significantly increased orthostatic MAP compared with the no drug and midodrine trials. 3. There was a trend for midodrine to increase MAP during HUT. 4. Modest suppression of renin and aldosterone responses to HUT with L-NAME and midodrine. 5. There was a significant relationship between change in MAP and change in CBF with HUT among the participants tested (r^2=0.592).
Senard et al. 1991 France Case-control Level 3 N=7	**Population:** A 45-year-old participant with chronic complete traumatic paraplegia; 6 non-SCI male controls. **Treatment:** Clonidine (150 µg, 2X/day) and midodrine (specific alpha 1-agonist) (10 mg, 2X daily). Heart rate assessed by blinded tester. **Outcome Measures**: Blood pressure, heart parameters, plasma catecholamine, alpha-adrenoceptor sensitivity.	1. The increase in systolic blood pressure induced by midodrine (10 mg) was significantly higher in the tetraplegic patient (change of 56 mmHg) compared to controls (change of 15 mmHg). 2. Midodrine and clonidine alone or the two drugs in combination led to an increase in resting BP and decrease severity of OH.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Barber et al. 2000 USA Case series Level 4 N=2	**Population:** 2 cases of acute motor complete tetraplegia. **Treatment:** Fludrocortisone acetate 0.1 mg 4X/day or midodrine 10 mg 3X/day. **Outcome Measures**: Blood pressure, heart rate, and symptoms of OH.	1. No effect of fludrocortisone on OH. 2. Fludrocortisone in both patients resulted in pitting edema of hands and lower limbs. 3. Initiation of midodrine hydrochloride resolved orthostatic symptoms in both individuals without any complications.
Frisbie & Steele 1997 USA Retrospective chart review and survey Level 3/5 N=231	**Population:** N=231 SCI; ephedrine (medically treated for OH) group age, 57±15 years; duration of injury 26±15 years. SCI no ephedrine group: 51±15 years, duration of injury 22±14 years. **Treatment:** Retrospective chart review of use of ephedrine (n=30), salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. **Outcome Measures**: OH symptoms, serum sodium and urine osmolality.	1. Single dose of ephedrine usually sufficient to prevent symptoms but observed that some patients failed to recognize need for repeat doses later in day. 2. Symptoms of OH were reduced consciousness (100% of participants), strength (75%), vision (56%) and breath (53%). Precipitating factors were hot weather (77%), bowel care (33%) and meals (30%). 3. Low blood sodium found in 54% of the OH patients and 16% of those without.
Frisbie, 2004 USA Observational Level 5 N=4	**Population:** Chronic cervical complete tetraplegia; AIS A. **Treatment:** Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily). **Outcome Measures**: Severity of OH, urinary output.	1. With decreasing ephedrine dose (and OH severity), there was an increase in mean daily output of urine sodium (from 50 to 181 mEq), water (from 1.5 to 5.3 L), rate of creatinine secretion, rates of water excretion, sodium concentrations, and reduced urine osmolality.

Discussion

Midodrine (ProAmatine)

Midodrine, a selective alpha1 adrenergic agonist, works by activating the alpha-adrenergic receptors of the arteriolar and venous vasculature, consequently increasing vascular tone and blood pressure. Midodrine has a half-life of approximately 25 minutes, meaning plasma levels of Midodrine peak at approximately half an hour after oral ingestion, with this amount halved every 25 minutes. However, the primary metabolite reaches peak blood concentrations about 1 to 2 hours after a dose of Midodrine and has a half-life of about 3 to 4 hours. The usual starting dose of Midodrine is 2.5mg, two or three times daily. Doses are increased quickly until a response occurs or a maximum recommended dose of 10 mg dose, 2-3 times per day (total 30 mg/day) is attained (Wright et al. 1998). Midodrine does not cross the blood-brain barrier and is not associated with CNS effects. Benefits of Midodrine for the management of OH in individuals with SCI were reported in three level 2 RCTs (Wecht et al. 2020; Wecht et al. 2023; Nieshoff et al. 2004), four level 2 prospective controlled trials (Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c; Wecht et al. 2010), three level 4 studies (Mukand et al. 2001; Barber et al. 2000; Senard et al. 1991) and one level 5 study (Mukand et al. 2001). Of note, a case report on 2 male individuals demonstrated urinary bladder dysreflexia with the use of midodrine (Vaidyanathan et al. 2007) which suggests that Midodrine should be employed cautiously.

Three randomized control trials examined the effects of midodrine on blood pressure in individuals with SCI (Wecht et al. 2020; Wecht et al. 2023; Nieshoff et al. 2004). 10mg of Midodrine was found to increase sBP 18±24 mmHg ($p<0.05$) in 41 individuals with SCI and hypotension, while the placebo increased sBP 4±13 mmHg ($p<0.05$) (Wecht et al. 2020). Additionally, Midodrine significantly increased average 30-day sBP by a mean of 12.6 mmHg ($p<0.0001$) and dBP by a mean of 7.7 mmHg ($p<0.0001$) compared to a placebo (Wecht et al. 2023). Further, the counts of sBP and dBP that remained below a predetermined target range were significantly reduced with Midodrine (~1.7 times lower, $p=0.001$ and ~1.5 times lower, $p< 0.001$, respectively) compared to placebo (Wecht et al. 2023). Similarly, the counts of sBP and dBP recordings within the predetermined target range were significantly increased with Midodrine (~2-times higher, $p<0.001$ and ~1.5-times higher, $p<0.001$, respectively) compared to placebo (Wecht et al. 2023). In the RCT by Nieshoff et al. (2004), sBP increased during peak exercise in 3 of the 4 participants and exercise performance was also enhanced with Midodrine. Moreover, there are four additional prospective controlled trials (n=10-20), which support the positive effect of midodrine on orthostatic tolerance (Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c; Wecht et al. 2010). Nevertheless, it is important to confirm this evidence with larger trials.

Fludrocortisone (Florinef)

Fludrocortisone is a mineralocorticoid that induces more sodium to be released into the bloodstream. Since water follows the movement of sodium, fludrocortisone subsequently increases blood volume. Furthermore, fludrocortisone may enhance the sensitivity of blood vessels to circulating catecholamines (Van Lieshout et al. 2000; Schatz, 1984). The starting dose is generally 0.1 mg daily, and blood pressure will rise gradually over several days with the

maximum effect at 1-2 weeks. Doses should be adjusted at weekly or biweekly intervals. Adverse effects include hypokalemia (low potassium), which occurs in 50% of individuals, hypomagnesemia, which occurs in 5% of individuals, and headaches. Hypokalemia and hypomagnesemia may need to be corrected with supplements. Moreover, fludrocortisone should not be used in people with congestive heart failure because of its effect on sodium retention. Overall, the benefit of Fludrocortisone has not been sufficiently proven in individuals with SCI. One level 4 case series (Barber et al. 2000), and one level 3 retrospective chart review (Frisbie & Steele 1997) have described the use of fludrocortisone for the management of OH in a SCI population.

Barber et al. (2000) studied two individuals and did not observe an effect of fludrocortisone. Frisbie and Steele (1997) combined fludrocortisone with other pharmacological and physical agents in three participants; however, since outcomes specific to this group were not described, the specific effects of fludrocortisone could not be discerned. Therefore, there is level 4 evidence (Barber et al. 2000) from one case series of two patients that fludrocortisone is not effective for OH in SCI.

Ephedrine

Ephedrine, a non-selective, alpha and beta receptor agonist, acts both centrally and peripherally. Its peripheral actions are attributed to both norepinephrine release and to direct effects on receptors. Ephedrine raises blood pressure by increasing cardiac output as well as inducing peripheral vasoconstriction. It is typically administered orally at a dosage of 12.5-25 mg, three times a day. Side effects may include tachycardia, tremor, and supine hypertension. Further, its plasma half-life ranges from 3 to 6 hours (Kobayashi et al. 2003). Systematic reviews of the literature found level 3 evidence based on one retrospective chart review (Frisbie & Steele 1997) and a cross-sectional observation study (Frisbie, 2004). Frisbie (2004) reported that daily urinary output of sodium and fluid was inversely related to the prescribed dose of Ephedrine in 4 participants with OH. While results suggest that Ephedrine resulted in an improvement in hyponatremia, renal conservation of water still exceeded that of sodium in 3 of the 4 cases. Frisbie and Steele (1997) report in their retrospective review of 30 individuals that taking one dose of Ephedrine in the morning is usually sufficient to reduce symptoms of OH; however, some participants failed to recognize the need for a repeated dose later in the day.

L-threo-3,4-dihydroxyphenylserine (L-DOPS, Droxidopa)

L-DOPS is an exogenous, neutral amino acid that is also a precursor of noradrenalin. The pre-post study by Wecht et al. (2013) found that the use of increased doses of L-threo-3,4-dihydroxyphenylserine (droxidopa 100 mg, 200 mg, 400 mg) in hypotensive individuals did not cause excessive increases in supine blood pressure. Additionally, the 400-mg dose of droxidopa was found to be effective for increasing seated blood pressure for up to 3 hours. The expected fall in blood pressure when transferred to the seated position from supine was prevented with droxidopa 200 and 400mg, suggesting that L-threo-3,4-dihydroxyphenylserine is relatively safe and moderately effective for treating OH in people with SCI (Wecht et al. 2013).

Nitro-L-arginine methyl ester (L-NAME)

L-NAME decreases the production of the vasodilator, nitric oxide, by inhibiting the expression of its enzyme, nitric oxide synthase. Increased nitric oxide release has been associated with orthostatic intolerance after cardiovascular deconditioning and has been proposed to play a role in OH after SCI (Wecht et al. 2007). Three studies (La Fountaine et al. 2013; Wecht et al. 2009; Wecht, 2011) examined the use of L-NAME in the treatment of OH following SCI. These studies found that after infusion of 1.0 or 2.0 mg/kg of L-NAME, individuals with tetraplegia had a higher mean arterial pressure in response to orthostatic challenge (a head tilt procedure) compared to those who received a placebo. It should be noted that the increase in mean arterial pressure in the treatment group was not maintained over the entire head tilt procedure for all 3 studies; in La Fountaine et al. (2013), the effect was maintained for 1 additional hour post-infusion.

The studies addressing the pharmacological management of OH following SCI are limited by a small number of trials with few participants and numerous case reports. Furthermore, it is often difficult to determine the effects of individual medications when used in combination therapies. However, there is sufficient evidence to support the inclusion of Midodrine hydrochloride in the management protocol of OH. Further research is needed to quantify the effects of other pharmacological interventions that have been shown to be effective in conditions other than spinal cord injury.

Conclusions

There is level 1/2 evidence from 2 RCTs (Wecht et al. 2020; Wecht et al. 2023) that Midodrine may be effective in increasing BP in individuals with SCI who have OH.

There is level 2 evidence (from 1 RCT and 4 prospective controlled trials) (Nieshoff et al. 2004; Wecht, 2010; Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c) that Midodrine may be effective in reducing OH in individuals with SCI.

There is level 2 evidence (from 4 prospective controlled trials) (Wecht et al. 2011, Wecht et al. 2009; Wecht et al. 2008; Wecht et al. 2007) that L-NAME may be effective for reducing OH.

There is level 4 evidence (from 1 case series) (Barber et al. 2000) that fludrocortisone is not effective for OH in SCI.

There is level 3/5 evidence (from 1 retrospective chart review and survey) (Frisbie & Steele 1997) that Ephedrine may prevent some symptoms of OH.

There is level 4 evidence (from 1 pre-post study) (Wecht et al. 2013) that droxidopa may be effective for reducing OH.

Key Points

Midodrine hydrochloride should be included in the management protocol of OH in people with spinal cord injury.

There is limited evidence that the following agents are effective for the management of OH in SCI: ergotamine, fludrocortisone, ephedrine, L-DOPS, L-NAME.

5 Non-pharmacological Management of OH in SCI

In the literature on non-pharmacological management of OH in SCI, three studies involved the regulation of fluid and sodium intake, while others investigated physical modalities such as abdominal binders, whole-body vibration, physical activities, and electrical muscle stimulation.

Table 5. Non-pharmacological Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Gillis et al. 2008 Belgium Reviewed published articles from 1966 to April 2007 N=13 n=138 **Level of evidence:** Downs & Black scale **Type of study:** Parallel group, cross-over, quasi-random assignment AMSTAR: 5	**Methods:** Key word literature search for non-pharmacological management of OH during early rehab in SCI. **Databases:** PubMed/MEDLINE, OVID/EMBASE, CENTRAL	1. The evidence is inconclusive whether compression/pressure, upper body exercise and biofeedback therapies are able to control OH. 2. Upper body exercise may be more relevant to lower-level paraplegia where sympathetic outflow is intact and motor functionality is present. 3. FES can attenuate the drop in BP by 8/4 mm Hg during an orthostatic challenge and is promising technology. However, few studies utilized patients in the acute stage.

5.1 Fluid and Sodium Intake in Management of OH in SCI

OH is common among people with higher levels of SCI and may be present without symptoms. It often coexists with abnormal sodium and fluid metabolism; therefore, increases in fluid intake and a diet high in salt/sodium may expand extracellular fluid volume and improve orthostatic responses. This simple dietary intervention appears to be effective in individuals with idiopathic OH without SCI (Claydon & Hainsworth 2004; Davidson et al. 1976).

Table 6. Fluid and Sodium Intake for Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Frisbie & Steele 1997 USA Retrospective chart review and survey Level 3/5 N=231	**Population:** SCI; Ephedrine (medically treated for OH) group: mean(SD) age 57(15) years, mean(SD) duration of paralysis 26(15) years; No ephedrine group: mean(SD) age 51(15.2) years, mean(SD) YPI 22(13.5). **Treatment:** Retrospective chart review of use of ephedrine (n=30), sodium/salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. **Outcome Measures**: OH symptoms, serum sodium and urine osmolality.	1. 3/4 patients on ephedrine who started sodium/salt supplementation with meals became independent of ephedrine use. 2. Symptoms of OH were reduced consciousness (100% of participants), strength (75%), vision (56%) and breathe (53%). Precipitating factors were hot weather (77%) bowel care (33%) and meals (30%). 3. Low blood sodium found in 54% of the ephedrine (OH) patients and 16% of those without.
Frisbie, 2004 USA Case series Level 4 N=4	**Population:** Chronic cervical complete tetraplegia; AIS A **Treatment:** Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily) **Outcome Measures**: Severity of OH, urinary output.	1. With decreasing ephedrine dose (and OH severity), there was a mean increase in daily output of urine sodium (from 50 to 181 mEq), water (from 1.5 to 5.3 L), rate of creatinine secretion sodium concentrations, and rates of water excretion, and a decrease in urine osmolality.

Discussion

Three out of four participants taking sodium/salt supplementation with meals in Frisbie and Steele's (1997) study became independent of their use of Ephedrine. Frisbie (2004) demonstrated that the estimated daily intake of sodium and water was inversely related to participants' Ephedrine requirements and suggested that greater sodium and water intake may lead to a more balanced renal action. Frisbie & Steele (1997) results suggest that sodium and fluid regulation in conjunction with other pharmacological interventions may reduce symptoms of OH. However, as no evidence exists on the effect of sodium/salt or fluid regulation alone for OH management in SCI, these conclusions should be interpreted with caution.

Conclusion

While there are currently no guidelines suggesting appropriate water and sodium intakes specific to individuals with SCI, expert recommendation suggests increasing fluid and sodium intake could help treat OH symptoms (Krassioukov et al. 2021).

Key Points

The benefits of sodium/salt loading have not been sufficiently proven effective in individuals with SCI.

5.2 Blood Pooling Prevention in Management of OH in SCI

The application of external counter pressure using devices such as abdominal binders or pressure stockings is thought to decrease the capacitance of vasculature beds in the legs and abdominal cavity, both major areas of blood pooling during seating and standing.

Table 7. External Pressure Interventions for Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Wadsworth et al. 2012 Australia RCT Level 2 PEDro=4 N=14	**Population:** 14 adults with complete SCI (C3-T1; mean (SD) age: 32(16), range 18-73. **Treatment:** Abdominal binder (AB) on/off while seated in an upright wheelchair, with three repeated measures at 6 weeks, 3 months, 6 months after	1. No statistically significant improvement in mean arterial pressure (MAP) with use of the abdominal binder. 2. Variable responses: MAP greater with the AB at the 1st and 3rd time points; MAP was less with the AB at the 2nd time point. 3. Measures of supine and seated blood pressure were taken (allowing diagnosis of OH) but this was not a

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	commencing daily use of an upright wheelchair. **Outcome measures:** Forced vital capacity, forced expiratory volume, peak expiratory flow, max inspiratory and expiratory pressures, mean arterial pressure (MAP), max sustained vowel time, sound pressure level.	key outcome. 7 occasions of OH were found across participants as indicated by systolic blood pressure changes; 4 had OH regardless of AB application and 3 had OH without the AB only.
Hopman et al. 1998a The Netherlands RCT Level 2 PEDro=5 N=9	**Population:** 9 males, 5 with tetraplegia, 4 with paraplegia; 8 complete, 1 incomplete. **Treatment**: 5 discontinuous submaximal arm ergometer exercise tests on different days at 20, 40 and 60% of maximum power output while: 1) sitting, 2) supine, 3) sitting plus an anti-G suit, 4) sitting plus stockings and abdominal binder, and 5) sitting plus FES of the leg muscles. **Outcome measures:** Oxygen uptake (VO_2), carbon dioxide output, respiratory parameters, HR, BP, stroke volume, cardiac output.	1. Both FES and anti-G suit increased BP in participants with tetraplegia whereas binders and stockings reduced HR in those with tetraplegia 2. The interventions did not improve BP responses in participants with paraplegia, however FES and anti-G suit lowered HR.
Hopman et al. 1998b USA RCT Level 2 PEDro=4 N=9	**Population:** Same participants as above study. **Treatment:** 5 conditions as above except at maximal power output. **Outcome Measures:** VO_2, carbon dioxide output, respiratory parameters, HR, BP, stroke volume, cardiac output.	1. The supine posture increased peak VO_2 in people with tetraplegia, but reduced HR in those with paraplegia compared to sitting. 2. The relatively low pressure generated by stockings and bindings did not improve the venous system or cardiovascular responses during exercise. The positive circulatory benefits from FES and the anti-G suite observed in submaximal exercise (Hopman et al. 1998a) was not found for maximal exercise.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Krassioukov & Harkema 2006 Canada Prospective controlled trial Level 2 N=20	**Population**: 6 individuals with complete tetraplegia; 5 with complete paraplegia; AIS A; 9 controls without SCI. **Treatment:** With and without harness for locomotor training during supine, sitting and standing (within participant analysis). **Outcomes measures:** BP and HR.	1. Orthostatic stress significantly decreased arterial BP only in individuals with cervical SCI. 2. Harness application had no effect on cardiovascular parameters in controls, whereas diastolic BP was significantly increased in those with SCI. 3. Orthostatic changes in cervical SCI when sitting were ameliorated by harness application. However, while standing with harness, individuals with cervical SCI still developed OH.
Kerk et al. 1995 USA Prospective controlled trial Level 2 N=6	**Population:** Chronic complete paraplegia. **Treatment:** Crossover design: with and without an abdominal binder. **Outcome Measures:** BP, HR, VO_2max, respiratory parameters, and wheelchair propulsion.	1. 5/6 participants demonstrated a mean increase of 31% in forced vital capacity with binder compared to without, which was not significant but this may be because the sixth participant showed an 18% decrease in forced vital capacity when wearing the binder. 2. BP, HR, VO_2max increased significantly with increased exercise intensity and during maximal exercise, but these variables were not significantly affected by the use of the binder.
Rimaud et al. 2012 France Pre-post Level 4 N=9	**Population:** 9 men with (8 were highly-trained athletes who competed regularly at the national or international level); Level of lesion: >T6 (n=4), <T6 (n=5); age in years: 34±12 years; range 24-53; duration of injury: 10±10 years; range 2-34. **Treatment:** Two maximal wheelchair exercise tests with and without graduated compression stockings (GCS). **Outcome measures:** Heart rate variability (HRV): high frequency (HF), low frequency (LF), and LF/HF ratio; Norepinephrine	1. Increase in sympathetic activity and decrease in parasympathetic activity after maximal exercise in participants when wearing GCS as shown by the increase in LF and decrease in HF components; results further supported by an enhanced sympathetic activity at rest in SCI, as demonstrated by a significant increase in noradrenergic response when wearing GCS. 2. When wearing GCS: LF increased significantly and HF_{post} decreased significantly leading to an enhanced LF/HF ratio and a significant increase in resting NOR.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(NOR) and epinephrine (EPI); BP, heart rate, max power output, oxygen uptake, stroke volume, cardiac output.	
Rimaud et al. 2008 France Pre-post Level 4 N=9	**Population:** 9 men with chronic traumatic SCI, were divided into 2 groups: high paraplegia with lesion levels between T4 and T6 (n=4), and low paraplegia with lesion levels between T10 and L1 (n = 5) **Treatment:** 2 plethysmography tests: with and without graduated compression knee-length stockings (GCS) at rest. **Outcome Measures:** venous capacitance (VC); venous outflow (VO); heart rate; blood pressure.	1. No significant difference in HR or BP for either group or either treatment. 2. In both groups, VC values were lower with GCS than without. 3. VC and VO did not differ significantly with or without GCS.
Helmi et al. 2013 The Netherlands Case report Level 4 N=1	**Population:** A 61-year-old male with C3/C4 traumatic SCI with symptoms of presyncope as a result of severe OH after 60° head-up tilt. **Treatment:** Inflatable external leg compression (ELC); minimal ELC pressure to prevent OH (15 mmHg) found via tolerability test then applied in different positions (supine, 45°, and 60° head-up tilt). **Outcome measures:** External leg compression (ELC) pressure, mean arterial pressure (MAP), cardiac index, stroke volume index, heart rate, perfusion index (PI), peripheral tissue oxygen saturation (StO).	1. A 28% decrease in MAP when pressure decreased to 7 mmHg, below this level, dizziness rapidly occurred. 2. With the application of ELC 15 mmHg pressure during 45° and 60° head-up tilt: a. Stroke volume index and heart rate were maintained with no presyncopal symptoms. 3. Global and peripheral perfusion parameters improved.

Discussion

A systematic review by Krassioukov et al (2009) found prospective controlled trials showing that pressure from elstic stockings and abdominal binders may improve cardiovascular physiologic responses during submaximal upper-extremity exercises. The studies examining external pressure interventions generally test different pressure conditions with the same group of individuals (e.g. with and without stockings) either in a randomized order (RCT) (Wadsworth et al. 2012; Hopman et al. 1998a; Hopman et al. 1998b) or assigned order (non-RCT) (Helmi et al. 2013; Rimaud et al. 2012, Rimaud et al. 2008; Krassioukov & Harkema 2006; Kerk et al. 1995).

The application of these interventions must be interpreted with caution, as none of these studies assessed more than the effect of pressure application during acute phase. Whether these effects would persist with chronic use or cause any detrimental effects upon removal after extended use is unknown. Rimaud et al. (2008) suggested that graduated compression stockings worn by individuals with paraplegia may prevent blood pooling in the legs after observing a decrease in venous capacitance. However, these effects were seen when the participants were at rest and in the absence of orthostatic stress. Additionally, Rimaud et al. (2012) found that with the graduated compression stockings, sympathetic activity increased and parasympathetic activity decreased after maximal exercise in men with SCI. Furthermore, Kerk et al. (1995) reported that the application of an abdominal binder did not significantly improve cardiovascular or kinematic variables at submaximal or maximal levels of exercise. Similarly, a RCT by Wadsworth et al. (2012) found that abdominal binders did not significantly affect mean arterial pressure, and Bhambhani (2002) concluded that the use of abdominal binders does not influence cardiovascular responses. Conversely, Hopman et al. (1998b) demonstrated with nine participants with SCI that stockings and an abdominal binder have effects on cardiovascular responses during submaximal exercises, but not during maximal exercises. Moreover, Krassioukov and Harkema (2006) found that the use of a harness (which applies abdominal pressure) during locomotor training increased diastolic BP in those with SCI, but not in individuals without SCI.

Conclusion

There is conflicting evidence based on limited research that elastic stockings/abdominal binders have any effect on cardiovascular responses in individuals with SCI.

There is level 2 evidence (Krassioukov & Harkema 2006) that application of a harness in individuals with SCI could alter baseline cardiovascular parameters and orthostatic responses (e.g., during submaximal arm exercise).

Key Points

Pressure from elastic stockings and abdominal binders may improve cardiovascular physiologic responses during exercise; however, more research is needed to make clinical suggestions.

5.3 Whole-Body Vibration in Management of OH in SCI

Whole-body vibration (WBV) exercise is performed on a platform that generates vertical sinusoidal vibrations, stimulating muscle spindles and resulting in muscle contractions. The effect of WBV exercise on muscle activity is elicited through reflex muscle activation (Bongiovanni et al. 1990) and muscle twitch potentiation (Cochrane et al. 2010).

Table 8. Whole-Body Vibration in Management of OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Yarar-Fisher 2013 USA RCT (matched) Level 1 PEDro=6 N=21	**Population:** 11 men with SCI (mean age: 49±7 years; C4-T6; AIS A or B; ≥1 year post-injury) and 10 men without SCI: age: 48±8 years. **Treatment:** Randomly assigned to 30, 40 and 50 Hz synchronous-vertical whole-body vibration (WBV) with an amplitude (peak to peak) of ≈2 mm on three separate days. **Outcome measures:** Heart rate, mean arterial pressure (MAP), stroke volume, cardiac output, oxygen consumption (VO_2), relative changes in oxygenated, deoxygenated and total heme groups.	1. Both groups demonstrated small but significant increase in VO_2, oxygenated heme and total heme groups; increases were larger in the SCI compared to the control group. 2. Significant decrease in deoxygenated heme in the SCI group. 3. No frequency effect was observed. 4. WBV responses did not appear sufficient to induce cardiovascular benefits in the SCI group. 5. WBV maintained mean arterial pressure levels above the pre-WBV standing values.

Discussion

There is one RCT by Yarar-Fisher et al. (2013) that examined the effect of whole-body vibration (WBV) on blood pressure while standing and found that lower limb peripheral blood flow improved post-WBV. However, the clinical application of WBV in preventing orthostatic hypotension has not yet been studied.

Conclusion

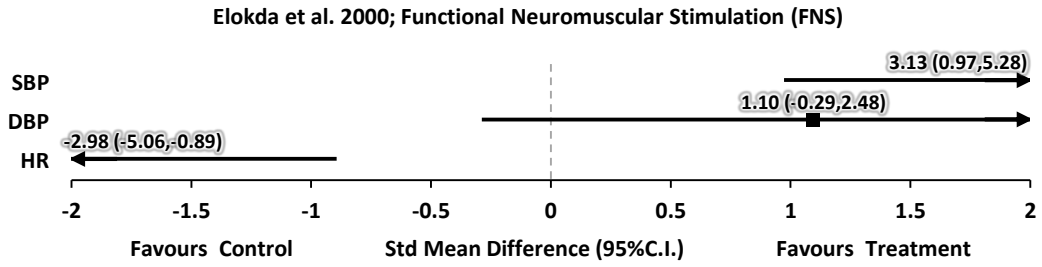
There is level 1 evidence (Yarar-Fisher et al. 2013) that whole-body vibration increases standing mean arterial pressure in individuals with SCI.

5.4 Effect of Functional Electrical Stimulation (FES) on OH in SCI

The application of FES triggers intermittent muscle contractions that activate the physiologic muscle pump. The physiologic muscle pump facilitates venous return via compression of the superficial and deep veins of the legs.

Table 9. FES on OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Faghri & Yount 2002 USA RCT Level 2 PEDro=2 N=29	**Population:** 7 individuals with paraplegia, 7 with tetraplegia; 4 incomplete and 10 complete injuries; 15 controls without SCI. **Treatment:** Random order of standing with or without FES (30 mins) for participants with SCI; voluntary tiptoe contractions during 30 minutes standing for participants without SCI. **Outcome Measures:** Hemodynamics during supine-sitting-30 min standing.	1. Significant reductions (up to 10%) in BP measures for participants with SCI from sitting to passive standing; but minimal changes when moving to FES standing. 2. After 30 min of passive standing there was a reduction in stroke volume and cardiac output. 3. After 30 min of FES standing, the pre-standing hemodynamics were maintained except for a significant reduction in SV.
Sampson et al. 2000 USA RCT Level 2 PEDro=3 N=6	**Population:** Motor complete SCI (lesions above T6); 3 with recent injury, 3 with long standing injury **Treatment:** With and without lower-extremity FES while tilted by 10° increments every 3 minutes, from 0-90° with varying intensities of stimulation. **Outcome Measures:** BP, HR, perceived syncope score.	1. HR increased for both groups with increasing incline angle. Mean diastolic BP was lower for the recent SCI group (105 mmHg) compared with chronic (123 mmHg). 2. Systolic and diastolic BP increased with increasing FES stimulation intensities and BP decreased with increasing incline angle of tilt regardless of the site of stimulation. 3. Participants tolerated higher angles of incline with FES than without. The higher the intensity of FES, regardless of stimulation site, the greater the tilt incline tolerated.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Elokda et al. 2000 USA RCT Level 2 PEDro=3 N=5	**Population:** 2 individuals with tetraplegia, 3 with paraplegia; all complete injuries; 2-4 weeks post-injury. **Treatment:** Tilt table - 6 minutes at each tilt angle (0, 15, 30, 45 and 60 degrees), with 4 minutes of recovery between each, with or without bilateral ankle plantar flexor and knee extensor electrical stimulation. Application order or absence of functional neuromuscular stimulation (FNS) was counterbalanced. **Outcome Measures:** HR, BP, perceived exertion.	1. At tilt angles of 15, 30, 45 and 60 degrees, systolic BP was significantly lower when FNS was not applied compared to when it was administered, and it was more marked with increasing tilt angles. 2. There was a progressive decrease in BP with increasing tilt angle and this increase was less pronounced in the FNS condition. 3. Post hoc analysis showed that HR was significantly higher with FNS compared to without FNS at 60 degrees tilt.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
Raymond et al. 2001 Australia Prospective controlled trial Level 2 N=16	**Population:** 8 male individuals with complete paraplegia, 8 male controls without SCI. **Treatment:** Lower-body negative pressure (LBNP) was used to provide the orthostatic challenge. Participants were evaluated: (1) during supine rest, (2) supine rest with submaximal arm crank exercises (ACE), (3) ACE+LBNP, and	1. ES increased stroke volume from ACE+LBNP to ACE+LBNP+ES condition for SCI group. 2. ES did not affect oxygen uptake or cardiac output in the SCI group.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(4) ACE+LBNP+leg electrical stimulation (ES). Controls participated in the first 3 trial only. **Outcome measures**: HR, stroke volume, cardiac output.	
Faghri et al. 2001 USA Prospective controlled trial Level 2 N=14	**Population:** 7 individuals with tetraplegia, 7 with paraplegia; 4 incomplete and 10 complete injuries. **Treatment:** FES augmented standing (active) and non-FES standing (passive), for 30min duration; tests were separated by at least 24 hours. **Outcome Measures:** Hemodynamics.	1. BP changed 8-9% when moving from sitting to passive standing (no FES). 2. The augmented FES condition prevented BP change when moving from sitting to standing.
Chao & Cheing 2005 China Post-test Level 4 N=16	**Population:** Motor complete tetraplegia **Treatment**: Progressive HUT maneuver with and without the FES to 4 muscle groups. **Outcome Measures:** BP, HR, perceived presyncope score.	1. Increasing tilt angle without FES significantly reduced systolic and diastolic BP and increased HR. 2. Adding FES to HUT significantly attenuated the drop in systolic BP by 3.7±1.1 mmHg, the drop in diastolic BP by 2.3±0.9 mmHg, and HR increased by 1.0±0.5 beats/min for every 15 degrees increment in the tilt angle. 3. FES increased the overall mean standing time by 14.3±3.9 min.
Daunoraviciene et al. 2018 Lithuania Pre-post Level 4 N=6, N=3 SCI	**Population:** N=6, 3 SCI, 3 stroke **Treatment:** 10 sessions of physical therapy with the verticalization robot, Erigo, during primary inpatient rehabilitation. Passive leg movements were started for 10-20 minutes if the participant was stable at 20 degrees. If the participant was stable after the first training exercise	1. Verticalization with FES reduced the occurrence of orthostatic hypotension and stabilised blood pressure (124.67 ± 7.57 mmHg to 114.67 ± 2.31 mmHg) and HR (65.67 ± 5.69 bpm to 64.00 ± 5.29 bpm), especially in participants with SCI. 2. Robotic training in combination with FES is safe and effective for gradually improving the cardiovascular system,

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	and had good orthostatic tolerance, sBP, and dBP, FES was applied to the quadriceps and calf muscles for 5 mins. **Outcome Measures:** Functional recovery, sBP, dBP, pain, and emotions.	orthostatic reactions, and postural control
Yoshida et al. 2013 Canada Cross-sectional Level 5 N=10	**Population:** 10 adults with SCI (C4-T7); 44±11 years; range 27-59; AIS: A (n=5), B (n=3), C (n=1), D (n=1); duration of injury: 10±9 years; range 2-29. **Treatment:** During head-up tilt (HUT), participants underwent four 10 min conditions in random sequence: 1) no intervention 2) passive stepping 3) isometric functional electrical stimulation (FES) of leg muscles 4) FES of leg muscles combined with passive stepping (dynamic FES). **Outcome measures:** Blood pressure (BP), heart rate, stroke volume, systemic vascular resistance, EMG signals of leg muscles, cross-sectional area of the inferior vena cava.	1. Incidents of OH during tests (based on changes in BP of participants): 6 during head-up tilt (HUT), 5 during passive stepping, 4 during isometric FES, 3 during dynamic FES. Despite this, no participants reported perceived symptoms of OH during the experiments. 2. FES and passive stepping independently mitigated a ↓ in stroke volume and helped maintain mean BP. 3. Effects of FES on stroke volume and mean BP were greater during passive stepping. FES and passive stepping combined didn't interfere with each other but did not synergistically ↑ stroke volume or mean BP.
Craven et al. 2013 UK Cross-sectional Level 5 N=6	**Population:** 6 individuals with SCI (C3-T9); Lesion grade: 3 complete (cSCI), 3 incomplete (iSCI); 22±4 years; range 18-25), iSCI 50±6; range 44-54); duration of injury: cSCI 18±3 years; range 16-21, iSCI 32±20 years; range 9-46). **Treatment:** Three experimental sessions (passive, active and FES-assisted) using a Robotic Assisted Tilt-Table (RATT); five phases of testing protocol for each session	1. Head-up tilt (HUT) tolerated well; no instances of hypotension or autonomic dysreflexia. 2. Incomplete (iSCI) participants: no change in oxygen uptake, respiratory exchange ratio (RER), minute ventilation, or heart rate (HR) in the first three testing phases; volitional participation in the stepping cycle and addition of functional electrical stimulation (FES) (phase 4a and b) led to significant ↑ in oxygen uptake,

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(phase 1&2: body positioning; phase 3: robotic orthoses with full guidance force; phase 4a: reduced guidance force for robotic orthoses, increased volitional effort; phase 4b: added FES to augment volitional force). **Outcome measures:** Oxygen uptake, respiratory exchange ratio (RER), minute ventilation, heart rate (HR), mean arterial blood pressure (MAP).	Respiratory exchange ratio (RER), minute ventilation, and HR; no significant change in mean arterial pressure (MAP). 3. Complete (cSCI) participants: small statistically significant ↑ in minute ventilation. 4. iSCI and cSCI participants: no difference in RER, minute ventilation, or HR response between groups in the first three testing phases. During phase 4b oxygen uptake, minute ventilation, and HR of participants with iSCI was significantly larger than those with cSCI. MAP was significantly larger across all phases for people with iSCI.
Faghri et al. 1992 USA Pre-post Level 4 N=13	**Population:** 6 people with paraplegia (T4-T10); 7 with tetraplegia (C4-C7). **Treatment**: FES-leg cycle ergometer (FES-LCE) training, 3X/week, for about 12 weeks (36 sessions). **Outcome Measures**: Oxygen uptake, pulmonary ventilation (VE), respiratory exchange ratio (RER), BP, HR, stroke volume (SV) and cardiac output (Q).	1. After training, resting HR and systolic BP were increased in participants with tetraplegia but were reduced in individuals with paraplegia. 2. In both groups, HR and BP during submaximal exercise significantly decreased and stroke volume and cardiac output significantly increased after training. 3. These results suggest that FES-LCE training improves peripheral muscular and central cardiovascular fitness in people with SCI.
Davis et al. 1990; USA Pre-post Level 4 N=12	**Population:** 12 males with paraplegia (T5-L2); FES Group, n=6; Non-FES (Control) group, n=6. **Treatment**: Sub-maximal and maximal arm-crank exercise with or without FES of paralyzed leg muscles. **Outcome Measures**: Peak VO_2, expired ventilation (V_E), perceived exertion respiratory exchange ratio	1. No significant differences between the FES and Control groups in terms of peak VO_2 (2.09 l/min), maximal HR, V_E, respiratory exchange ratio and perceived exertion. 2. No differences in power output or VO_2 during peripheral FES application but stroke volume and Q were higher during the FES- induced leg contractions on individuals that demonstrated visible isometric

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(RER), BP, HR, resting stroke volume (SV) and cardiac output (Q), total peripheral resistance.	contractions. Neither rest nor exercise HR was significantly influenced by lower limb FES. Increase of peripheral and overall ratings of perceived exertion. 3. HR, SV and Q were not significantly altered at rest or during hybrid exercise in Control group. Decrease of peripheral and overall ratings of perceived exertion. 4. No changes in BP, impedance indexes of myocardial contractility and differentiated subjective ratings of perceived exertion during hybrid exercise compared with non-FES conditions.

Discussion

FES may be an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI. Several studies have suggested that FES-induced contractions of the leg muscles increases cardiac output and stroke volume, which increases venous return (Raymond et al. 2001). Subsequently, this increases ventricular filling and left ventricular end-diastolic volume (i.e., enhanced cardiac preload). According to the Frank-Starling effect, an increase in ventricular preload will lead to greater stretch of the myocytes and a concomitant increase in left ventricular stroke volume. The increased stroke volume may produce greater cardiac output and consequently, greater arterial blood pressure. In this manner, FES-induced contraction of the leg muscles may attenuate the drop in systolic BP during an orthostatic challenge.

FES-induced contractions of the leg muscles may also restore the body's ability to redistribute blood from below the level of the lesion back to the heart. Davis et al. (1990) found that FES of the leg muscles resulted in increased cardiac output and stroke volume in 6 males with paraplegia performing maximal arm-crank exercise. These results suggest that FES of leg muscles could alleviate the lower limb pooling effect during orthostatic challenges. Chi et al. (2008) suggested that alleviation of the pooling effect could be further enhanced when FES of leg muscles is combined with passive mobilization. However, the clinical utility of this combination must be examined further in people with SCI as participants in Chi et al. (2008) did not have SCI. Further, a study by Daunoraviciene et al. (2018) found that FES applied to the quadriceps and calf muscles reduced the occurrence of OH and stabilised blood pressure and

HR when verticalized by Erigo, a verticalization robot. A cross-sectional study by Yoshida et al. (2013) compared isometric FES of leg muscles vs. passive stepping vs. isometric FES + passive stepping. They found that both FES and passive stepping increased stroke volume and mean BP, but that the highest increase resulted from combined FES + stepping; however, the two interventions did not interact to synergistically increase stroke volume and mean aBP.

Contrastingly, in a study by Phillips et al. (2018), all participants experienced OH during an orthostatic challenge which was reduced with FES; however, lower-limb skeletal muscle contraction did not occur, meaning the reduction in OH cannot be attributed to skeletal muscle pump action.

FES results in a dose-dependent increase in BP independent of the stimulation site, which may be a useful treatment adjunct to minimise cardiovascular changes during postural orthostatic stress in individuals with acute SCI (Sampson et al. 2000). Three level 2 RCTs (Faghri & Yount 2002; Elokda et al. 2000; Sampson et al. 2000) and five non-randomized controlled trials (Chao & Cheing 2005; Raymond et al. 2001; Faghri et al. 2001; Faghri et al. 1992; Davis et al. 1990) provide support for the use of FES in individuals with SCI. FES of the lower extremity could be used by people with SCI as an adjunct during standing to prevent OH and circulatory hypokinesis. An FES-induced leg muscle contraction can delay OH caused by tilting and allow people with tetraplegia to stand up more frequently and for longer durations (Elokda et al. 2000; Sampson et al. 2000). This effect may be more beneficial to those with tetraplegia who have a greater degree of decentralized cardiovascular autonomic control and may not be able to adjust their hemodynamics to the change in position (Faghri et al. 2001).

Current protocols predominantly evaluate BP after a single application of FES with a single change in position. The feasibility and practicality of implementing FES to influence orthostatic BP over time needs to be further explored.

Conclusion

There is level 2 evidence (from small, lower quality RCTs) (Faghri & Yount 2002; Elokda et al. 2000; Sampson et al. 2000) and level 4 evidence (from one pre-post) (Daunoraviciene et al. 2018) that FES is an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI.

Key Points

The use of FES is an effective adjunct treatment to minimize cardiovascular changes during changes in position.

5.5 Spinal Cord Stimulation on OH in SCI

Spinal cord stimulation, or epidural stimulation, is a form of FES that uses electrical currents on the lower spinal cord to stimulate the nerves and cause muscle contractions. An electrode is implanted into the epidural space behind the spine and electrical currents are sent directly to the bypassing brain-to-spinal cord pathways to help reactivate remaining intact neural networks that facilitate the movements to stand and walk.

Transcutaneous spinal stimulation (TSS) is another type of spinal cord stimulation that is non-invasive and uses electrical impulses applied to the skin to stimulate the spinal cord and potentially restore or improve motor function.

Table 10. Epidural Stimulation on OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Luz et al. 2023 Germany N=10 **Level of evidence:** **Type of study:** Scoping Review 2 case reports, 7 case series, 1 cohort study	**Methods:** Key word literature search for clinical studies reporting the effects of ESCS on lower and upper extremity sensorimotor function as well as on autonomic dysfunction after SCI. **Databases:** Medline, Cochrane, and Nature Medicine library	1. Transcutaneous and epidural spinal cord stimulation increased blood pressure by 10-40 mmHg during orthostasis-challenging situations such as moving from supine to sitting or standing.
Flett et al. 2022 Canada N= 19 N=1889 **Level of evidence:** **Type of study:** 10 case reports, 7 case series, 1 parallel group design, 1	**Methods:** Key word literature search for English-language journals restricted to the adult population with SCI on July 9, 2020 and repeated in May 2021. **Databases:** Medline, EMBASE, Scopus, CINAHL, SportDiscus, and Cochrane	1. 5 studies demonstrate the possibility of increasing BP during orthostatic challenge (including supine to sitting, sitting to standing, or receiving a head-up tilt test while secured to a tilt-table) using ESCS or TSCS 2. TSCS at T7/T8 reduced rectal stimulation-induced rises in BP but increased orthostatic challenge-related BP responses

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
double blind crossover		
Aslan et al. 2018 North America Pre-post Level 4 N=7	**Population:** N=7 males with chronic C5-T4 SCI **Treatment:** All participants were assessed for orthostatic tolerance prior to scES implantation. EMG signals were recorded bilaterally while the participant was supine or standing in response to scES. Data from 3 min of continuous blood pressure recordings were obtained after the participant completed the transition from sit to stand, and the EMG voltage had reached the level to sustain stable standing. **Outcome measures:** Beat-by-beat blood pressure, ECG, and electromyography	1. Individuals who demonstrated orthostatic intolerance during the orthostatic stress test (group 1) showed increases in sBP, dBP, and HR in response to increases in voltage of scES. Individuals who did not show orthostatic intolerance (group 2) demonstrated no increase in BP. 2. Individuals in group 1 experienced profound drops in BP upon standing accompanied by feelings of dizziness or fatigue without scES. With scES, the drop in BP and orthostatic symptoms were reduced. Individuals in group 2 did not experience a drop in BP upon standing and the application of scES did not increase their BP further.
Phillips et al. 2018 USA Pre-post Level 4 N=5	**Population:** N=5, 4 individuals with motor-complete cervical injury, 1 individual with motor-complete thoracic injury **Treatment:** 15 minutes of supine rest while being fitted with assessment equipment, followed by 10 minutes of supine rest, followed by a progressive orthostatic challenge. Participants rank their nausea/dizziness 1-10 each minute. Once BP decreased to clinically indicate OH, 30Hz of transcutaneous stimulation was applied via a self-adhesive electrode and was increased from	1. All participants experienced clinically defined OH which was reduced with stimulation at the TVII level. However, lower-limb skeletal muscle contraction did not occur, meaning the pressor response was not attributed to skeletal muscle pump action. 2. Heart rate did not decrease with stimulation leading SV to still be reduced

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	10mA until BP was normalised, up to a maximum of 70mA. **Outcome Measures:** Left brachial artery BP, and beat by beat blood flow velocity in the middle and posterior cerebral arteries.	
Harkema et al. 2018a US Case series Level 4 N=4	**Population:** N=4 with SCI, orthostatic hypotension, persistent low resting blood pressure, and symptoms of autonomic dysreflexia **Treatment:** participants completed 2 hour sessions of daily CV-scES training, measuring continuous blood pressure **Outcome Measures:** continuous blood pressure to assess hemodynamic response to orthostatic stress throughout training, with and without stimulation, sBP, dBP, and HR	1. Daily CV-scES training resolved orthostatic hypotension. Prior to training, participants experienced a significant decrease in mean BP and an increase in HR without stimulation, but with stimulation, sitting BP did not change significantly from supine values, and HR did not increase as significantly. 2. Similar results were seen after daily CV-scES training, even when presented with orthostatic stress without stimulation.
Harkema et al. 2018b US Prospective cohort study Level 2 N=4	**Population:** N=4 with chronic motor complete, cervical SCI **Treatment:** Participants rested in seated position for 2h with continuous BP and HR monitoring. CV-scES was configurated to maintain sBP within 105-120mmHg for 5 sessions of 2 hours each over 2 weeks. **Outcomes measures:** sBP, dBP, HR	1. Mean arterial pressure, sBP, and dBP increased significantly (p=0.0001) for each participant in response to CV-scES. Upon cessation of CV-scES, the rise in BP returned near or below each participant's baseline values within 15 minutes. 2. 3 individuals had no significant change in HR while 1 had a significant decrease during stimulation. Once CV-scES was turned off, HR was significantly greater than baseline for each participant. 3. Individuals reported physical changes during the sessions including: (1) a feeling of alertness or heightened awareness; (2)

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		increased ability to project their voice and carry on conversations; (3) increased capacity to breathe and cough; and (4) overall improved sense of well-being.

Discussion

A few studies have examined the effect of scES on OH symptoms and challenges. Preliminary results show that scES upon standing may increase sBP, dBP, and HR in individuals who demonstrate orthostatic intolerance (Aslan et al. 2018; Harkema et al. 2018b), but does not affect those who do not experience OH symptoms (Aslan et al. 2018). While the cessation of scES results in BP and HR returning to baseline (Harkema et al. 2018b), Harkema et al. (2018a) suggested that daily scES training may provide individuals with a BP increase and HR decrease upon sitting even when presented with orthostatic stress without stimulation.

Moreover, Aslan et al. (2018) found that individuals who demonstrated orthostatic intolerance upon standing experienced dizziness or fatigue without scES; however, these symptoms were mitigated with the use of scES. Further, individuals reported enhanced (1) feelings of alertness or heightened awareness; (2) ability to project their voice and have conversations; (3) capacity to breathe and cough; and (4) overall sense of well-being with scES (Harkema et al. 2018b).

Similarly, transcutaneous stimulation is a promising non-invasive tool for treatment of OH in people with SCI. A study by Phillips et al. (2018) found that transcutaneous stimulation at the TVII level reduced OH in all participants. However, heart rate did not decrease with stimulation, resulting in SV still being reduced. Additionally lower-limb skeletal muscle contraction did not occur, meaning that the pressor response was not attributed to skeletal muscle pump action.

Further research will be necessary to expand on the possibilities of spinal stimulation therapy and its effects on OH and other associated conditions in people with SCI.

Conclusion

There is level 4 evidence (from one pre-post) (Aslan et al. 2018) that scES reduced the drop in BP and orthostatic symptoms upon standing in individuals with SCI who demonstrated orthostatic intolerance.

There is level 2 evidence (from one prospective cohort study) (Harkema et al. 2018a) that daily CV-scES training reduced the drop in BP from supine to sitting, even when presented with orthostatic stress without stimulation,

There is level 2 evidence (from one prospective cohort study) (Harkema et al. 2018b) that CV-scES increases BP and enhanced individuals' (1) feelings of alertness or heightened awareness; (2) ability to project their voice and have conversations; (3) capacity to breathe and cough; and (4) overall improved sense of well-being.

There is level 4 evidence (from one pre-post) (Phillips et al. 2018) that TSS at the TVII level reduced OH in all participants; however, the reduction in blood pressure following TSS cannot be attributed to skeletal muscle pump action.

5.6 Effect of Exercise on OH in SCI

Following exercise, individuals with SCI may experience improvements in the autonomic regulation of their cardiovascular system (Lopes et al. 1984). Exercise, or even passive movement of the legs, could potentially attenuate the reduced central blood volume in individuals with SCI during an orthostatic challenge. For example, Dela et al. (2003), found a pronounced increase in BP in individuals with tetraplegia when their legs were passively moved on a cycle ergometer. There is also evidence that exercise training may enhance sympathetic outflow in individuals with SCI, as shown by an increase in catecholamine response to maximal arm ergometry exercise (Bloomfield et al. 1994).

Table 11. Exercise on OH in SCI

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Lopes et al. 1984 USA RCT Level 2 PEDro=2 N=12	**Population:** 5 tetraplegia, 1 paraplegia; 6 controls. **Treatment:** Random assignment to active exercise (60 bilateral forearm flexion and extension movements per minute during the first and third minute of each tilt angle) versus no upper limb exercises during tilt from 0-70 degrees by 10 degrees increments at five-minute intervals until BP dropped below 70/40. **Outcome measures:** BP, hypotensive symptoms.	1. No significant difference between the active upper extremity exercise group versus the non-exercise group with reference to orthostatic tolerance to progressive vertical tilt.
	Population: 10 men with tetraplegia, age: 29±6 years who were on a wheelchair basketball	1. During supine rest, trained participants with tetraplegia had

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Otsuka et al. 2008 Japan Prospective controlled trial Level 2 N=30	team and had physical training for at least 2hr/day, 2 days/week, for 2 years; 10 untrained men with tetraplegia, age 32±6 years and 10 sedentary men without SCI, age 23±2 years were included as controls. **Treatment:** regular physical activity training **Outcome Measures:** HR, BP; electrocardiogram; autonomic nervous system activity in supine and 60° sitting position.	significantly lower HR than the controls without SCI. 2. HR increased from supine to sitting position in trained and untrained participants with tetraplegia. 3. Untrained participants with tetraplegia, but not trained participants with tetraplegia demonstrated significant orthostatic responses (increased sympathetic activity and reduced vagal activity).
Ditor et al. 2005; Canada Pre-post Level 4 N=8	**Population:** Sensory incomplete (AIS B-C) cervical SCI (C4-C5). **Treatment:** 6 months of body weight-supported treadmill training (BWSTT). **Outcomes measures:** HR, BP, and orthostatic responses, heart-rate variability.	1. Resting HR was reduced but no change in resting BP after BWSTT. 2. BWSTT did not improve BP or HR during head-up tilt (HUT).

Discussion

Only three studies have attempted to assess the effect of exercise on orthostatic tolerance in people with SCI. Lopes et al. (1984) found no effects on orthostatic tolerance with the addition of upper extremity exercises during a progressive head-up tilt (HUT) protocol. These findings are not surprising given the small muscle mass involved in the upper limbs and the fact that venous pooling occurs primarily in the lower limbs. Ditor et al. (2005) demonstrated that individuals with incomplete tetraplegia retain the ability to make positive changes in cardiovascular autonomic regulation with BWSTT. However, six months of BWSTT did not adversely affect orthostatic tolerance in participants with SCI. The authors found this encouraging as it suggests that orthostatic tolerance can be retained after exercise training, even if it reduces peripheral vascular resistance. Otsuka et al. (2008) found that individuals with complete tetraplegia who were involved in regular physical activity training (2 hrs/day, 2 days/wk, ≥2 yrs) demonstrated greater orthostatic tolerance than inactive individuals with SCI (<30 mins/wk).

Conclusion

There is level 2 evidence (from 1 RCT) (Lopes et al. 1984) that simultaneous upper extremity exercises does not improve orthostatic tolerance during a progressive tilt exercise.

There is level 4 evidence (from 1 pre-post study) (Ditor et al. 2005) that 6 months of BWSTT does not significantly improve orthostatic tolerance during a tilt test.

There is level 2 evidence (from 1 prospective controlled trial) (Otsuka et al. 2008) that regular physical activity (2hrs/day, 2x/wk, ≥ 2yrs) may improve orthostatic tolerance during a tilt test.

Key Points

Simultaneous arm exercise during a tilt test is not effective for improving orthostatic tolerance.

The benefits of body-weight supported treadmill training for management of OH have not been sufficiently proven in SCI.

There is limited evidence that regular physical activity may improve orthostatic tolerance during a tilt test.

5.7 Effect of Standing on OH in SCI

Active stand training that emphasizes weight bearing is thought to stimulate the neuromuscular system below the level of injury in individuals with SCI and may affect the response to orthostatic stress by increasing venous return (Harkema et al. 2008).

Table 12. Standing on OH in SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Harkema et al. 2008 USA Pre-post Level 4 N=8	**Population:** 8 individuals with SCI, all AIS grade A (4 cervical, 4 thoracic), with no cardiopulmonary disease, aged between 21-55, mean(SD) 33.8(12.6) yrs. **Treatment:** Stand locomotor training (stand LT), for 60 minutes, five times per week.	1. OH present prior to training was not evident after 80 sessions of stand LT. 2. Significant improvements in cardiovascular response to standing in participants with cervical SCI. 3. Resting arterial BP increased significantly in individuals with cervical SCI after 80 sessions.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: BP and HR, measured while seated, seated with a harness, and standing with a harness; weight bearing load on legs; measurements taken before training, after 40 sessions, and after 80 sessions of training.	4. Hemodynamic parameters showed no significant difference pre- and post-training in participants with thoracic SCI. 5. All participants were able to bear more weight on legs after training.

Discussion

Only one study examined the effect of active stand training using the body weight support treadmill system on cardiovascular function among individuals with complete SCI. Harkema et al. (2008) found that after 80 sessions (60 minutes/session; 5x/week) of active stand training, individuals with complete cervical SCI demonstrated increased resting blood pressure and improvements in the cardiovascular responses to standing.

Conclusion

There is level 4 evidence (from 1 pre-post study) (Harkema et al. 2008) that 80 sessions of active stand training improves cardiovascular control such as response to orthostatic stress after cervical SCI.

Key Points

There is limited evidence that active stand training improves the response to orthostatic stress in people with cervical SCI.

6 General Discussion

The majority of our present understanding on the pathophysiology and management of the incapacitating symptoms of OH is derived from the management of OH in individuals with both central autonomic neurodegenerative disorders, such as multiple system atrophy and Parkinson's disease, and peripheral autonomic disorders, such as autonomic peripheral neuropathies and pure autonomic failure (Freeman, 2003; Mathias, 1995). From previous studies on individuals without SCI, it is well established that combining patient education with the use of

pharmacological and non-pharmacological modalities could lead to successful management of OH. Earlier literature suggested that the therapeutic goal for management of OH is not to normalize BP values, but rather to ameliorate symptoms while avoiding side effects (Kaufmann et al. 2006). However, evidence in the general medical literature supports associations between chronic asymptomatic hypotension and increased reporting of tiredness, malaise, fatigue and depression (Wessely et al. 1990; Pilgrim et al. 1992; Rosengren et al. 1993; Barrett-Connor et al. 1994), as well as deficits in cognitive performance (Costa et al. 1998; Morris et al. 2002; Weisz et al. 2002; Duschek et al. 2003). Asymptomatic hypotensive individuals with SCI actually performed significantly more poorly on tasks of memory and attention processing compared to a matched (i.e., for level of injury, self-reported incidence of traumatic brain injury and IQ) cohort of normotensive individuals with SCI (Jegede et al. 2010). Additionally, asymptomatic OH is associated with adverse changes in mood and cognition (Czajkowska et al. 2010), as well as increased morbidity and mortality (Benvenuto et al. 2011; Fedorowski et al. 2010). Lastly, diastolic blood pressure below 70 mmHg was found to be associated with increased all-cause mortality (Tringali et al. 2013).

The general approach to managing OH is to implement therapeutic interventions incrementally, depending on the severity of symptoms (Kaufmann et al. 2006). It is also known from previous studies in non-SCI populations that non-pharmacologic measures alone are often insufficient to prevent symptoms of OH. Thus, pharmacological interventions are needed, particularly in SCI patients with moderate to severe OH symptoms.

Although a wide array of physical and pharmacological measures are recommended for the general management of OH (Kaufman et al. 2006), very few have been evaluated for use in SCI. Of the pharmacological interventions, only midodrine has some evidence supporting its use and FES is one of the only non-pharmacological interventions having evidence to support efficacy, although limited. Furthermore, the number of studies addressing the pharmacological management of OH following SCI are few. It is often difficult to determine the effects of individual medications when they are used in combination therapies. Nonetheless, Midodrine hydrochloride should be included in the management of OH in individuals with SCI, while further research is needed to quantify the effects of other pharmacological interventions that have shown to be effective in other conditions of neurogenic OH.

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Abbreviations

AB	Abdominal Binder
BP	Blood Pressure
BWSTT	Body Weight Supported Treadmill Training
dBP/ DBP	Diastolic Blood Pressure
ELC	External Leg Compression
ESCS	Epidural Spinal Cord Stimulation
FES	Functional Electrical Stimulation
FNS	Functional Neuromuscular Stimulation
GCS	Graduated Compression Stockings
HR	Heart Rate
HUT	Head-up Tilt
LBNP	Lower Body Negative Pressure
L-DOPS, Droxidopa	L-threo-3,4-dihydroxyphenylserine
L-NAME	L-arginine-N-methyl-ester
MAP	Mean Arterial Pressure
OH	Orthostatic Hypotension
RATT	Robotic Assisted Tilt-Table
RER	Respiratory Exchange Ratio
sBP/ SBP	Systolic Bloor Pressure
scES	Spinal Cord Epidural Stimulation
TSCS	Transcutaneous Spinal Cord Stimulation
WBV	Whole Body Vibration