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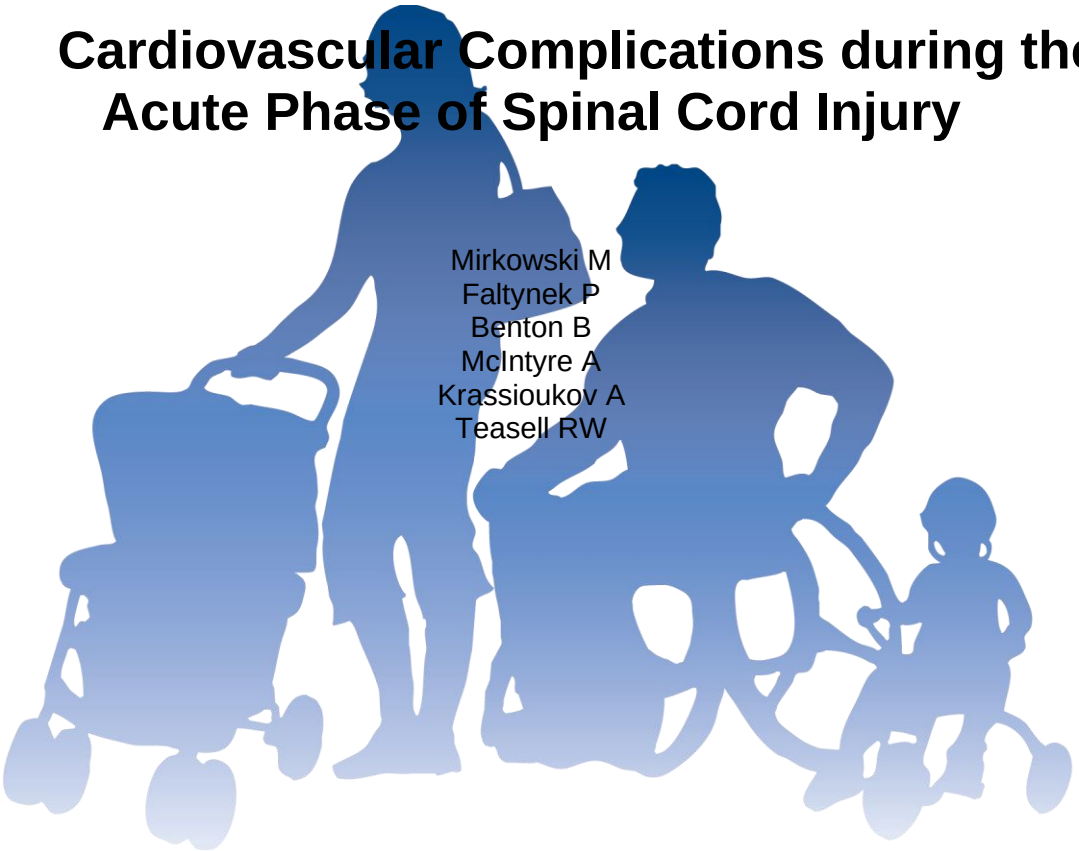
Cardiovascular Complications during the Acute Phase of Spinal Cord Injury



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Key Points

Pseudoephedrine may be an effective adjuvant for the treatment of neurogenic shock during the acute phase post SCI; however, pseudoephedrine may require up to one month for effectiveness and may result in higher complication rates for older patients.

The use of functional electrical stimulation in combination with tilt tables may be effective for the management of orthostatic hypotension during the acute and subacute phase post SCI.

Tilt table verticalization may be effective for lowering heart rate in patients post SCI.

Midodrine hydrochloride may be effective for the management of orthostatic hypotension during the acute phase post SCI.

Methylprednisolone appear to not be effective for the management of heart rate variability post SCI.

Hemodynamic support during the acute phase post SCI has been associated with improved neurological outcomes but no cause and effect relationship has been established.

Oral albuterol appears to be effective for the management of bradycardia during the acute phase post SCI.

Cardiac pacemaker implantation appears to be effective for the management of refractory bradycardia during the acute phase post SCI.

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Cardiovascular Complications during the Acute Phase of Spinal Cord Injury

1.0 Executive Summary

Cardiovascular complications post SCI fall broadly into four categories; neurogenic shock, orthostatic hypotension, hemodynamic changes, and bradycardia and arrythmias. Cardiovascular complications are common following SCI due to secondary dysfunction of the autonomic nervous system (Malmqvist et al. 2015). Given cardiovascular control is heavily dependent on neural control from medullar and spinal cord circuits, it is highly likely that SCI patients will experience some cardiovascular dysfunction. Currently there is no consensus as to whether injury severity is related to cardiovascular dysfunction (West et al. 2013).

Neurogenic Shock

Disrupted sympathetic and parasympathetic activity can lead to changes in arterial BP and HR. Neurogenic shock refers to the presence of bradycardia and arterial hypotension without a clear etiology (Furlan & Fehlings, 2008; Krassioukov, 2009; Popa et al. 2010). Bradycardia is defined as a HR of less than 60 beats per minute, and arterial hypotension is defined as a systolic BP below 90 mmHg and a diastolic BP of less than 60 mmHg (Popa et al. 2010; Wecht et al. 2013). Lower HR and lower BP is common among acute SCI patients due to reduced SNS activity. Initially post SCI, rates of neurogenic shock have been found to be anywhere between 7% and 24%, with 53% of cervical SCI patients presenting with neurogenic shock (Mallek et al. 2012; Ruiz et al. 2018). Treatments for neurogenic shock are primarily pharmacological. Vasopressor administration, in the form of pseudoephedrine, is the most commonly reported treatment, although there is a lack of strong evidence to support the continued use of pseudoephedrine as an intervention for neurogenic shock (Wood et al. 2014).

Orthostatic Hypotension (OH)

OH is identified as a minimum decrease in systolic BP of 20 mmHg, or a minimum decrease of 10 mmHg in diastolic BP when patients are moved to an upright position from lying posture. Observed incidences of OH in the SCI population are between 60-70%, with those with cervical and upper thoracic injuries having slightly higher incidence rates. For the treatment of orthostatic hypotension, tilt tables in combination with functional electrical stimulation are the predominant non-pharmacological interventions. Combining tilt tables with FES has been shown to be effective for improving and raising BP in SCI populations significantly (Tesini et al. 2013; Elokda et al. 2000). Tilt tables alone have been shown to reduce BP further, so tilt tables should be used in combination with FES; otherwise, there is the risk of further reducing BP in patients.

Hemodynamic Changes

Management of hemodynamic changes during the acute phase of SCI has focused on the effectiveness of early aggressive support on neurological outcomes. In general, hemodynamic management involves a multi-pronged approach which includes administering fluids, vasopressors, decompressive surgery, and pulmonary catheters. Two studies have shown that this type of aggressive treatment may be effective for improving neurological outcomes post SCI (Vale et al. 1997; Levi et al. 1993).

Conclusions

Incidences of cardiovascular complications post SCI are high, as vasculature control is provided by the T1 to L2 segments of the spinal cord. Proactively treating hemodynamic instability may improve neurological outcomes; treatment reacting to hemodynamic abnormalities post SCI has limited evidence and focuses on a combination of pharmacological and non-pharmacological treatments.

2.0 Methods

A key word literature search for scientific articles published from January 1, 1990 to August 31, 2018 investigating acute cardiovascular complications following spinal cord injury was conducted using the following online databases: MEDLINE, CINAHL, Scopus, EMBASE and Cochrane Library. Population key words (i.e., spinal cord injury, paraplegia, tetraplegia, and quadriplegia) and cardiovascular complication key words (i.e., neurogenic shock, bradycardia, arterial hypotension, orthostatic hypotension, and cardiovascular dysfunction) were used in combination. The search was limited to English publications that were either journal articles, reviews or systematic reviews (excluding case reports) with at least three adults (≥18 years) with spinal cord injury. More than 50% of participants included in the study had to have spinal cord injuries, unless the results were stratified. It should be noted that articles were considered suitable for inclusion in this chapter if all, or the majority of, participants in each study were approximately within 3 months of sustaining a SCI.

3.0 Introduction

The autonomic nervous system (ANS) is important for management and regulation of cardiovascular function. As such, spinal cord injury (SCI) is commonly associated with cardiovascular complications due to autonomic dysfunction (Malmqvist et al. 2015). As autonomic innervation of the cardiovascular system varies according to location along the spinal cord, abnormalities that arise following SCI are specific to the level of injury (Partida et al. 2016). Understanding cardiovascular dysfunction among individuals with SCI is crucial as it is a significant complication in the acute recovery of SCI.

4.0 Anatomy of the Autonomic Nervous System (ANS)

The ANS, both central and peripheral nervous system components, is crucial to proper cardiovascular control, and is affected by SCI (Furlan & Fehlings, 2008). The ANS controls involuntary responses relaying information from the central nervous system to target organs. The ANS is comprised of two opposing components, the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS), which provide balanced regulation. Two populations of neurons comprising efferent pathways involved in the transmission of information from the central nervous system to target organs. Preganglionic neurons reside centrally in brainstem or spinal cord gray matter and synapse onto peripheral postganglionic neurons, which are directly connected to and project onto the target organ. Parasympathetic preganglionic neurons are located within the nuclei of the four cranial nerves (CN III, VII, IX, X) as well as the sacral spine segments (S2-S4); therefore, parasympathetic outflow is both cranial and sacral. Sympathetic outflow is thoracolumbar, as preganglionic neurons are located within the thoracic (T1-T12) and upper lumbar (L1-L2) segments of the spinal cord.

The heart receives dual innervation from both the PNS and SNS. Parasympathetic cardiac innervation originates from the cardiovascular nuclei within the medulla oblongata located in the

brainstem and innervates the heart via the vagus nerve (CN X) and then through the sinoatrial node; it reduces heart rate (HR) and heart contractility. Sympathetic cardiac innervation stems from the upper thoracic segments of the spinal cord (T1-T5) and has a stimulating effect on these same functions of the heart. The sympathetic division of the ANS is also responsible for controlling the smooth muscle of peripheral blood vessels by inducing vasoconstriction, while there exists no corresponding parasympathetic innervation of the peripheral vasculature. Modulation of sympathetic and parasympathetic activity is determined by the baroreflex system, which monitors changes in arterial blood pressure (BP) by means of baroreceptors located in the aortic arch, carotid sinus and coronary arteries. Further, chemoreceptors in the carotid bodies detect changes in blood oxygen and carbon dioxide concentrations, and relay the information to help establish hemodynamic homeostasis. Together, the PNS and SNS interact to allow regulation of HR, BP and vagal tone (Furlan & Fehlings, 2008; Hagen, Rekand, Gronning, & Faerestrand, 2012; Krassioukov, 2009; Occhi et al. 2002; Popa et al. 2010; Sampson et al. 2000).

5.0 Effect of Disrupted Autonomic Control on the Cardiovascular System

An intact spinal cord is required for optimal autonomic function and cardiovascular stability (Furlan & Fehlings, 2008). Changes in cardiovascular function are lesion-dependent and unique to each SCI patient. Generally, higher-level spinal cord injuries result in the greatest degree of cardiovascular impairment and as such, cardiovascular complications subsequent to SCI are directly related to the neurological level of injury. After SCI, autonomic control of regions below the level of the lesion can be severely disrupted. Higher-level SCIs, particularly cervical or high-thoracic (T6 or above) injuries, are associated with significant SNS dysfunction as a consequence of the loss of supraspinal control of the SNS; this is considered the major cause of post-SCI hemodynamic imbalance and regulatory changes. Parasympathetic control of cardiac function is preserved following SCI as innervation to the heart is carried out via the vagal nerve and does not transmit through the spinal cord. Disruption of autonomic function caused by SCI results in disproportionate involvement of the SNS in comparison to the PNS in terms of hemodynamic regulation. Hypoactive sympathetic outflow together with unopposed parasympathetic activity through the intact vagal nerve leads to imbalanced autonomic control and disordered cardiac function, including clinical manifestations such as bradycardia, low resting blood pressure, and even cardiac arrest , which is particularly prominent in the acute phase post-SCI (Furlan & Fehlings, 2008; Phillips et al. 2012; Teasell et al. 2000; West et al. 2012). Regardless of the level of spinal cord injury, all blood vessels are still innervated. The SCI does not result in denervation, simply the central control is lost.

The relationship between injury severity (complete versus incomplete) and resulting cardiovascular dysregulation is less well understood and no clear association has yet been established (West et al. 2013). One of the consistent trends which has been observed is that baroreflex function and sensitivity is disrupted after SCI, although this is a more regular finding in high-level injuries (Phillips et al. 2012). Baroreflex dysfunction in SCI is thought to be influenced by increased stiffening of arteries, where stretch-receptors are located that transmit information on systemic BP (Phillips et al. 2014). Other observed alterations in cardiac function include electrocardiographic abnormalities, mean arterial blood pressure, increased BP during the night, and white matter loss (Furlan et al. 2016; Furlan, Fehlings et al. 2003; Summers et al. 2013; Goh et al. 2015).

The association between physiological dysfunction and cardiovascular complications occurring during acute SCI has been evaluated by five studies.

An observational study by Krstačić et al. (2013) assessed autonomic dysfuntion after SCI and the effect of the resulting altered sympathetic activity on the cardiovascular system. Acute cervical SCI patients were monitored beginning on their first day of hospital admission. The patients were evaluated for cardiac autonomic balance using an electrocardiogram to analyze heart rate variability (HRV) in time and frequnecy domains. As a parameter of HRV, the ratio of low to high freqencies represents sympathovagal balance, and was significantly reduced in the SCI patient group compared to the control group (0.41 versus 1.71, $p<0.001$); this indicates the presence of altered sympathetic activity in acute cervical SCI patients. Goh et al. (2017) observed that tetraplegics consistently had reduced blood pressure compared to paraplegics, and mobilizing controls in the acute phase. This difference, however, was no longer observable one year post admission.

Furlan et al. (2003) demonstrated an association between the location and severity of pathology in the spinal cord and cardiovascular dysfunction following SCI. This observational study retrospectively compared cervical SCI patients who developed severe cardiovascular dysfunction (Group 1) to those with no or minor cardiovascular dysfunction (Group 2). A control group of patients (Group 3) who had intact central nervous systems was also included for comparison purposes, and all patient information was collected during a 5-week post-injury period. Axonal preservation in the dorsal aspects of the lateral funiculus (Area I) and in the white matter adjacent to the dorsolateral aspects of the intermediolateral cell column (Area II) was significantly lower in Group 1 than in Group 2 participants ($p<0.034$ and $p=0.013$, respectively). There was an observed axonal loss of ~70% in Area I in Group 1 compared to 20% in Group 2 patients, and a 20% loss in Area II in Group 1 compared to 15% in Group 2 patients, suggesting the dorsal aspects of the lateral funiculus were the more likely site of descending vasomotor pathways contributing to cardiovascular dysfunction after SCI. Furlan et al. (2016) later found that there was no association between severity of SCI and cardiovascular dysfunction detectible by electrocardiograms. This suggests cardiovascular complications as a result of SCI may not be related to the severity of SCI but that the majority of those with an SCI are vulnerable to cardiac complications.

Finally, in an observational study by Summers et al. (2013), SCI patients were studied within the early stages of their emergency department resuscitation to determine the pathophysiology underlying neurogenic shock. Hemodynamic variables were collected from patients who were diagnosed with neurogenic shock using impedance cardiography. Etiology was variable; it was observed as a decrease in peripheral vascular resistance in 33% of patients, a loss of vascular capacitance in 22% of patients, or a combination of both, as seen in 33% of patients. Etiology was solely cardiac in the remaining 11% of patients.

6.0 Cardiovascular Complications during Acute SCI

As different regions of the spinal cord are responsible for different cardiac functions there are a variety of cardiovascular complications which can arise as a result of SCI. The supraspinal control of the heart is controlled at the C1-C8 level, sympathetic outflow to the heart is also affected by the T1-T5 level, and sympathetic control of the heart is maintained by the T6-T12 level (Malmqvist et al. 2015). As regions along the entire spinal cord are responsible for varying components of cardiac function, almost any SCI at the thoracic and cervical level can result is cardiovascular complications.

6.1 Neurogenic Shock

Disrupted sympathetic innervation and unopposed parasympathetic activity after a cervical or high-thoracic SCI leads to cardiovascular abnormalities, which includes profound changes in arterial BP and HR particularly in the acute phase. However, these complications can be short-term (acute), long-term (chronic) or both. During the acute phase of SCI, patients typically present with neurogenic shock, which refers to a condition that is characterized by the simultaneous presence of bradycardia and arterial hypotension without any other determined etiology. Together these conditions are recognized as an acute complication occurring following SCI (Furlan & Fehlings, 2008; Krassioukov, 2009; Popa et al. 2010).

Neurogenic shock is thought to be a consequence of a sudden reduction of sympathetic activity and output peripherally after SCI, in particular higher-level SCIs. Eight studies were found which investigated the incidence of neurogenic shock during acute SCI. Most of the studies used the term “neurogenic shock” when defining outcome measures, while others explicitly stated neurogenic shock as being determined by the presence of hypotension and bradycardia or by the presence of hypotension alone.

Zipnick et al. (1993) retrospectively reviewed patients who were admitted to an emergency department and noted an incidence of 7% acute neurogenic shock at the time of hospital arrival. Mallek et al. (2012) reviewed patients admitted to a trauma center beginning from their time of admission and observed a neurogenic shock incidence of 8.8% (16/180 patients); of those who endured neurogenic shock, 62.5% (n=10) of these patients had cervical SCI whereas 25.0% (n=4) had thoracic SCI and the remaining 2 patients had multiple levels of injury. In a more recent study, Ruiz et al. (2018) found slightly higher rates of neurogenic shock for those with cervical SCI at 53.6%. Guly et al. (2008) reviewed patients at first presentation to the emergency department. The incidence of neurogenic shock was subdivided by level of injury; 19.3%, 7%, and 3% of cervical, thoracic, and lumbar SCI patients developed neurogenic shock, respectively. Nakao et al. (2012) reviewed cervical SCI patients at 1 month after sustaining injury to investigate the incidence of hypotension. The authors defined hypotension as systolic atrial pressure <90mmHg or requiring intravenous administration of crystaloids and vasopressive agents. Within this population, 45.3% of patients were hypotensive. In a study by Bilello et al. (2003), patients who had sustained a high cervical (C1-C5) injury were reviewed and compared to patients who had sustained a lower cervical (C6-C7) injury. Patients were studied during the initial 24 hours of their intensive care unit stay (ICU). Neurogenic shock developed in 31% and 24% of high cervical injury and low cervical injury patients, respectively, although there was no significant difference in frequency of occurrence between these groups ($p=0.56$). Grossman et al. (2012) sought to determine the incidence of various acute complications that arise following SCI. Acutely injured patients were included in the study beginning from the time of hospital admission. Cardiac complications accounted for 21% of the most frequent severe complications, of which 45% involved severe bradycardia. Ravensbergen et al. (2014) evaluated SCI patients where data was collected on 5 occasions: at the start of and 3 months into inpatient rehabilitation, at rehabilitation discharge, and at 1 and 5 years after discharge. At the start of inpatient rehabilitation, participants were on average 100 days post injury, and the incidence of hypotension and bradycardia were recorded individually. Within this population, 33% of patients had hypotension and 4.5% of patients had bradycardia at the start of rehabilitation. The authors noted that there was no significant change in the prevalence of these complications over time. Finally, Tuli et al. (2007) conducted a post-hoc analysis as part of a multicenter RCT in part to assess the incidence of neurogenic shock among cervical SCI patients. Patients were acutely injured and were assessed beginning at their time of arrival at

the emergency department. Neurogenic shock developed in 13% of patients and was higher among AIS A (17%) and B (18%) patients compared to AIS C/D (7%) patients.

6.2 Orthostatic Hypotension (OH)

Orthostatic hypotension following SCI is commonly seen in patients with high SCI, especially early after injury (Sampson et al. 2000). Arterial hypotension is defined as a systolic BP below 90 mmHg and a diastolic BP of less than 60 mmHg (Popa et al. 2010; Wecht et al. 2013). OH occurs when there is a significant decrease in BP during postural changes, and may be symptomatic or asymptomatic (Illman et al. 2000). More specifically, OH is characterized by a decrease in systolic BP of 20 mmHg or more or a reduction in diastolic pressure of 10 mmHg or more on assuming an upright posture from a supine position (Claydon et al. 2006); it is often accompanied by an increase in HR as well. Postural hypotension for injuries above the thoracic SNS output is related to the absence of reflex vasoconstriction and pooling of blood in extremities due to reduced SNS efferent activity in response to sudden postural changes (Teasell et al. 1996).

The incidence of OH during acute SCI has been evaluated by two observational studies. Illman et al. (2000) observed patients who were undergoing initial physiotherapy treatments. BP was monitored during the baseline rest period, mobilisation treatment period, and upon resumption of the resting period. OH occurred during 73.6% of treatment sessions, and was present for all patients on at least one treatment occasion. The incidence of OH was higher among tetraplegic patients compared to paraplegic patients. Sidorov et al. (2008) performed a retrospective review of patients admitted to an acute SCI unit, beginning from the time of hospital admission and continuing for the duration of the first month following injury. The observed incidence of OH in this population was 60%, with a significantly higher occurrence among patients with cervical and upper thoracic SCI than among those with lower thoracic and lumbar SCI ($p<0.01$).

6.3 Autonomic Dysreflexia (AD)

Acute SCI patients may also experience autonomic dysreflexia, a condition characterized by transient episodes of hypertension and imbalanced reflex sympathetic discharge in response to stimulation below the level of injury. AD is a life threatening condition and if not recognised and timely managed could result in significant complications and even death (Dolinak et al. 2007; Pan et al. 2005; Wan et al. 2014). During AD, systolic BP can reach up to 300 mmHg and is accompanied by symptoms such as headache, slow HR and upper body flushing. This reaction is seen in SCI patients with lesions above level T6, with rare occurrences in injuries below this level (Karlsson, 2006; Krassioukov et al. 2003). AD is recognized as a cardiovascular complication more characteristic of subacute or chronic SCI but has been observed in some cases to occur earlier (Krassioukov, 2009; Krassioukov et al. 2003; Silver, 2000).

AD is well recognized as a complication characteristic of chronic SCI, as it does not occur immediately but can rather take several weeks or even months to develop post injury (Karlsson, 2006; Teasell et al. 2000). AD is clinically defined as a systolic blood pressure that rises above baseline by at least 20 mmHg (Krassioukov et al. 2012). To date, AD has also been documented to occur as an acute complication of SCI, although rarely. Only one observational study was found which investigated the incidence of this complication during acute SCI. Krassioukov et al. (2003) retrospectively reviewed the incidence of early episodes of AD within a group of acute SCI patients. In this population, 5.2% of patients developed early episodes of AD, occurring between four and seven days post injury. All individuals with evidence of early AD had complete cervical injuries. A case series by Silver (2000) of four patients with acute cord

transections reported the presence of early AD between days seven and 31 after sustaining injury.

6.4 Bradycardia and Arrhythmias

Bradycardia is defined as a HR of less than 60 beats per minute (bpm). Lower basal HR is regarded as a consequence of reduced SNS activity in the initial stages following SCI (Teasell et al. 1996). Those with cervical or high thoracic injuries are at particular risk of bradycardia and other arrhythmias. These injuries lead to dysrhythmias due to intact parasympathetic control combined with impaired supraspinal sympathetic control which leads to unchecked parasympathetic tone (Biering-Sørensen et al. 2018). The first few weeks after SCI is the most common time point for bradycardia or arrhythmias to occur, and become less common as time goes on (Biering-Sørensen et al. 2018). A study by Hector and colleagues (2013) found that in the first two weeks after cervical SCI the incidence of bradycardia was 14 to 77%. When looking at HR less than 50 bpm, the authors found this changed to 26 to 64% of cervical SCI patients, and a frequency of 0 to 13% in thoracic or lumbar SCI (Hector et al. 2013). Lastly, the authors found that bradycardia peaked 4 to 6 days after the cervical SCI (Hector et al. 2013). Other arrhythmias post-SCI occurred in 18 to 27% of cervical injuries, and none in thoracic or lumbar SCIs (Hector et al. 2013). The authors recommend using 24 hour ECG recordings as opposed to 12 hour recordings because many arrhythmias may be missed (Hector et al. 2013).

7.0 Interventions for Treatment of Cardiovascular Complications during Acute SCI

The majority of cardiovascular interventions are either pharmacological or surgical in nature. As complications often arise from the dysregulation of the autonomic nervous system, pharmacological means are the least invasive method to re-establish regulatory control. The following studies all include interventions aimed at improving the function of the autonomic nervous system post SCI.

7.1 Interventions for Treatment of Neurogenic Shock

The treatment of neurogenic shock requires correction of bradycardia and arterial hypotension, beginning with proper fluid resuscitation. There is limited evidence on the treatment of neurogenic shock despite it being a common complication.

7.1.1 Pharmacological Interventions for Treatment of Neurogenic Shock

Studies addressing the pharmacological management of neurogenic shock in acute SCI are limited. One study investigated the effect of pseudoephedrine as an adjuvant therapy in acute SCI patients (Wood et al. 2014). Pseudoephedrine is a stimulant and amphetamine.

Table 1. Pseudoephedrine as an Adjunctive Therapy for Treatment of Neurogenic Shock

Author Year Country Research Design Sample Size	Methods	Outcomes
Readdy et al., 2015 United States Cohort N=34	**Population:** Mean age: 61.53yr; Gender: males=28, females=6; Mean injury severity score=23.52; Mean ICU LOS (days)=11.67. **Interventions:** Vasopressor administration **Outcome Measures:** American Spinal Injury Association grade improvement, vasopressure administration, complications.	1. Nineteen patients (56%) saw an improvement of at least one ASIA scale score. 2. Thirty-one patients had dopamine administered, 22 had phenylephrine, 27 had dopamine administered first, 7 had phenylephrine administered first,

Author Year Country Research Design Sample Size	Methods	Outcomes
		18 patients had 2 vasopressors, and 12 had 2 or more vasopressors concurrently. 3. 90% of patients over 55 years old experienced complications, this is compared to 52% of younger patients. This effect was seen regardless of injury severity, ASIA scale score, and steroid administration. 4. Cardiogenic complications occurred in 26 patients, while the second highest complication was respiratory failure and urinary tract infections.
Phillips et al., (2014a) Canada PCT N=16	**Population:** Mean age=30yr (SCI Group), mean age=26yr (Able-bodied, AB Group); Gender: males=7, females=1 (SCI Group), males=7, females=1 (AB Group); Level of injury: C4-C7; Severity of injury: AIS A-B. **Intervention:** Patients with SCI (SCI Group) were given 10 mg of midodrine and compared to able-bodied controls (AB Group) who were not given treatment. Patients were transferred to a tilt table and tilted from supine to 30º, 45º, and 60º angles; hemodynamic data was collected at each position. This tilting procedure was conducted over 2d, during which SCI patients were administered midodrine or given no treatment in a randomized order. **Outcome Measures:** Baroreflex Sensitivity (BRS) and Common Carotid Artery (CCA) stiffness. **Chronicity:** 7 SCI patients were 6.5-11 weeks post injury, 1 SCI patient was 144wk post injury.	1. Arterial stiffness was elevated in SCI patients when in the upright position compared to AB controls ($p<0.05$). 2. In the SCI Group, there was a significant negative association between BRS and arterial stiffness in the upright position ($p=0.03$); no significant relationship was found in the AB Group ($p=0.15$). 3. Reduced BRS is related to increased arterial stiffness in SCI patients. 4. Midodrine led to increased BP and reduced HR in SCI patients compared to AB controls. 5. No changes in BRS or CCA parameters occurred after midodrine administration in SCI patients.
Wood et al., (2014) USA Case Series N=38	**Population:** Mean age=38.8 yr; Gender: males=29, females=9; Level of injury: C1-C7, below C7; Severity of injury: mean Injury Severity Score (ISS)=35. **Intervention:** Retrospective review of SCI patients admitted to an Intensive Care Unit (ICU) who were administered pseudoephedrine for more than one day or were receiving vasopressor support and/or atropine. **Outcome Measures:** Discontinued vasopressor use, decreased use of atropine, reduced bradycardic episodes. **Chronicity:** Mean ICU length of stay was 39d.	1. Pseudoephedrine success was observed in 31 of 38 (82%) patients. 2. Mean duration of pseudoephedrine therapy was 32d.

Discussion

A case series conducted by Wood et al. (2014) investigated the effectiveness of pseudoephedrine as an adjunctive therapy option to the use of vasopressors and atropine in

acute SCI. Patients who were administered pseudoephedrine for more than one day during their hospital stay or who received vasopressor support and/or atropine were retrospectively reviewed. Treatment with pseudoephedrine was considered successful based on discontinued vasopressor and atropine use, or a reduction in bradycardic episodes following pseudoephedrine administration; effectiveness was observed in 31 of 38 (82%) of patients. The mean duration of pseudoephedrine therapy was 32 days on average. A cohort study by Readdy et al. (2015) found that patients over the age of 55 had higher rates of complications. Cardiac complications occurred in 26% of patients. Complications regardless of severity of injury and vasopressor use.

Phillips et al. (2014) conducted a prospective controlled study to examine the association between baroreflex sensitivity (BRS) and common carotid artery (CCA) stiffness, as well as the influence of midodrine on BRS and arterial stiffness. The majority of SCI participants included in this study were within 6.5-11 weeks of injury, although 1 participant had chronic SCI and was 144 weeks after injury at the time of the study. Arterial stiffness was elevated in SCI patients compared to able-bodied controls when in the upright position ($p<0.05$). BRS and arterial stiffness were found to be negatively associated in the upright position in SCI patients ($p=0.03$), indicating that reduced BRS is related to increased arterial stiffness following SCI. Midodrine administration led to increased BP and reduced HR in SCI patients; however, it had no effect on BRS or CCA parameters.

Conclusion

There is level 4 evidence (from one case series study; Wood et al. 2014) that pseudoephedrine may be an effective adjuvant for the treatment of neurogenic shock in acute SCI patients; however, this pharmacological agent may require up to one month for effectiveness.

There is level 2 evidence (from one PCT; Phillips et al. 2014a) that midodrine may lead to increased blood pressure and reduced heart rate in SCI populations compared to health controls.

Pseudoephedrine may be an effective adjuvant for the treatment of neurogenic shock during the acute phase post SCI; however, pseudoephedrine may require up to one month for effectiveness and may result in higher complication rates for older patients.

7.2 Interventions for Treatment of Orthostatic Hypotension

OH can be managed through both non-pharmacological and pharmacological methods, although initial therapy emphasizes non-pharmacological treatment. Adequate fluid and salt intake is advised to maintain plasma volume while consumption of diuretics such as alcohol and caffeine is discouraged. SCI patients need also be aware of symptoms associated with OH and assume a recumbent position once symptomatic (Claydon et al. 2006; Popa et al. 2010). Non-pharmacological management may also include electrical stimulation of limbs, as well as compression/pressure devices (Gillis et al. 2008). Pharmacological management of OH includes using fludrocortisone, a cortiscosteroid, to expand plasma volume. Alternatively, midodrine hydrochloride, a sympathomimetic alpha$_1$-agonist, improves OH by increasing BP through

peripheral vasoconstriction, thus increasing total peripheral vascular resistance (Claydon et al. 2006; Phillips et al. 2014).

7.2.1 Non-pharmacological Interventions for Treatment of Orthostatic Hypotension

To date, studies addressing the non-pharmacological management of OH in acute SCI are limited. There have been several more non-pharmacological modalities of treatment studied in the chronic SCI population, including fluid intake and salt loading, use of elastic stockings and abdominal binders, harness application, whole-body vibration, exercise, and standing training (refer to SCIRE Orthostatic Hypotension rehabilitation evidence chapter).

Table 3. Non-pharmacological Management of Orthostatic Hypotension during Acute SCI

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Tesini et al., (2013) Switzerland RCT Crossover PEDro=4 N=9	**Population:** Median age=30.1yr; Gender: males=6, females=3; Level of injury: C4-T4; Severity of injury: AIS A-C. **Intervention:** Patients were positioned on a tilt-table at 0°, 15°, 30°, 45°, 60°, and 70° with individual electrical stimulation intensities depending on each patient; Patients underwent this tilting procedure for each of the following randomly assigned stimulation sites: A) abdominal muscles, B) lower limb muscles (Mm. gastrocnemii, hamstrings, Mm. quadriceps) C) combination of A and B, D) control (diagnostic) session. **Outcome Measures:** Systolic BP, diastolic BP, Mean Arterial Pressure (MAP), and Perceived Presyncope Score (PPS). **Chronicity:** Patients were 20-135 days (median=34 days) post injury.	1. BP did not differ significantly between the interventions (A, B, C, D) at any degree of incline ($p>0.05$). 2. BP was more stable up to 30° for A, B, and C interventions compared to D.
Elokda et al., (2000) USA RCT PEDro=3 N=5	**Population:** Mean age=29yr; Gender: males=5, females=0; Level of injury: C6-T8. **Intervention:** Acute SCI patients were examined during tilting (0°, 15°, 30°, 45°, 60°), with or without Functional Neuromuscular Stimulation (FNS) of the knee extensors and foot plantar flexors in a randomized treatment order. **Outcome Measures:** HR, systolic BP, diastolic BP. **Chronicity:** Patients were 1-6wk post injury (mean=3wk).	1. At 15°, 30°, 45°, and 60° tilt test positions, systolic BP without FNS was significantly lower than with FNS ($p=0.05$, $p=0.0001$, $p=0.04$, $p=0.007$, respectively). 2. At 30° and 45° tilt test positions, diastolic BP without FNS was lower than that with FNS ($p=0.02$, $p=0.01$, respectively). 3. HR progressively increased with tilt angle. 4. At the 60° tilt test position; HR was significantly higher with FNS than without FNS ($p<0.05$).

Author Year Country Research Design PEDro Sample Size	Methods	Outcomes
Sampson et al., (2000) Canada Pre-Post N_{Intial}=6 N_{Final}=3	**Population:** Mean age=30.3yr; Gender: males=6, females=0; Level of injury: C4-T4; Severity of injury: AIS A-B. **Intervention:** Patients were tilted by 10° increments from 0° to 90° at four Functional Electrical Stimulation (FES) intensities (0, 48, 96, and 160 mA); this tilting procedure was conducted for 2 separate stimulation sites: 1) quadriceps and pretibial muscles, and 2) patellae and malleoli. The order of stimulation intensities was randomized for each testing session. **Outcome Measures:** HR, systolic BP, diastolic BP, Perceived Presyncope Score (PPS). **Chronicity:** 3 patients had acute SCI (8-10wk post injury), 3 patients had chronic SCI (10-14yr post injury).	1. Mean systolic BP increased significantly with increasing stimulation intensities (p=0.001). 2. Mean diastolic BP increased significantly with increasing stimulation intensities (p=0.0019). 3. Mean systolic BP and diastolic BP decreased with increasing levels of incline angle (p<0.001). 4. Site of stimulation did not affect systolic BP or diastolic BP. 5. HR increased significantly with angle of incline (p<0.001). 6. Presyncopal symptoms were significantly greater with increased degrees of incline (p<0.001).
Daunoraviciene et al., (2018) Lithuania Pre-Post N=6	**Population:** ***Combined SCI and Stroke population:*** Mean age: 58.83yr; Gender: males=5, females=1; Severity of injury: AIS: C=3. **Interventions:** Verticalization training occurred with the use of a robotic tilt table, there were 10 sessions in total. Verticalization started at 20° and finished at 80°. During each 20-40 min session patients also experienced passive leg movement exercises if they remained stable throughout verticalization. **Outcome Measures:** Heart Rate (HR), Blood Pressure (BP), Berg Balance Scale (BBS) score, lower limb range of motion, (PASS), patient opinion of treatment. *Results reported for SCI only. **Chronicity:** Post-acute rehabilitation (2-4wk)	1. Compared to before treatment SCI patient's heart rate and systolic BP significantly decreased post treatment (p<0.05). BBS scores significantly increased post treatment (p<0.05). 2. Lower limb range of motion did not significantly change over the course of treatment. 3. PASS scores significantly increased post treatment in SCI patients (p<0.05). 4. SCI patients subjectively felt less confident in their training compared to stroke patients.

Discussion

Three studies have examined the non-pharmacological management of OH during acute SCI with electrical stimulation and tilt table verticalization. In a RCT by Elokda et al. (2000), five patients who were, on average, 3 weeks post SCI were examined during a tilting procedure with or without functional neuromuscular stimulation (FNS) of the knee extensors and foot plantar flexors. The effect of FNS on postural-related orthostatic stress was measured at 0°, 15°, 30°, 45°, 60° tilt angles. Measures of systolic BP at 15° (p=0.05), 30° (p<0.001), 45° (p=0.04), and 60° (p=0.07) positions without FNS were significantly lower than with stimulation, while measures of diastolic BP at 30° (p=0.02) and 45° (p=0.01) without stimulation were lower than with FNS. Sampson et al. (2000) studied six patients in a RCT who underwent a tilting

procedure at four functional electrical stimulation (FES) intensities (0, 48, 96, and 160 mA). Half of the participating subjects recruited for this study had an acute/subacute SCI as they were studied at 8-10 weeks post injury, while the other half were 10-14 years post injury (chronic phase of SCI). Patients were tilted by 10° increments from 0° to 90° during separate stimulation of the quadriceps and pretibial muscles, and at the patellae and malleoli. The authors observed a dose-dependent increase in BP, regardless of stimulation site. The mean systolic ($p=0.001$) and diastolic BP ($p=0.0019$) increased significantly with increasing stimulation intensities. Tesini et al. (2013) recruited nine patients who were a median of 34 days after injury. Participants were positioned on a tilt-table at increasing angles (0°, 15°, 30°, 45°, 60°, and 70°) with varying electrical stimulation intensities being used according to each patient. The tilting procedure was conducted for three sites of stimulation, which included the abdominal muscles, lower limb muscles, and a combination of abdominal and lower limb muscles, as well as a baseline measure without stimulation. Although a tendency towards the beneficial use of ES for OH was seen, BP was not observed to differ significantly between the interventions at any degree of incline ($p>0.05$ for all); however, the numbers were small.

In a more recent pre-post study, Daunoraviciene et al. (2018), found that tilt table verticalization was effective at significantly decreasing heart rate and systolic BP in SCI populations. Although this study aimed to assess motor function, there were significant effects on cardiovascular parameters which have implications for the management of OH.

Conclusion

There is level 2 evidence* (*from one RCT, one PCT and one pre-post; Tesini et al. 2013; Elokda et al. 2000; Sampson et al. 2000) that tilt tables in combination with functional electrical stimulation can effectively raise blood pressure in an SCI population, but not with tilt tables alone.

There is level 4 evidence (from one pre-post study; Daunoraviciene et al. 2018) that tilt table verticalization can significantly lower cardiovascular parameters in SCI patients.

The use of functional electrical stimulation in combination with tilt tables may be effective for the management of orthostatic hypotension during the acute and subacute phase post SCI.

Tilt table verticalization may be effective for lowering heart rate in patients post SCI.

7.2.2 Pharmacological Interventions for Treatment of Orthostatic Hypotension

Two studies have examined pharmacological interventions (midodrine and methylprednisolone) for the treatment of OH. While midodrine hydrochloride in acute OH has also been studied in case report format (Barber et al. 2000; Mukand et al. 2001), these studies did not meet SCIRE inclusion criteria. Several other pharmacological agents have been studied in the chronic SCI population, including fludrocortisone, dihydroergotamine, ephedrine, L-threo-3,4-dihydroxyphenylserine (LDOPS), nitro-L-arginine methyl ester (L-NAME), although little evidence exists regarding their use for OH in chronic SCI (refer to SCIRE Orthostatic Hypotension rehabilitation evidence chapter).

Table 4. Pharmacological Management of Orthostatic Hypotension during Acute SCI

Author Year Country PEDro Score Research Design Sample Size	Methods	Outcomes
Phillips et al., (2014b) Canada RCT crossover PEDro=3 N=20	**Population:** Mean age=30.7yr; Gender: males=7, females=3; Level of injury: C4-T5; Severity of injury: AIS A-B. Population demographics as stated above are for SCI patiently only. This study also included 10 age- and sex-matched able-bodied control individuals. **Intervention:** Patients were progressively tilted from supine to 30°, 45°, and 60°; this tilting procedure was conducted over 2 days, during which SCI patients were administered 10 mg of midodrine (treatment) or given no treatment (control, baseline measure) in a randomized order. **Outcome Measures:** Resolution of orthostatic hypotension (OH), Mean Arterial Pressure (MAP). **Chronicity:** 8 patients were <1yr post injury (6.5-11wk); 2 patients were >1yr post injury (144-324wk).	1. Midodrine lessened the decline in MAP from 0 to 60s after tilt; Posterior cerebral artery blood velocity did not decline as much 30-60s after tilt in the treatment group compared to the control group ($p<0.05$). 2. Midodrine led to a 59% improvement in orthostatic tolerance in the treatment group compared to the control group ($p<0.01$).
Krstacic et al., (2016) Croatia Prospective Controlled Trial N=40	**Population:** Tetraplegia. **Interventions:** Patients received either methylprednisolone or no treatment. The methylprednisolone group received an initial bolus of 30 mg/kg followed by 5.4 mg/kg every hour for 23hr. All patients had heart rate variability monitored by an electrocardiogram holter monitor. **Outcome Measures:** Heart rate frequency domains, heart variability time domains. **Chronicity:** Treatment was initiated within 8hr of injury.	1. There were no statistically significant results between groups on measures of heart rate variability.

Discussion

Two studies examined the impact of pharmacological management on OH during acute SCI. Phillips et al. (2014) conducted a RCT examining the effectiveness of midodrine for OH in10 SCI patients, the majority of which had acute injuries (6.5-11 weeks after injury). This study did also include two patients with chronic SCI who were 144-324 weeks after injury. Patients were subjected to a tilt-table procedure in which they were progressively tilted from supine position to 30°, 45°, and 60° angles. This procedure was conducted over two days, during which time the SCI patients were randomly assigned to receive 10 mg of midodrine orally, or no treatment (baseline measure). Improvement in orthostatic tolerance was observed in 59% of patients who received midodrine; this was a significant improvement compared to those who received no treatment ($p<0.01$). A more recent prospective controlled trial by Krstacic et al. (2016), examined the effects of methylprednisolone on heart rate in an SCI population. However, this

study found no significant differences between groups over a treatment period of 23 hours. Heart rate variability was monitored via an electrocardiogram holter monitor.

Conclusion

There is level 2 evidence (from one RCT crossover; Phillips et al. 2014) that midodrine hydrochloride leads to improved orthostatic tolerance in acute SCI patients.

There is level 2 evidence (from one PCT; Krstacic et al. 2016) that methylprednisolone may have no effects on heart rate variability in SCI populations.

Midodrine hydrochloride may be effective for the management of orthostatic hypotension during the acute phase post SCI.

Methylprednisolone appear to not be effective for the management of heart rate variability post SCI.

7.3 Interventions for Hemodynamic Management

The available evidence to date regarding hemodynamic management during the acute phase of SCI has focused on the association of early aggressive support and improved neurological outcomes. No cause and effect relationships have been established.

Table 5. Early Hemodynamic Management during Acute SCI

Author Year Country Research Design Sample Size	Methods	Outcomes
Vale et al., (1997) USA Pre-Post N=64	**Population:** Gender: males=29, females=6 (cervical SCI), males=25, females=4 (thoracic SCI); Level of injury: cervical (C3-C7), thoracic (T4-T12); Severity of injury: AIS A-D. **Intervention:** Prospective assessment of patients treated in the Intensive Care Unit (ICU) with aggressive hemodynamic support (including the use of arterial BP catheters, Swan-Ganz pulmonary artery catheters, intravenous fluids, colloid, vasopressors, and surgery for decompression and stabilization) as necessary to maintain Mean Arterial Pressure (MAP) >85 mmHg. **Outcome Measures:** Neurological improvement as per AIS classification. **Chronicity:** Patients were studied beginning within 36h of injury. Follow-up examinations were performed for each patient at 6, 12, and 18 mo post injury.	1. 60% of patients with complete cervical SCI and 33% of patients with complete thoracic SCI improved at least 1 ASIA grade at the last follow-up examination. 2. 92% of patients with incomplete cervical SCI and 88% of patients with incomplete thoracic SCI demonstrated improvement in neurological function 1yr post injury.
Levi et al., (1993) USA Pre-Post N=50	**Population:** Mean age=39.7 yr; Gender: males=88%, females=12%; Level of injury: cervical; Severity of injury: complete (78%), incomplete (22%). **Intervention:** Prospective assessment of patients treated in the Intensive Care Unit (ICU) with invasive hemodynamic monitoring and support (including the use of arterial line and Swan-Ganz catheters, fluid replacement, operative stabilization, and dopamine	1. Neurological function improved by at least one Frankel grade in 20 of 50 (40%) patients. 2. Neurological function remained the same in 21 of 50 (42%) of patients.

Author Year Country Research Design Sample Size	Methods	Outcomes
	and/or dobutamine) as necessary to maintain Mean Arterial Pressure (MAP) >90 mmHg. **Outcome Measures:** Neurological improvement as per modified Frankel classification. **Chronicity:** Patients were studied initially within the first week of injury. Follow-up examinations were performed at 6wk following injury.	

Discussion

Two studies have examined the association of early aggressive hemodynamic management and neurological improvement over time following SCI. In a study by Vale et al. (1997), 64 patients were treated with aggressive hemodynamic support as needed to maintain a MAP above 85 mmHg while in the ICU. Medical management included the use of arterial BP catheters, Swan-Ganz pulmonary artery catheters, intravenous fluids, colloid, and vasopressors. Surgery was also performed for decompression and stabilization. Treatment was initiated early after injury, beginning within 36 hours of sustaining SCI, and follow-up examinations were performed at 6-, 12-, and 18-month intervals. Improvement by at least 1 American Spinal Injury Assessment (ASIA) grade was observed in 60% of patients with complete cervical SCI and 33% of patients with complete thoracic SCI at the time of their last examination. Improvement in neurological function after 1 year following injury was observed in 92% of patients with incomplete cervical SCI and 88% of patients with incomplete thoracic SCI. Interpretation of this outcome must be taken with caution as there is no comparator group and thus, natural recovery could be occurring alongside the effects of hemodynamic support.

A similar study by Levi et al. (1993) examined 50 patients with cervical SCI who went through invasive hemodynamic monitoring and support during their ICU stay, beginning within the first week of injury. The treatment protocol included the use of arterial line and Swan-Ganz catheters, fluid replacement, operative stabilization, and dopamine and/or dobutamine as necessary to maintain a MAP of more than 90 mmHg. At 6 weeks following injury, improvement in neurological function was observed in 40% of patients and remained the same in 42% of patients. These studies need to be interpreted with care because no cause and effect relationship was established, and recovery may have occurred regardless of hemodynamic support.

Conclusion

There is level 4 evidence (from two pre-post studies; Vale et al. 1997; Levi et al. 1993) that aggressive hemodynamic support in acute SCI patients is associated with improved neurological function.

Hemodynamic support during the acute phase post SCI has been associated with improved neurological outcomes but no cause and effect relationship has been established.

7.4 Interventions for Treatment of Bradycardia

Current pharmacological management of bradycardia in SCI patients involves the use of different agents including phosphodiesterase inhibitors (e.g., aminophylline, theophylline), vasopressors, and chronotropic agents (e.g., atropine, epinephrine, norepinephrine) (Biering-Sørensen et al. 2018). Cardiac pacemaker implantation as therapy for bradycardia is only reserved for those patients with refractory bradycardia who do not respond to pharmacologic treatment (Evans et al. 2014; Franga et al. 2006; Ruiz-Arango et al. 2006; Sadaka et al. 2010; Wood et al. 2014). Treatment may warrant both alpha and beta-adrenergic actions as there is a loss of sympathetic tone and at the same time a need for chronotropic support (Biering-Sørensen et al. 2018).

7.4.1 Pharmacological Interventions for Treatment of Bradycardia

There is limited evidence to date regarding pharmacological interventions used for the management of bradycardia in acute SCI. Only two studies have been found which investigated albuterol as treatment for bradycardia in acute SCI patients. However, the effectiveness of other pharmacological agents (aminophylline and theophylline) for acute bradycardia post SCI has been studied in case reports which did not meet our inclusion criteria (Pasnoori & Leesar, 2004; Sadaka et al. 2010; Schulz-Stubner, 2005; Whitman et al. 2008).

Table 6. Oral Albuterol for Treatment of Badycardia in Acute SCI

Author Year Country Research Design Sample Size	Methods	Outcomes
Rollstin et al., (2016) United States Case Series N=11	**Population:** Mean age: 48yr; Gender: males=9, females=2; Mean time post injury= 10 days; Severity of injury: ASIA: A=7, B=3, unknown=1. **Interventions:** Oral albuterol **Outcome Measures:** Incidence of bradycardic events.	1. Patients had significantly fewer bradycardic events after albuterol initiation (p=0.013).
Evans et al., (2014) USA Case Control N=18	**Population:** Median age=49yr (albuterol group), median age=51 yr (no-albuterol group); Gender: males=75%, females=25% (albuterol group), males=80%, females=20% (no-albuterol group); Level of injury: C5 or higher (n=7, albuterol group), C5 or higher (n=7, no-albuterol group); Severity of injury: median injury severity score (ISS)=36.5, AIS A-C (albuterol group), median ISS=26, AIS A-B (no albuterol group). **Intervention:** Retrospective review of cervical SCI patients from a trauma center comparing those who were given (albuterol group) versus those who were not given (no-albuterol group) oral albuterol. **Outcome Measures:** Incidence of bradycardia; Hospital days requiring chronotropic use; Total atropine administered. **Chronicity:** Patients receiving albuterol were treated for a median of 5 days (range: 1-116 days); Patients not receiving albuterol were monitored for the initial 2wk of hospitalization.	1. All patients developed bradycardia: time to bradycardic episode was 0-13 days in the albuterol group, and 0-23 days in the no-albuterol group. 2. The median number of bradycardic episodes was significantly lower in patients receiving albuterol versus those not receiving albuterol (1.8 versus 4.3, p=0.08). 3. Hospital days on chronotropic agents were significantly lower in patients receiving albuterol versus those not receiving albuterol (0 versus 5.5, p=0.05). 4. The median total of atropine administered was significantly higher in patients not receiving albuterol versus those receiving albuterol (1 mg versus 0 mg, p=0.013).

Discussion

Two studies investigated the effectiveness of oral albuterol for treatment of bradycardia during acute SCI. Evans et al. (2014) conducted a case control study in which 18 patients with cervical SCI were retrospectively reviewed; 8 patients who were treated with oral albuterol during hospitalization following injury were compared to 10 patients not given this treatment. All patients developed bradycardia, however the median of bradycardic episodes was significantly lower (1.8) in patients receiving albuterol compared to patients not receiving albuterol (4.3, p=0.08). The authors also noted that the median total of atropine administered was significantly lower in patients given albuterol (0 mg) than in patients not given albuterol (1 mg, p=0.013). Rollistin et al. (2016) similarly found that patients given oral albuterol when compared to baseline assessment, had significantly fewer episodes of bradycardic events.

Conclusion

There is level 3 evidence (from one case control; Evans et al. 2014) that oral albuterol reduces bradycardic episodes in acute SCI patients.

Oral albuterol appears to be effective for the management of bradycardia during the acute phase post SCI.

7.4.2 Surgical Interventions for Treatment of Bradycardia

Evidence for non-pharmacological management of bradycardia in acute SCI has been surgical and focuses on the effectiveness of cardiac pacemaker placement.

Table 7. Cardiac Pacemaker Placement for Treatment of Bradycardia in Acute SCI

Author Year Country Research Design Sample Size	Methods	Outcomes
Moerman et al., (2011) USA Case Series N=106	**Population:** Mean age=46 yr; Gender: males=6, females=0; Level of injury: C2 to C7-T1; Severity of injury: average Injury Severity Score (ISS)=50 (21-75). **Intervention:** Retrospective review of cervical SCI patients from a trauma center registry to assess those necessitating cardiac pacemaker placement. **Outcome Measures:** Incidence of bradycardia; Resolution of bradyarrythmias/asystolic events. **Chronicity:** Time from admission to placement of cardiac pacemaker was 7-24 days (mean=11.5 days).	1. 15 (14%) patients had bradycardia. 2. Initial episodes of bradycardia occurred 3-9 days after admission (mean=5.7 days). 3. 7 (47%) patients underwent pacemaker placement; 6 had reviewable data and were included in the study. 4. Cardiac pacemaker placement led to resolution of all bradycardic episodes.
Franga et al., (2006) USA Case Series N=30	**Population:** Mean age=38 yr; Gender: males=3, females=2; Level of injury: cervical, high (C1-C5) or low (C6-C7); Severity of injury: complete.	1. 5 of 30 (17%) patients developed recurrent bradyarrythmias and/or asystole and underwent cardiac pacemaker implantation.

Author Year Country Research Design Sample Size	Methods	Outcomes
	Intervention: Retrospective review of cervical SCI patients from a trauma database who developed recurrent bradyarrythmias requiring aggressive medical management and cardiac pacemaker implantation. **Outcome Measures:** Incidence of bradycardia; Resolution of bradyarrythmias/asystolic events. **Chronicity:** Patients underwent pacemaker placement 16-36 days after injury.	2. No symptomatic bradycardic/asystolic events were noted after successful pacemaker placement.

Discussion

Two studies examined the implantation of cardiac pacemakers for the treatment of bradycardia during acute SCI. Pacemaker insertion occurred 9-17 days after injury. Compared to patients not requiring a cardiac pacemaker, patients who underwent pacemaker placement had bradycardic episodes over a significantly longer period of time (p=0.01) and a trend towards later bradycardic onset (p=0.05).

A case series by Franga et al. (2006) retrospectively reviewed five cervical SCI patients who developed recurrent bradyarrythmias requiring aggressive management and subsequently underwent cardiac pacemaker placement 16-36 days afer injury. No symptomatic bradycardic events occurred following successful pacemaker placement. In another case series by Moerman et al. (2011), 106 cervical SCI patients were reviewed from a trauma center registry. Of these patients, 14% were documented to have bradycardia, of which 47% underwent pacemaker placement. However, only 6 were deemed to have reviewable data; in these cardiac pacemaker placement led to resolution of all bradycardic episodes.

Conclusion

There is level 4 evidence (from two case series; Moerman et al. 2011; Franga et al. 2006) that cardiac pacemaker implantation eliminates bradycardic events in acute SCI patients.

Cardiac pacemaker implantation appears to be effective for the management of refractory bradycardia during the acute phase post SCI.

8.0 Summary

There is level 4 evidence (from one case series study; Wood et al. 2014) that pseudoephedrine may be an effective adjuvant for the treatment of neurogenic shock in acute SCI patients; however, this pharmacological agent may require up to one month for effectiveness.

There is level 2 evidence (from one PCT; Phillips et al. 2014a) that midodrine may lead to increased blood pressure and reduced heart rate in SCI populations compared to health controls.

There is level 2 evidence (from one RCT, one PCT and one pre-post; Tesini et al. 2013; Elokda et al. 2000; Sampson et al. 2000) that tilt tables in combination with functional electrical stimulation can effectively raise blood pressure in an SCI population, but not with tilt tables alone.

There is level 4 evidence (from one pre-post study; Daunoraviciene et al. 2018) that tilt table verticalization can significantly lower cardiovascular parameters in SCI patients.

There is level 2 evidence (from one RCT crossover; Phillips et al. 2014) that midodrine hydrochloride leads to improved orthostatic tolerance in acute SCI patients.

There is level 2 evidence (from one PCT; Krstacic et al. 2016) that methylprednisolone may have no effects on heart rate variability in SCI populations.

There is level 4 evidence (from two pre-post studies; Vale et al. 1997; Levi et al. 1993) that aggressive hemodynamic support in acute SCI patients is associated with improved neurological function.

There is level 3 evidence (from one case control; Evans et al. 2014) that oral albuterol reduces bradycardic episodes in acute SCI patients.

There is level 4 evidence (from two case series; Moerman et al. 2011; Franga et al. 2006) that cardiac pacemaker implantation eliminates bradycardic events in acute SCI patients.

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Abbreviations

AD	Autonomic Dysreflexia
AIS	ASIA Impairment Scale
ASIA	American Spinal Injury Association
ANS	Autonomic Nervous System
BRS	Baroreflex Sensitivity
BP	Blood Pressure
CCA	Common Carotid Artery
FES	Functional Electrical Stimulation
FNS	Functional Neuromuscular Stimulation
HR	Heart Rate
HRV	Heart Rate Variability
ICU	Intensive Care Unit
ISS	Injury Severity Score
MAP	Mean Arterial Pressure
OH	Orthostatic Hypotension
PNS	Parasympathetic Nervous System
PPS	Perceived Presyncope Score
RCT	Randomized Controlled Trial
SCI	Spinal Cord Injury
SNS	Sympathetic Nervous System