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Implication of altered autonomic control for orthostatic tolerance in SCI

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ABSTRACT

Neural output from the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) are integrated to appropriately control cardiovascular responses during routine activities of daily living including orthostatic positioning. Sympathetic control of the upper extremity vasculature and the heart arises from the thoracic cord between T1 and T5, whereas splanchnic bed and lower extremity vasculature receive sympathetic neural input from the lower cord between segments T5 and L2. Although the vasculature is not directly innervated by the parasympathetic nervous system, the SA node is innervated by post-ganglionic vagal nerve fibers via cranial nerve X. Segmental differences in sympathetic cardiovascular innervation highlight the effect of lesion level on orthostatic cardiovascular control following spinal cord injury (SCI). Due to impaired sympathetic cardiovascular control, many individuals with SCI, particularly those with lesions above T6, are prone to orthostatic hypotension (OH) and orthostatic intolerance (OI). Symptomatic OH, which may result in OI, is a consequence of episodic reductions in cerebral perfusion pressure and the symptoms may include: dizziness, lightheadedness, nausea, blurred vision, ringing in the ears, headache and syncope. However, many, if not most, individuals with SCI who experience persistent and episodic hypotension and OH do not report symptoms of cerebral hypoperfusion and therefore do not raise clinical concern. This review will discuss the mechanism underlying OH and OI following SCI, and will review our knowledge to date regarding the prevalence, consequences and possible treatment options for these conditions in the SCI population.

1. Introduction

The cardi5the autonomic nervous system (ANS) and sympathetic and parasympathetic influences are integrated to appropriately control heart rate (HR) and blood pressure (BP) during routine activities of daily living. Sympathetic control of the upper extremity vasculature and the heart arises from the thoracic cord between T1 and T5, whereas the splanchnic bed and lower extremity vasculature receive sympathetic neural input from the lower cord between T5 and L2. Although the vasculature is not directly innervated by the parasympathetic nervous system, the SA node is innervated by post-ganglionic vagal nerve fibers via cranial nerve X. Synergistic cardiac control by both branches of the ANS and segmental differences in sympathetic vascular innervation underscore the influence of lesion level on the HR and BP responses to daily activities following spinal cord injury (SCI) (Krassioukov and Claydon, 2006a).

Due to impaired ANS cardiovascular control, many individuals with SCI, particularly those with lesions above T6, are prone to persistent hypotension and bradycardia, with episodic falls in BP during upright positioning and severe increases in BP during autonomic dysreflexia (AD). While the definition of hypotension and bradycardia may vary, the *International Standards to Document Remaining Autonomic Function after Spinal Cord Injury* suggests a supine systolic blood pressure (SBP) below 90 mm Hg and a resting heart rate (HR) under 60 bpm (Krassioukov et al., 2012). The autonomic standards also recommends recording the presence or absence of orthostatic hypotension (OH), which is defined by the American Academy of Neurology and the American Autonomic Society as a reduction in SBP or diastolic blood pressure (DBP) of $\geq 20/10$ mm Hg within 3 min of standing (upright posture), with or without symptoms of orthostatic intolerance (OI) (Freeman et al., 2011). Although many individuals with SCI demonstrate falls in BP during orthostatic repositioning which meet the definition of OH, most do not report symptoms of OI.

OI reflects a constellation of neurological symptoms associated with episodic reductions in cerebral perfusion pressure. The most common complaints are light-headedness, dizziness or pre-syncope and syncope, as well as non-specific symptoms of generalized weakness, fatigue, nausea, cognitive slowing, blurred vision, leg buckling or headache. OI is generally considered a form of ANS dysfunction in association with OH, postural tachycardia syndrome and neurally-mediated hypotension

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and increased prevalence of OI is reported in conditions of chronic disease (Frith et al., 2014).

1.1. Mechanisms of OH & OI

In general, compromised adrenergic response to upright postures is believed to be the principal etiology responsible for OH and OI in the SCI population. Markedly reduced plasma norepinephrine (NE) concentrations in persons with cervical lesions compared to healthy uninjured controls in the supine and upright positions is reported and is thought to be responsible for persistent hypotension and OH (Claydon and Krassioukov, 2006a; Guttmann et al., 1963; Mathias et al., 1975; Wecht et al., 2008). Individuals with lesions below the cervical spine tend to have normal to high levels of plasma NE concentrations (Schmid et al., 1998a, 1998b) and, as a result, are less prone to hypotension, OH and OI (Krassioukov et al., 2009; Rosado-Rivera et al., 2011). Although markedly low plasma NE concentrations and postural hypotension persist in many individuals with chronic cervical lesions, symptoms associated with cerebral hypoperfusion abate over time and increased dependency on the renin-angiotensin-aldosterone system (RAAS) is believed to play a key role in reducing the severity of postural hypotension and the associated neurological symptoms (Mathias et al., 1975, 1980, 1981; Wecht et al., 2005). Heightened reliance on the RAAS for orthostatic BP control occurs independent of the sympathetic nervous system in persons with tetrapleiga (Mathias et al., 1980) and, because of its effect to promote vascular inflammation (Becher et al., 2011; Pacurari et al., 2014), may contribute to the increased incidence of cardiovascular disease in this population (Groah et al., 2001). The relatively low incidence of OI in the SCI population, despite significant postural falls in BP, may also reflect changes in autoregulation of cerebral blood flow in persons with tetraplegia. Although orthostatic change in mean arterial pressure (MAP) was significantly greater in individuals with tetraplegia compared to uninjured controls (-29 ± 14 vs. -13 ± 9 mm Hg, respectively; $p < 0.05$) the change in cerebral blood flow velocity (CBFv), as measured by transcranial Doppler ultrasound, did not differ significantly between the groups (-29.5 ± 13.2 vs. -22.9 ± 10.4 cm/s, respectively) (Handrakis et al., 2009). This finding supports functional autoregulation of CBFv in persons with chronic tetraplegia and suggests a mechanism underlying the relatively low incidence of OI in this population.

Baroreceptor dysfunction may also result in OH and OI in persons with SCI, particularly in those with lesions above T6. The baroreceptor reflex is a complex integration of stretch receptors located in the carotid sinus and the aortic arch, which modulate sympathetic and parasympathetic activity in response to changes in arterial pressure during orthostatic repositioning. Several investigators have documented impaired circadian baroreceptor regulation of BP and HR in persons with tetraplegia (Christ, 1979; Munakata et al., 1997; Nitsche et al., 1996; Rosado-Rivera et al., 2011). Investigation into the function of the baroreceptors during OI has been reported following exposure to microgravity (Ertl et al., 2000) and conditions of earth-bound immobilization, such as prolonged head-down bed rest (Convertino et al., 1990) and SCI (Phillips et al., 2012; Vaziri, 2003). The findings consistently suggest blunted cardio-vagal responses following prolonged exposure to microgravitational environments and conditions. However, due to the anatomical origin of the cardio-vagal reflex (i.e., cranial nerve X) individuals with SCI would not be expected to demonstrate blunted orthostatic cardio-vagal responses (Phillips et al., 2012), and in fact our group has noted increased reliance on vagal withdrawal for cardiovascular homeostasis during an orthostatic maneuver in individuals with SCI (Wecht et al., 2003a, 2006). Evidence suggests that cardio-vagal activity is related to cerebral autoregulation to maintain adequate perfusion pressure during acute hypotension in young healthy volunteers (Ogoh et al., 2010), which may contribute to the relatively low prevalence of OI in individuals with SCI. On the other hand, diminished sympathetic baroreceptor activity leads to significant reductions in vasomotor tone and poor orthostatic BP regulation in individuals with SCI, particularly in those with high cord lesions (Claydon et al., 2006b; Krassioukov and Claydon, 2006a). However, most investigations that address the sympathetic response to orthostatic provocation in the SCI population rely on surrogate estimates (i.e., frequency analysis of HR and BP), which present challenges to data interpretation (Phillips et al., 2012). With that caveat, diminished low frequency SBP variability (LFsbp) and reduced low frequency to high frequency ratio of HR variability (LF/HF) have been reported during orthostasis in individuals with high level SCI (Houtman et al., 2000; Koh et al., 1994; Wecht et al., 2003a, 2006). Although greater reductions in MAP and cerebral oxygenation were noted in response to lower body negative pressure (LBNP) in individuals with SCI compared to healthy uninjured controls, symptoms of OI were comparable (Houtman et al., 2001), suggesting adaptive changes in autoregulation of CBFv. Thus, despite reduced sympathetic baroreflex responses to orthostasis and prominent OH, individuals with SCI appear to have adapted to persistent hypotension and OH with appropriate changes in regulation of cerebral perfusion pressure and CBFv.

Reduced skeletal muscle mass and smooth muscle vascular tone may also contribute to OH and OI in individuals with SCI. Recent evidence suggests that distension of the lower extremity vasculature causes activation of muscle sympathetic nerve activity and increases in MAP independent of the baroreceptor reflex (Cui et al., 2015). However, this local reflex may be absent or diminished in individuals with SCI and evidence suggests that reduction in reflex vasoconstriction to the splanchnic bed and the lower extremity vasculature results in venous blood pooling (Agarwal and Pepper, 2005; Claydon et al., 2006b; Krassioukov and Claydon, 2006a). In addition to reliance on local and baroreceptor reflex neural control of vasoconstriction, the deep veins of the lower extremity rely on skeletal muscle contractions during gravitational challenge to maintain adequate blood volume distribution (Buckey et al., 1988). In fact, excessive blood pooling has been shown to reduce intrathoracic, end-diastolic and left ventricular stroke volume leading to lower cardiac output and BP during orthostasis (Ten Harkel et al., 1994). In addition, small increases in BP following physical countermeasures, to combat lower extremity blood pooling, results in beneficial effects on orthostatic tolerance in patients with autonomic failure (van Lieshout et al., 1992). Paralysis and disuse of the lower extremity musculature in individuals with SCI, regardless of the level of lesion, results in marked skeletal muscle atrophy, which would be expected to further compromise the distribution of blood volume during orthostasis, resulting in greater leg blood pooling, OH and OI. However, we reported reduced calf circumference but similar venous capacitance during head-up tilt in individuals with paraplegia compared to uninjured controls (Wecht et al., 2003b) and Houtman et al. reported greater reductions in MAP but comparable changes in stroke volume and cardiac output during graded LBNP in individuals with tetraplegia compared to healthy controls (Houtman et al., 2001). Additionally, peak change in calf volume in response to LBNP was significantly reduced in subjects with paraplegia compared to uninjured healthy controls (Raymond et al., 1999). These data suggest that, although skeletal muscle atrophy is evident in subjects with SCI, structural changes in the lower extremity vasculature may limit venous distention and blood pooling thereby allowing these individuals to maintain cerebral perfusion pressure and CBFv during periods of OH, thus reducing the incidence of symptomatic OI.

1.2. Prevalence of OH & OI

The impact of SCI on orthostatic BP regulation can be profound. It is apparent from relevant literature that the duration, severity and level of injury may play pivotal roles in determining the extent and the prevalence of OH and OI in the SCI population.