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Alterations in cardiac autonomic control in spinal cord injury

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ABSTRACT

A spinal cord injury (SCI) interferes with the autonomic nervous system (ANS). The effect on the cardiovascular system will depend on the extent of damage to the spinal/central component of ANS. The cardiac changes are caused by loss of supraspinal sympathetic control and relatively increased parasympathetic cardiac control. Decreases in sympathetic activity result in heart rate and the arterial blood pressure changes, and may cause arrhythmias, in particular bradycardia, with the risk of cardiac arrest in those with cervical or high thoracic injuries. The objective of this review is to give an update of the current knowledge related to the alterations in cardiac autonomic control following SCI. With this purpose the review includes the following subheadings:

2. Neuro-anatomical plasticity and cardiac control
2.1 Autonomic nervous system and the heart
2.2 Alteration in autonomic control of the heart following spinal cord injury
3. Spinal shock and neurogenic shock
3.1 Pathophysiology of spinal shock
3.2 Pathophysiology of neurogenic shock
4. Autonomic dysreflexia
4.1 Pathophysiology of autonomic dysreflexia
4.2 Diagnosis of autonomic dysreflexia
5. Heart rate/electrocardiography following spinal cord injury
5.1 Acute phase
5.2 Chronic phase
6. Heart rate variability
6.1 Time domain analysis
6.2 Frequency domain analysis
6.3 QT-variability index
6.4 Nonlinear (fractal) indexes
7. Echocardiography

Abbreviations: SCI, spinal cord injury; ANS, autonomic nervous system; BP, blood pressure; HR, heart rate; SA, sinoatrial; AV, atrioventricular; RVLM, rostral ventral lateral medulla; SPN, sympathetic preganglionic neuron; LV, left ventricular; AD, autonomic dysreflexia; SBP, systolic blood pressure; OH, orthostatic hypotension; DBP, diastolic blood pressure; NLI, neurological level of injury; ISAFSCI, International Standards to Document Remaining Autonomic Function after Spinal Cord Injury; CGRP, calcitonin gene-related peptide; AIS, American Spinal Injury Association (ASIA) Impairment Scale; CPG, clinical practice guidelines; Bpm, beats per minute; B60, 60 bpm; B50, 50 bpm; ECG, electrocardiogram; QTVI, QT-variability index; HRV, HR variability; NN, normal to normal; SDNN, standard deviation of all NN intervals; SDANN, standard deviation of the average NN intervals; RMSSD, root mean squared differences of successive NN intervals; PNN50, NN50 divided by the total number of NN intervals; LFP, low frequency power; LF/HF, low frequency to high frequency ratio; HFP, high frequency power; TP, total power; DFA, detrended fluctuation analysis; e′, early relaxation velocity; s′, early systolic myocardial velocity; E, early peak trans mitral blood flow velocity; LVEF, left ventricular ejection fraction; ISCoS, International Spinal Cord Society; NIH, National Institutes of Health; NINDS, National Institute for Neurological Disorders and Stroke; CDE, Common Data Element.

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1. Introduction

A spinal cord injury (SCI), depending on the level and severity of the damage to the cord, will interfere with smaller or larger parts of the autonomic nervous system (ANS), i.e. may involve respiratory, cardiovascular, urinary bladder, bowel, and sexual function etc. The effect on the cardiovascular system will accordingly depend on the extent of damage to the spinal/central component of ANS. The cardiac changes following SCI are caused by loss of supraspinal sympathetic control, which correspond to a relatively increased parasympathetic and decreased sympathetic activity (Fig. 1). This results in changes in the heart rate (HR) and the arterial blood pressure (BP) (West et al., 2013), causing arrhythmia in particular bradycardia with the risk of cardiac arrest or tachyarrhythmia mostly in those with cervical or high thoracic injuries (Grigorean et al., 2009).

2. Neuro-anatomical plasticity and cardiac control

2.1. Autonomic nervous system and the heart

Balanced control from the ANS is crucial for coordinating cardiovascular function. Although blood vessels receive predominately sympathetic innervation (with the exception of cerebral vasculature and genital erectile tissue cavernous bodies), the heart receives innervation from both divisions of the autonomic system: sympathetic and parasympathetic (Calaresu and Yardley, 1988; Coote, 2013). The heart has a unique function, known as automaticity, i.e. the muscle cells (cardiomyocytes) can depolarize spontaneously even in the absence of neural innervation. In contrast to skeletal muscles, this unique (self-exciting) characteristic of the myocardium results in spontaneous rhythmic contractions of the heart. The rhythmic contractions of the heart (sinus rhythm) are coordinated by the sinoatrial (SA) and atrioventricular (AV) nodes. The SA node (located in the upper wall of the right atrium and known as the “cardiac pacemaker”) is responsible for the generation of the wave of electrical impulses that initiates atrial contraction, which propagates to the AV node (localized in the lower right atrium). From the AV node electrical signals are conducted through the bundles of specialized myocardial fibers (known as Purkinje fibers) leading to ventricular contraction. Although the heart's rhythmic contractions occur spontaneously, the rate and rhythm of the contractions, as well as the force of the contractions (i.e., the contractility), can be adjusted by nervous or hormonal influences. Numerous neuroanatomical studies have demonstrated that cardiac sympathetic nerve fibers innervate the SA and AV nodes, the atria, the ventricles, and conducting tissue, whereas the parasympathetic fibers supply innervation to the SA and AV nodes alone (Coote, 2013).

It is known that numerous cortical and sub-cortical supraspinal centers (e.g., insula, anterior cingulate, medial prefrontal cortex, locus coeruleus and hypothalamus) provide excitatory and inhibitory influences on cardiovascular functions. Medullary neurons within the rostral ventral lateral medulla (RVLM) are considered to be the major sympathetic cardiovascular regulatory region responsible for maintenance and regulation of BP, with all other cardiovascular centers converging on this group of neurons (Krassioukov, 2009; Lebedev et al., 1986; Schreihofer et al., 2000). The sympatho-excitatory neurons within the RVLM provide input via descending spinal autonomic pathways to the sympathetic preganglionic neurons (SPNs), which are located within the spinal gray matter (majority of SPNs are located within the lateral horns) in spinal segments T1-L2. In terms of the parasympathetic division of the ANS, the vagal nerve exits the central nervous system supraspinally, and reaches the heart without traversing the spinal cord. Increases in sympathetic activity lead to increased HR, cardiac contractility, and vascular constriction; together leading to increased BP. On the other hand, vagal cardiovascular responses are limited to reducing HR and cardiac contractility and are widely appreciated to not extend to the vasculature itself, except in specific regions, including blood vessels of the salivary glands, gastrointestinal glands, genital erectile tissue, and potentially the cerebrovasculature (Suzuki et al., 1990).

2.2. Alteration in autonomic control of the heart following spinal cord injury

As is evident from clinical and animal experiments, there are noticeable alterations occurring in cardiac and other autonomic functions following SCI. The latest evidence suggests that the underlying mechanisms of cardiovascular changes following SCI result from significant alterations within a variety of autonomic circuits. These include the following: 1) the disruption of descending spinal cardiovascular pathways (Furlan et al., 2003); 2) initial sympathetic hypoactivity due to loss of supraspinal tonic sympathetic excitation (Maiorov et al., 1997); 3) alterations in the morphology of SPN's (Kalincik et al., 2010; Krassioukov and Weaver, 1996; Krenz and Weaver, 1998; Lujan et al., 2010); 4) plastic changes of the spinal circuits (i.e., dorsal root afferent sprouting, potential formation of aberrant synaptic connections (Krenz et al., 1999), or aberrant inputs to the spinal interneurons (Krassioukov et al., 2002); 5) altered sympatho-sensory plasticity (Ramer et al., 2012); and 6) altered peripheral neurovascular responsiveness (Alan et al., 2010; Phillips et al., 2016).

It has to be acknowledged that we are just beginning to understand the mechanisms underlying autonomic dysfunction following SCI. This is most certainly due to the complexity of the ANS as well as the limitations in using an animal model that may not fully represent clinical realities of patients following SCI. Presently, only a limited number of studies have addressed the alterations within autonomic circuits that involve cardiac/autonomic control. Due to only a hand-full of studies focused in this area, there is still no consensus on the specific changes within the autonomic circuits following SCI.

Most studies which describe the morphological changes within the spinal autonomic circuits have focused on spinal SPNs after SCI (Kalincik et al., 2010; Krassioukov and Weaver, 1996; Krenz and Weaver, 1998). According to earlier studies examining plastic changes following SCI, there was transient atrophy of SPNs innervating adrenal medulla below the injury (Krassioukov and Weaver, 1996). These investigators reported no change in SPNs morphology (soma size, dendritic length or number of primary dendrites) rostral to the transection, whereas caudally all observed parameters were decreased one week after SCI (Krassioukov and Weaver, 1996). These authors also documented that the morphology and dendritic arbor of SPNs were re-established one month post SCI (Krassioukov and Weaver, 1996). In a further study, to clarify the timeline of these changes, it was established that these plastic changes caudal to the injury were reversed around two weeks post injury (Krenz and Weaver, 1998). Interestingly more recent studies have contrasted these earlier findings. In the study by Kalincik et al., pronounced changes in soma size and in overall dendritic length in SPNs rostral compared to those caudal to the lesion were

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