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# Autonomic Nervous System Dysfunction Following Spinal Cord Injury: Cardiovascular, Cerebrovascular, and Thermoregulatory Effects

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**Abstract** Deficits in motor and sensory function secondary to spinal cord injury (SCI) are well appreciated and can be clinically assessed using the International Standards for the Neurological Classification of SCI (ISNCSCI), which were revised in 2010 and a dataset published in 2012. Subsequently, the International Standard on documentation of remaining Autonomic Function after SCI was established in 2012, which is to be used as an adjunct to the ISNCSCI exam. The autonomic nervous system is responsible, solely, or in part, for regulation of many physiological processes and the impact of SCI on this regulatory process cannot be overstated. However, given that most of these physiological processes occur without voluntary or conscience action, assessment of deficits in autonomic control is limited to end-organ function. Over the past 10 years, our knowledge regarding the underling pathophysiology of autonomic dysfunction after SCI has greatly improved. This review will focus on what is currently known and published regarding the loss of integral autonomic control of the heart and circulation and the consequent effects on the cerebral vasculature and thermoregulation.

**Keywords** Paraplegia · Tetraplegia · Parasympathetic · Sympathetic · Baroreceptor reflex

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## Introduction

### Underlying Pathophysiology of Abnormal Cardiovascular Control Following SCI

A variety of autonomic circuits have been highlighted that possibly contribute to abnormal autonomic regulatory control after spinal cord injury (SCI) [1]. The latest evidence suggests that disruption of descending spinal sympathetic pathways leads to a minimum of six neuroanatomical changes that influence autonomic cardiovascular control: (1) initial sympathetic hypo-activity due to loss of supraspinal tonic sympathetic excitation [2], (2) alterations in the morphology of sympathetic preganglionic neurons (SPN) [3], (3) plastic changes within the spinal circuits [4] (i.e., dorsal root afferent sprouting, potential formation of aberrant synaptic connections [5], or aberrant inputs to the spinal interneurons), (4) altered sympatho-sensory plasticity [6], (5) altered peripheral neurovascular responsiveness [7], and (6) cumulative effect of tertiary factors. These factors will be briefly discussed below.

#### *Autonomic Pathways and SPN Plasticity*

It is appreciated that during the acute stage after SCI (within the first few months) the SPN atrophy; however, recent evidence suggests that, over time, they may re-gain somewhat normal morphology (i.e., similar soma size as pre-injury, but more dendritic arbor and aberrant connections) [8]. It is most likely that the loss of electrical input from descending projections of medullary neurons, which are thought to synapse directly with SPN, and the consequent reduction in trophic support results in the initial atrophy of SPN. In the very early phase after SCI, loss of descending inhibitory pathways predisposes individuals to early episodes of autonomic dysreflexia (AD), while subsequent atrophy of SPN leads to an intermediate period where AD may be less severe [8]. Disrupted descending pathways, as well as atrophied SPN, likely contribute to reduced sympathetic tone and very low resting blood pressure as well as the increased prevalence of orthostatic hypotension (OH) during the acute period following injury. As the phase of injury transitions into the more chronic stage, AD may manifest again [1], and is most commonly documented during the sub-acute and chronic stages of SCI [9]. In fact, AD often manifests 2–3 months after SCI in those with lesions above the T6 spinal segment [10].

#### *Dorsal Afferents and Intraspinal Plasticity*

Exaggerated sensory input to the spinal cord occurs caudal to the site of injury after SCI. Evidence from animal studies suggests that dorsal root afferents sprout along with an enlargement of soma size in the dorsal root ganglia after SCI [5, 11]. Specifically, there is an intrusion of calcitonin gene-related peptide immunoreactive (CGRP+) afferent fibers further into the spinal cord (quantified as increased CGRP+ fibers in Lamina II–V post SCI) [12], accompanied by somal hypertrophy of the transient receptor potential cation channel sub family V member 1 (TRPV1) in the dorsal root ganglia [6]. It is likely that primary afferents such as CGRP+ axons in the dorsal root ganglion sprout and extend from their proper location (Laminae I–II) [8]. Increased sprouting of primary afferents, would generate new intraspinal circuits [4], which is a suspected mechanism underlying AD due to similar time-courses [4, 11] and its relation to AD severity [13].

#### *Peripheral Vasculature Component*

An additional autonomic alteration associated with vascular dysfunction after SCI includes hyper-responsiveness to alpha-adrenergic stimulation. Heightened mesenteric artery responsive to the pressor agent phenylephrine has been demonstrated in rodents after SCI, which was secondary to impaired neuronal reuptake [14, 15]. An exaggerated pressor response to norepinephrine [16] and a nitric oxide synthase inhibitor (L-NAME) [17] has been reported in humans with SCI compared to intact controls. In addition, it has been reported that sympathetically correlated spinal interneurons are hypersensitive to afferent stimuli after SCI [4, 8]. Together, the combination of vascular hyper-responsive interneurons and increased influence from primary afferents, creates a ‘perfect-storm’ of neural reorganization that predisposes to episodes of transient hypertension in response to nociceptive or non-nociceptive afferent stimulation (i.e., AD). Reductions in AD severity have been reported after interventions showing no reduction in blood vessel hyper-responsiveness [14], suggesting other factors, such as altered sympatho-sensory plasticity, may be playing a more central role.

### The Heart

#### *Cardiac Structure and Function*

Cardiovascular decline is apparent through a number of deleterious alterations in the cardiovascular end-organs; some of which occur at a remarkably rapid rate [18•]. Several studies have reported a lesion-dependent impairment in cardiac structure and function. Evidence of reduced cardiac dimension and mass is reported in individuals with tetraplegia [19], whereas more equivocal data are reported in those with paraplegia [20]. The effect of SCI on ventricular function is less clear, and there are a number of articles reporting diminished systolic and

diastolic function [19–21] as those reporting similar function [22, 23] compared to able-bodied controls. Differences in cardiac structure and function in rodents with SCI at the high-thoracic (T3 complete transection) [24] versus mid-thoracic level (T5 complete transection) [25•, 26] illuminate the role of decentralized supraspinal sympathetic cardiac control in the development of cardiac abnormalities post-SCI. Specifically, high-thoracic SCI compromises cardiac size and contractile function while increasing relative wall thickness and myocardial collagen expression in the left ventricle. In rats with mid-thoracic SCI, cardiac fibrotic remodeling is also reported [26], but impaired contractile function is only present under beta-adrenergic blockade [25•]. It must be appreciated that volume unloading may be the principle mechanism responsible for cardiac decline in cervical/high thoracic SCI. Specifically, reductions in blood volume, sub-lesional muscle pump activity, and sympathetically mediated vasoconstriction limit cardiac pre-load and ventricular filling [27].

In humans with cervical SCI, external compression of the abdomen and/or lower limbs acutely improves venous return and stroke volume [28, 29]. However, in those with preserved supraspinal sympathetic cardiac control, volume support via external compression is largely ineffective in improving cardiac function [30], suggesting other factors must be responsible for cardiac dysfunction in this subgroup. In rodents with SCI, chronic passive-lower limb cycling improves cardiac function and mitigates the decline in cardiac contractility likely through long-term improvements in venous return, resulting in mitigated cardiac fibrosis [24]. Intriguingly, rodent studies of mid-thoracic SCI report increased density of left-ventricular myocardial sympathetic nerve fiber terminals (hyper-innervation) along with increased dendritic arborization of the cardiac pre- and post-ganglionic sympathetic neurons [31]. This hyper-innervation may be one mechanism by which rodents are able to maintain contractile function in the face of reduced cardiac filling, since beta-blockade revealed a much greater reduction in cardiac contractility in mid-thoracic SCI rats than in uninjured controls [31]. Unfortunately, there appears to be a number of deleterious consequences of this hyper-innervation, including an increased susceptibility to arrhythmias, which has been reported in both rodents and humans with SCI [32, 33].

Although the literature to date is limited by varied inclusion criteria and often a lack of controlling for both level of injury and autonomic completeness of injury, the pattern of findings to date suggests that cervical and/or high thoracic SCI is associated with reduced cardiac dimensions and systolic function that is likely caused by reduced cardiac filling. For mid-to-low thoracic SCI, the degree of cardiac dysfunction appears to be reduced—although alterations in sympathetic innervation of the heart likely underlie electrocardiographic abnormalities reported in this population. Promising interventions are available to promote cardiac filling, but future studies that carefully control inclusion criteria are required to confirm their effectiveness and exact mechanism of action.

### *Heart Rate Variability and Autonomic Cardiac Control*

Although cardiac pacemaker cells of the heart provide an intrinsic heart rate (HR) without neural influence, extrinsic (to the heart) autonomic control modulates HR under resting and provocative conditions. Cardiac parasympathetic fibers originate from the vagus nerve to hyperpolarize the pacemaker cells and reduce HR; whereas sympathetic fibers originating from the upper thoracic cord increase the rate of depolarization and increase HR and contractile forces. Therefore, high-thoracic or cervical SCI will affect autonomic modulation of the heart. The degree of cardiac autonomic impairment post-SCI can be ascertained using HR variability (HRV) techniques, which define the variability (msec) between consecutive heart beats in both the time and frequency domains [34].

Several investigators have used frequency domain measures of HRV to demonstrate signal amplitudes in the high and low frequency bandwidths in the SCI population. Measurable signals were evident in both the high and low frequency bandwidths, albeit reduced, in individuals with paraplegia and tetraplegia [35–38]; however, the LF:HF ratio was comparable to able-bodied controls suggesting maintained sympatho-vagal balance [39]. More importantly, HRV techniques can be used to determine efficacy of therapeutic intervention; and improvement in autonomic cardiac modulation with exercise training has been reported after SCI [35]. While several studies have reported that HRV is equally reliable after SCI as in the able-bodied population [40, 41], other studies have called the validity of HRV use in the SCI population into question [42]. Furthermore, although appropriate changes in HRV are reported following cholinergic blockade (with atropine sulfate) in subjects with SCI, responses to β-blockade (with Metoprolol Tartrate) were blunted, suggesting that HRV may not accurately reflect cardiac sympathovagal balance [43]. It is important to note that HRV techniques do not directly measure neural outflow to the heart, but reflect the heart's response to neural outflow. The difference between actual neuronal activity and the cardiac response may be amplified in the SCI population because the heart may not respond to autonomic stimulation in the same manner as pre-injury. Specifically, alterations in sinoatrial node responsiveness to endogenous vagal stimulation [44] or profound physical inactivity [45, 46] may alter cardiac responses to neuronal stimulus after SCI.

## Blood Pressure Abnormalities

### *Autonomic Dysreflexia*

Episodes of AD are characterized by an acute elevation of systolic blood pressure (SBP) of at least 20 mmHg [47], which occurs in response to painful or non-painful stimuli below injury. It is well appreciated that AD occurs in both the acute and chronic phases of SCI [47, 48], and is more frequently reported in those with SCI above T6 [49] with complete lesions [50]. Episodes of AD may be accompanied by a pounding headache, and flushing above the injury, which if left untreated, could result in life-threatening complications including cerebral hemorrhage, retinal detachment, seizures, cardiac arrhythmias, and death [51]. The most common triggers for AD include bladder or bowel distention, but AD can also be brought on by spasms, pressure sores, and even pressure from a tight shoe lace [47]. Catheterization and manipulation of an indwelling urethral catheter can lead to AD, in addition to urinary tract infection, detrusor sphincter dyssynergia, and bladder percussion [52]. There are also a number of iatrogenic triggers such as cystoscopy, penile vibrostimulation, or electrostimulation for ejaculation and electrical stimulation of the muscles of the lower extremity [53, 54]. The intensity of AD episodes is variable and not all episodes are severe, but many episodes of AD are silent and asymptomatic (i.e., patient does not recognize it even though blood pressure is increased) or may be characterized by sweating and/or piloerection alone [48, 55].

Finally, it should be noted that, although AD is certainly a life-threatening emergency [56] and may be unpleasant [57], there are reports of individuals with SCI voluntarily inducing AD in order to increase their BP to improve athletic performance [58]. Induction of AD to enhance performance is referred to as "boosting" and is considered unethical and illegal by the International Paralympics Committee Medical Commissions. That aside, it must be appreciated that the occurrence of boosting in athletic competition is a testament to the devastating functional limitations imposed by autonomic cardiovascular dysfunction after SCI.

### *Hypotension and Orthostatic Hypotension*

In 1978, the World Health Organization defined hypotension as a SBP below 110 mmHg in men and below 100 mmHg in women without regard to diastolic blood pressure (DBP) [59]. A recent article describing the effects of low DBP on mortality however, reported significantly increased risk in veterans with a DBP below 70 mmHg [60]. Hypotension may or may not be accompanied by symptoms of cerebral hypoperfusion, and reports are mounting of adverse associations between asymptomatic hypotension, cognitive deficits [61] and reduced parameters of quality of life (QOL) [62, 63]. The American Autonomic Society, the European Federation of Autonomic Societies, the Autonomic Research Group of the World Federation of Neurology, and the Autonomic Disorders section of the American Academy of Neurology recently revised the definition of OH as a sustained reduction of SBP or DBP of $\geq$20/10 mmHg within 3 min of standing [64]. There may be dissociation between symptoms of orthostatic intolerance (i.e., dizziness) and the orthostatic fall in BP [65], and asymptomatic OH is associated with increased all-cause mortality in middle-aged adults [66], cognitive impairment and hopelessness [67]. Due to decentralized autonomic cardiovascular control, many individuals with high-level SCI (above T6) are hypotensive with periods of substantial OH during seated positioning [68]. While there is a general appreciation for the impact of hypotension and OH during the acute period following injury [69], the impact of these BP abnormalities is less well understood in the chronic phase of injury (>1 year). However, we have documented impaired memory and processing speed in hypotensive individuals with SCI compared to a normotensive SCI cohort and have identified adverse changes in health-related QOL [70, 71]. We speculate that the association between hypotension, cognitive dysfunction, and reduced QOL may relate to adverse changes in static and dynamic regulation of cerebral blood flow (CBF) velocity in the middle [72•] and posterior cerebral arteries [73] following SCI.

## The Cerebral Circulation

The brain is allocated a disproportionate amount of blood relative to its mass, and receives approximately 20 % of cardiac output although it only makes up 2 % of body mass. Therefore, matching of brain blood flow to metabolic demand is essential, not only for normal cognitive functioning, but to avoid cerebral ischemia and syncope, which can result after only 3 s of disrupted CBF. However, our understanding of cerebrovascular alterations after SCI is relatively infantile, and in dire need of progression. Three primary clinical issues after SCI are at least partially mediated by cerebrovascular dysfunction after SCI [74, 75]. These include: (1) a 300–400 % increased risk of stroke, (2) global cognitive dysfunction, and (3) marked orthostatic intolerance. In those with high thoracic and cervical (high-level) SCI, CBF to the middle cerebral artery (i.e., the largest artery of the brain responsible for 80 % of CBF) is preserved during an orthostatic challenge [76, 77]; however, the posterior circulation (vertebrobasilar/posterior cerebral artery) blood flow is compromised [77]. This is a critical issue, because the posterior circulation perfuses the medulla oblongata, associated

autonomic control centers, and discrete regions responsible for consciousness [78]. This region has been shown to be differentially sensitive to orthostatic challenges compared with other cerebrovascular regions [79]. Impaired substrate delivery to, and by-product removal from the brainstem may be a common pathway before developing symptoms of pre-syncope, and is likely responsible for the increased prevalence of orthostatic intolerance found in those with high-level SCI.

Another deficit noted after high-level SCI is a complete abrogation of cerebrovascular reactivity during cognition [73]. Further, a mismatch between cognitive performance and changes in cerebrovascular resistance has been reported in subjects with SCI [72•]. Such cerebrovascular abnormalities are associated with a decline in cognitive performance, and it appears that hypotension may be a major contributing factor [71, 80]. The effects of chronic asymptomatic hypotension and episodic OH on the cerebral circulation represent similar causal factors (i.e., reduced blood flow/loading) [80] as previously discussed pertaining to the decline in cardiac function [24]. Increasing systemic BP improves CBF [81, 82], and may improve neurovascular coupling and cognition; however, other factors likely play a role because improvements did not elevate metrics to those observed in non-SCI individuals [77].

Very recently, our preliminary findings demonstrated that after experimental T3 spinal transection, the cerebral arteries undergo rapid inward remodeling and stiffening, as well as profibrosis characterized by increased collagen and decreased elastin [83]. Furthermore, in this study, 1 month of daily AD induction resulted in cerebrovasculature endothelial dysfunction and arterial stiffening [83]. We do not presently understand the timeline of cerebrovascular dysfunction after initial SCI, or the role level injury may play, but it is possible that rapid deconditioning after SCI extends to the cerebrovasculature, and that decentralized supraspinal sympathetic control may contribute to more severe cerebrovascular dysfunction as compared to those with mid-thoracic injury.

## The Cutaneous Microcirculation

The cutaneous microcirculation provides blood for both epidermal nutrition and the dissipation of body heat. The macrovasculature has nutrient-laden and oxygen-rich blood to perfuse the tissues through a vast capillary bed, which has a parallel network of venules and veins for the subsequent removal of cellular metabolic waste. Hydrostatic and colloid osmotic pressures (i.e., outward, inward, and opposition) regulate the net movement of fluid and solutes from the arterial end of the capillary into the interstitium and then back into the venous capillary bed. Under normal conditions, it is estimated that ~90 % of the outward-moving fluid is reabsorbed at the venous portion of the capillary bed and the remaining fluid is returned to the circulation through the lymphatic system. In normotensive states, this dynamic fluid exchange operates within the systemic capillaries over a range of 10–35 mmHg, where vasomotor activity is generated in the ascending arterioles [84] and contributes to oscillations of cutaneous blood flow. These oscillations are influenced by the heart, ventilation, myogenic, neurogenic, and endothelial domains [85], which, due to autonomic impairment, may lead to microcirculatory dysfunction in persons with SCI [86].

It can be assumed that adverse changes in microcirculatory function contribute to skin breakdown and pressure ulcer formation [87, 88], and may be primarily responsible for delayed healing of wounds in the SCI population [89]. Due to lower extremity paralysis, an initial rapid, and then progressive and insidious lean tissue atrophy occurs post-SCI, which is exacerbated by a dearth of muscular tone and volitional contractions that also contribute to impaired lymphatic flow, reduced interstitial drainage, and fluid accumulation in the extravascular compartments leading to dependent edema. Furthermore, there is a proportional (to lean tissue mass) reduction in the cross-sectional area of the arterial vasculature [90], resulting in an absolute reduction of lower extremity blood flow [90], with a decline of up to 50–75 % in skin blood flow under seated conditions [88]. Moreover, traumatic high-level SCI dramatically attenuates or fully ablates supraspinal control of sympathetic cardiovascular autonomic outflow [38]. This deficit of neural control contributes to a reduced number of α- and β-adrenergic receptors in sub-lesional vascular beds, thereby limiting the vasomotor regulatory capacity of the cutaneous circulation [91]. Recent evidence suggests that local sympathetic activity of the insensate cutaneous microcirculation remains intact [92]. However, the dearth of adrenergic receptors [91], reduced basal and inducible plasma catecholamines [93], and the presence of endothelium-associated dysfunction [94] may limit the latency and magnitude of vasomotor responses to periods of reduced cutaneous perfusion, particularly in compressed skin adjacent to bony prominences.

Due, in part, to autonomic dysfunction, persons with SCI are at increased risk for microcirculatory dysfunction and compromised skin blood flow, related factors which increase the likelihood of developing skin breakdown and chronic, poorly healing pressure ulcers and may also contribute to thermoregulatory dysfunction.

## Temperature Regulation

Core body temperature (Tcore) is ~37.0 °C and is maintained within a precise range (i.e., ±0.6 °C) by behavioral

adjustments to thermal discomfort and involuntary hypothalamic modulation of thermoregulatory mechanisms in response to a wide range of hot or cold ambient temperatures [95].

Deviations in Tcore outside this narrow range may adversely affect cognition, hemodynamic stability, muscle strength, and organ system function [96].

*Heat Exposure*

Exposure to hot ambient temperatures results in cutaneous vasodilatation and sweating, via a sympathetic-mediated thermolytic response [97, 98]. In fact, skin blood flow, which is approximately 5 % of cardiac output during thermoneutral conditions, increases to as much as 60 % during heat stress and, when augmented by increased cardiac output and redistribution of blood flow, can increase to 2600 % of baseline values [99]. Resting cardiac output can double during periods of hyperthermia (Tcore $\geq$38 °C) to increase convective heat loss [97], and modulation of cholinergic sudomotor nerves provides very efficient evaporative heat loss through sweating [100]. After SCI, interruption of thermal sensation and descending sympathetic pathways impairs hypothalamic regulation of sweating [101] and cutaneous vasodilatation below the level of lesion [102]. Maximal sweat responses to heat exposure (35–38 °C ambient temperatures) were only 20–30 % of what would be expected in able-bodied subjects in persons with high-level SCI, resulting in significant increases in Tcore.

*Cold Exposure*

Ambient temperatures below 37 °C cause a sympathetic-mediated thermogenic response, resulting in cutaneous vasoconstriction and a shift of blood volume from superficial to deeper central areas, thus, preserving Tcore [98]. Continued cold exposure induces involuntary shivering to increase heat production above basal metabolic rate [98]. Interruption of sensory and sympathetic pathways impairs hypothalamic regulation of cutaneous vasoconstriction and shivering below the lesion level after SCI. The inability to augment norepinephrine levels, due to interruption of supraspinal pathways, leads to steadily decreasing Tcore following cold exposure (18.0–24.0 °C) in persons with high-level SCI [102–104]. Shivering in persons with tetraplegia is typically delayed and limited [103], thereby, attenuating increases in metabolic rate (i.e., 50 % in those with SCI vs. 200–500 % in able-bodied) [102], and when combined with impaired vasoconstriction and lean tissue atrophy, results in an increased likelihood of subnormal Tcore (i.e., 35.5–36.5 °C), which has been reported in veteran in-patients with tetraplegia who were particularly vulnerable to hypothermia (<35.0 °C) [105]. Cold exposure may negatively impact cognitive performance in persons with tetraplegia, as we observed that declines in Tcore were associated with declines in working memory and executive function [104]. In addition, our preliminary findings suggest that during the winter, persons with tetraplegia report impairment in their ability to think clearly, keep scheduled physician appointments, perform instrumental activities of daily living, and travel outdoors [106].

## Conclusion

Autonomic nervous system dysfunction following SCI is not as well appreciated as that of motor and sensory neuronal impairment, nor is it easily assessed. Recent advances in both the clinical and basic science realms have made significant progress in improving our understanding of the underlying pathophysiology of autonomic dysfunction and are illuminating the secondary consequences, including those described above. Substantial limitations still exist regarding our ability to recognize, better characterize, and then appropriately treat disorders stemming from autonomic impairment in the SCI population. However, until we can identify and apply measurement tools that accurately assess autonomic nervous system dysfunction, widespread clinical management of these impairments will be focused on treatment of the end-organ dysfunction, with the inherent problems associated with treating "symptoms" of a disorder rather than the underlying "problem".

### Compliance with Ethics Guidelines

**Conflict of Interest** Jill M. Wecht, Michael F. La Fountaine, John P. Handrakis, Christopher R. West, Aaron Phillips, David S. Ditor, Hisham Sharif, William A. Bauman, and Andrei V. Krassioukov declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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