Autonomic dysreflexia: a cardiovascular disorder following spinal cord injury

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How to cite this article: Sharif H, Hou S (2017) Autonomic dysreflexia: a cardiovascular disorder following spinal cord injury. Neural Regen Res 12(9):1390-1400.

Funding: This work was supported by NIH NINDS R01NS099076, Morton Cure Paralysis Funds (MCPF).

Abstract
Autonomic dysreflexia (AD) is a serious cardiovascular disorder in patients with spinal cord injury (SCI). The primary underlying cause of AD is loss of supraspinal control over sympathetic preganglionic neurons (SPNs) caudal to the injury, which renders the SPNs hyper-responsive to stimulation. Central maladaptive plasticity, including C-fiber sprouting and propriospinal fiber proliferation exaggerates noxious afferent transmission to the SPNs, causing them to release massive sympathetic discharges that result in severe hypertensive episodes. In parallel, upregulated peripheral vascular sensitivity following SCI exacerbates the hypertensive response by augmenting gastric and pelvic vasoconstriction. Currently, the majority of clinically employed treatments for AD involve anti-hypertensive medications and Botox injections to the bladder. Although these approaches mitigate the severity of AD, they only yield transient effects and target the effector organs, rather than addressing the primary issue of central sympathetic dysregulation. As such, strategies that aim to restore supraspinal reinnervation of SPNs to improve cardiovascular sympathetic regulation are likely more effective for AD. Recent pre-clinical investigations show that cell transplantation therapy is efficacious in reestablishing spinal sympathetic connections and improving hemodynamic performance, which holds promise as a potential therapeutic approach.

Key Words: autonomic dysreflexia; hyper-reflexia; sympathetic dysfunction; C-fibers; propriospinal axons; α-adrenoceptors; stem cell transplantation

Introduction
Execution of normal autonomic activity is vital for all bodily systems to operate in a synchronous and harmonious manner. An insult to autonomic centers can therefore have a multitude of detrimental effects where physiological systems become incapable of responding to internal and/or external provocations, thus resulting in perpetual functional degradation. Spinal cord injury (SCI) is a unique disorder where almost every physiological system is compromised. Interrupted supraspinal regulatory signals to their target organs is the major cause for autonomic failure following SCI, which typically leads to reduced autonomic tone, maladaptive intraspinal plasticity and inappropriate reflexive responses to afferent input. Depending on the level and severity of the injury, individuals with SCI may experience respiratory disorders, sexual dysfunction, lower urinary tract complications, impaired thermoregulation, gastrointestinal disturbance, and cardiovascular dysfunction. It is therefore not surprising that individuals with SCI consider recovery of autonomic function to be paramount for improving quality of life (Anderson, 2004).

Cardiovascular dysfunction following SCI is of particular importance, as it is one of the leading causes of morbidity and mortality in this population (Myers et al., 2007). Although many of the cardiovascular ailments that manifest following SCI are associated with increased risk of death, special attention must be given to autonomic dysreflexia (AD), as it is the only cardiovascular condition to directly cause death or irrevocable damage to individuals with SCI (Dolinak and Balraj, 2007). AD is characterized by sudden episodic increases in blood pressure accompanied by baroreceptor-mediated bradycardia in response to noxious visceral or cutaneous stimulation below the injury level (Karlsson, 1999). Although approximately 90% of individuals with complete tetraplegia experience AD (Curt et al., 1997), there remains no effective permanent treatment for this disorder, partly due to our limited understanding of its pathophysiology. Nevertheless, studies show that AD is related to complex interactions between maladaptive intraspinal and peripheral plasticity that occur following SCI. Therefore, in order for researchers to circumvent previous impediments and develop clinically relevant and viable treatments for AD, it is imperative to have a comprehensive and up to date understanding of the purported mechanisms as well as previously employed treatments for AD. Accordingly, this review will discuss cardiovascular autonomic regulation and how it changes after SCI, followed by a detailed overview on the central and peripheral mechanisms underlying AD, as well as treatment considerations.

Autonomic Regulation of Cardiovascular Function
Cardiovascular function is regulated through the constant balance between sympathetic and parasympathetic function, which generally have opposing effects to one another. Sympathetic activity is excitatory, as it increases heart rate, cardiac contractility and blood pressure, while parasympathetic activity reduces heart rate and elicits a reflexive decrease in
blood pressure. Under normal conditions, baroreceptors relay excitatory and/or inhibitory afferents to the nucleus tractus solitarius (NTS) in the brainstem, via the vagus and glossopharyngeal nerves. From the NTS, secondary neurons project directly to cardiovascular centers which formulate appropriate modulatory signals, the net output of those commands, via the NTS, are a balance of inhibitory and excitatory efferents towards the heart and vasculature (Freire-Maia and Azevedo, 1990). For example, when arterial pressure is elevated, baroreceptors decrease their firing rate to supraspinal centers, which subsequently causes reflexive inhibition of sympathetic activity thus reducing heart rate and blood pressure. Conversely, when baroreceptors sense low arterial pressures, their slow firing rate prompts supraspinal centers to increase sympathetic outflow in order to induce compensatory tachycardia and raise blood pressure. Therefore, the machinery required for successful cardiovascular autonomic regulation involves reciprocal interplay between central and peripheral pathways. Damage to any part of this intricate system can result in tremendous cardiovascular autonomic impairments.

**Sympathetic cardiovascular regulation**

Sympathetic preganglionic neurons (SPNs) involved in cardiovascular regulation are located in the intermediolateral cell column (IML) of the lateral horn and gray commissure along T₁–L₂ spinal levels. The SPNs between T₁–L₂ are essential for cardiac sympathetic modulation, and they exit the spinal cord and synapse with the sympathetic chain ganglion to connect with sympathetic postganglionic neurons. During sympathetic stimulation, nicotinic receptors in the post ganglionic neurons are stimulated by cholingergic release, which results in norepinephrine release from the postganglionic neuron terminals. The released norepinephrine binds onto β₁-adrenoceptors in the sino-atrial and atrio-ventricular nodes, which augments depolarization rate and action potential propagation throughout the cardiac conduction pathways, thus increasing heart rate. Additionally, norepinephrine binds to myocardial β₁-adrenoceptors to increase cardiac contractility by enhancing intracellular calcium release and subsequent formation of actin-myosin cross bridges. The SPNs between T₁–L₂ connect with the collateral ganglia to then synapse directly onto the sympathetic postganglionic neurons. From there, norepinephrine is released and binds onto α₁-adrenoceptors expressed in smooth muscles of the splanchnic bed and the lower limbs. Sympathetic stimulation of the abdominal and splanchnic vasculature specifically plays a major role in increasing systemic blood pressure. Conversely, β₁-adrenoceptors are also found in smooth muscles but cause vasodilation when stimulated to increase organ blood perfusion (Figure 1). This organization is imperative for the sole purpose of the fight or flight response, which is to direct blood towards the most critical regions during autonomic excitement and shunt it away from the less critical areas. For example, at times of danger, vasoconstriction of the splanchnic vessels increases blood pressure, but also directs blood away from the area, as the abdominal organs are not needed to function during times of stress. As such, blood gets redirected towards skeletal muscles, that contain vasodilated blood vessels through stimulated α₁-adrenoceptor, which increases oxygen delivery and metabolic fuel utilization to enhance performance.

**Parasympathetic cardiovascular regulation**

Cardiac parasympathetic neurons are located in the dorsal motor nucleus of the vagus nerve and the nucleus ambiguous in the medulla oblongata. Parasympathetic preganglionic neurons project through the vagus and glossopharyngeal nerves, synapsing with postganglionic cells that in turn synapse onto the heart (Figure 1). Therefore, unlike sympathetic neurons, cardiac parasympathetic fibers are anatomically independent of the spinal cord. Acetylcholine is used as a messenger between the pre and post ganglionic neurons and is also released from the vagal neural terminals to exert its effects on target organs. Following acetylcholine release from postganglionic terminals; the neurotransmitter binds onto muscarinic receptors in the sinoatrial (SA) node to hyperpolarize the membrane potential, thus slowing down the rate of action potential formation and heart rate (Gordan et al., 2015). Although parasympathetic nerves do not have a direct effect on blood vessels, they can stimulate nitric oxide release, which results in vasodilation of smooth muscles.

![Figure 1 Illustration of normal cardiovascular autonomic control.](image)

For cardiac parasympathetic modulation, long parasympathetic preganglionic neurons within the vagus and glossopharyngeal nerves (Cranial nerves (CN) IX & X) exit from the medulla oblongata, synapsing with short parasympathetic preganglionic neurons which terminate on the sinoatrial (SA) and atrioventricular (AV) nodes to decrease heart rate through the action on acetylcholine. Peripheral blood vessels (v.) are not directly innervated by parasympathetic nerves. Conversely, for cardiac sympathetic regulation, short sympathetic preganglionic neurons from T₁–L₂ synapse with the autonomic chain, which then connects with long sympathetic postganglionic neurons that terminate on the sinoatrial and atrioventricular nodes, as well as myocardial tissue to increase heart rate and contractility. These nerves also innervate blood vessels of the head, neck and thoracic region in order to regulate blood flow to the upper body. Sympathetic preganglionic neurons below the T₅ segment bypass the sympathetic chain, travel through the collateral ganglia (celiac, superior mesenteric and inferior mesenteric ganglions (g.)) and synapses with sympathetic postganglionic neurons. These nerves terminate on blood vessels of the abdomen, pelvic region and lower limbs and cause vasoconstriction to increase blood pressure.
Supraspinal cardiovascular regulation
In an intact body, blood pressure and heart rate are in constant synchronous fluctuation within a physiological range, which is balanced by continuous excitatory and inhibitory drive over cardiovascular activity. Such a balance promotes normal basal vasomotor tone as well as appropriate pressor and depressor responses to autonomic perturbations. The brainstem contains several key regions that regulate pressor and depressor responses when stimulated and inhibited, respectively. The 5 main regions in the brainstem that do so are the 1) rostral ventrolateral medulla (RVLM), 2) rostral ventromedial medulla, 3) caudal raphe nuclei, 4) A5 cells in the pons and 5) paraventricular nucleus (PVN) of the hypothalamus (Chalmers et al., 1994). Basal and reflexive sympathetic tones are primarily provided by the lateral tegmental field (LTF) and the RVLM. The LTF projects and drives sympato-excitatory signals to the RVLM, however, the RVLM plays a chief role in increasing sympathetic outflow to the SPNs. Axons from the RVLM project directly towards the SPNs in the IML within the thoracolumbar spinal cord, which synapses with postganglionic sympathetic neurons, releasing norepinephrine to increase vasomotor tone, heart rate and cardiac contractility. Although the sources of excitatory and inhibitory drive to the RVLM remains unclear, anatomical studies suggest that numerous supraspinal regions converge and project to the RVLM to activate and/or dampen its activity (Dampney, 2016). Two of the most prominent regions that modulate RVLM activity are the caudal ventrolateral medulla (CVLM) and the caudal pres- sor area (CPA). The CVLM, located inferior to the RVLM, is the primary inhibitor of RVLM activity, thus causing a depressor response when activated (Campos et al., 2008). In contrast, the CPA primarily activates the RVLM by impeding the CVLM’s sympatho-inhibitory signals towards the RVLM, thus maintaining sympathetic tone (Ghali, 2017). Sympatho-modulation can also occur independently of the RVLM through regions such as the medullocervical pressor area and the gigantocellular depressor area (GDA). The medullocervical pressor is to increase blood pressure through direct activation of the SPNs within the IML (Ghali, 2017), bypassing the RVLM. Similarly, axons from the GDA extend to and depress several autonomic modulatory regions in the brainstem and the IML, causing inhibition of sympathetic activity, thus reducing blood pressure, chronotropy and inotropy (Aicher, 2003).

Cardiovascular Performance after SCI
The loss of supraspinal control over the SPNs controlling heart and blood vessels is the principal underlying cause of impaired cardiovascular function in individuals with SCI. Although modulatory descending signals from the brain are disrupted following SCI, spinal and peripheral cardiovascular circuitry caudal to the injury are not abrogated, but rather undergo maladaptive plasticity that initiates disordered activities. These include abnormal basal and orthostatic hemodynamics, cardiac arrhythmias, cardiac vagal dysfunction, and the focus of this paper, AD.

Hypotension and orthostatic hypotension
Recent guidelines for acute management of SCI consider hypotension as basal systolic blood pressure lower than 90 mmHg in humans (Walters et al., 2013). However, the goal mean arterial pressure in acute management of SCI is > 80-85 mmHg. Higher levels of SCI directly correlate with frequency and severity of hypotension, by compromising vascular sympathetic outflow, basal vascular tone, and thus, arterial pressure (Krassioukov and Claydon, 2006). In the chronic stage of SCI, prolonged hypotension can be asymptomatic, but nevertheless it is associated with chronic fatigue (Lucas et al., 2004), reduced health-related quality of life (Carlozzi et al., 2013), neurological deficits (Catapano et al., 2016) and increased risk of mortality.

Moreover, individuals with high level SCI often experience orthostatic hypotension, which is a drop in systolic blood pressure by at least 20 mmHg and diastolic by 10 mmHg upon the assumption of an upright position (Freeman et al., 2011). Such a drop in blood pressure is attributed to failed vascular sympathetic activation due to interrupted descending excitatory transmission. Failure to vasoconstrict during an orthostatic challenge results in reduced venous return and stroke volume, as well as excessive venous pooling in the lower limbs. Secondary mechanisms that contribute to orthostatic hypotension include hypovolemia, absence of skeletal pump activity, cardiovascular deconditioning and upregulation of vasodilatory agents (Claydon et al., 2006; Wecht et al., 2007). Classic symptoms of orthostatic hypotension include blurred vision, light headedness, dizziness, fatigue and syncope (Claydon et al., 2006). Additionally, orthostatic hypotension in individuals sustaining SCI may substantially limit a person’s ability to accomplish their activities of daily living and successfully participate and complete physical rehabilitation.

Cardiac arrhythmias and vagal dysfunction
Heart rate is tightly regulated by synchronous vagal and sympathetic modulatory outflow, therefore a high level SCI that disrupts such a balance may result in disordered heart rate activity. Almost all individuals with severe tetraplegia experience life-threatening bradycardia immediately after SCI, which is a resting heart rate of < 60 beats/min (Collins et al., 2006). This is mainly attributed to disrupted cardiac sympathetic outflow in conjunction with cardiac vagal dominance (Lehmann et al., 1987). Furthermore, injuries to the mid thoracic spine that cause hypotension may elicit tachycardia as a compensatory attempt to ameliorate basal hypotension. Such tachycardia is mediated by increased cardiac sympathetic arborization (Lujan et al., 2012) and altered ventricular calcium handling capacity (Rodenaugh et al., 2003), both of which are conducive for arrhythmogenesis.

In theory, cardiac parasympathetic activity should be preserved after SCI because vagus efferents travel directly from the medulla to effector organs. However, recent electrophysiological and animal studies show disordered cardiac vagal modulation after SCI. For example, head-up tilt experiments, which normally cause vagal withdrawal, fail to elicit a reduction in cardiac vagal activity in individuals with SCI (Wecht et
al., 2006). Conversely, cardiac vagal stimulation does not result in an expected drop in heart rate following SCI (Wecht et al., 2009). Moreover, the QT-variability index, a gauge of cardiac vagal activity when sympathetic tone is low (Sharif et al., 2015), is suggestive of reduced cardiac parasympathetic outflow in individuals with SCI (Ravensbergen et al., 2012). Recent clinical studies demonstrated impaired vago-vagal modulation over ventricular diastolic function following SCI (Sharif, unpublished), which might be explained by morphological changes in vagal preganglionic neurons (De Carlo, unpublished). These studies suggest a paradoxical impairment in cardiac vagal control following SCI, which merits further investigation.

**Autonomic Dysreflexia**

AD is a condition characterized by transient bursts of massive sympathetic discharges that result in dangerous episodic hypertension in response to a noxious stimulus below the level of injury (Karlsson, 1999). Clinically, AD is indicated when systolic blood pressure rises above baseline by at least 20 mmHg. However, since individuals with SCI are typically hypotensive, a rise of blood pressure towards “normal” ranges could also suggest a dysreflexic event. AD manifests in both acute and chronic stages of SCI, and although it is more prevalent in complete injuries above T6 (Mathais, 1992), individuals with incomplete SCI are prone to developing it as well (Helkowski et al., 2003). Noxious cutaneous and visceral stimuli below the neurological level trigger AD, but bladder and colorectal distention (CRD) are the most potent triggers for this response. Accordingly, CRD-induced AD via an inflatable balloon tipped catheter has become a well-established method for studying the hyper-reflexive response in animal studies (Krassioukov and Weaver, 1995; Krenz and Weaver, 1998a). However, a major limitation to this method is that it is not natural, as in these investigations, AD is stimulated in an artificial manner. Therefore, another method of evaluating AD in pre-clinical studies is by detecting the frequency of spontaneous AD, which refers to the number of hyperreflexic episodes experienced in a given period of time. Typically, blood pressure and heart rate are simultaneously measured over a 24-hour period via implantable telemetry, and whenever blood pressure spikes instantaneously by more than 20 mmHg, AD is signified (Figure 2).

The exact mechanisms underlying AD are still unknown, but formation of new intraspinal circuitry paralleled with peripheral vascular plasticity contribute to such a disorder (Figure 3). When afferent fibers below the injury transmit noxious inputs via the dorsal horn, SPNs caudal to the injury that undergo maladaptive plasticity respond by reflexively releasing massive amounts norepinephrine to the splanchnic region, which consequently causes severe hypertension. Due to damaged bulbospinal pathways, inhibitory efferent signals cannot reach and neutralize the activated SPNs below the injury, which results in rostral vasodilation and sustained caudal vasoconstriction. The presentation of AD can range from asymptomatic (Ekland et al., 2008) to mildly symptomatic to life-threatening (Vallès et al., 2005). Classic symptoms include sudden hypertension, throbbing headache, face flushing and sweating above injury level (Table 1). More severe consequences of AD include seizures (Fausel and Paski, 2014), cardiac arrhythmias (Pine et al., 1991), cerebrovascular hemorrhage (Vallès et al., 2005) and death (Dolinak and Balraj, 2007).

### Table 1 Signs and symptoms of autonomic dysreflexia

| Symptom                                      |
|----------------------------------------------|
| Elevated blood pressure by at least 20 mmHg from baseline |
| Pounding headache                            |
| Face and neck flushing                       |
| Profuse sweating above the level of injury   |
| Shivering                                    |
| Cutis anserina (goose bumps)                 |
| Blurred vision                               |
| Dizziness                                    |
| Nausea                                       |
| Eyes watering                                |
| Pronounced bradycardia/irregular heart beats |
| Rapid breathing                              |

**Interruption of supraspinal regulation**

As discussed in the previous sections, neurons in the brainstem and hypothalamus project to the spinal cord to modulate sympathetic activity and control basal and reflexive hemodynamics. For example, neurons in the C1 region of the RVLM release epinephrine for the tonic discharge of SPNs to sustain sympathetic outflow within a normal range (Guyenet et al., 1989), while those in the caudal raphe nuclei secrete serotonin to increase sympathetic activity (Marina et al., 2006). If the majority of serotonergic inputs are abolished, basal blood pressure decreases (Coote, 1990). Following SCI, these descending vasomotor pathways are partially or completely damaged. Resultant decrease in sympathetic activity and plasma levels of catecholamine cause hypotension at rest and during a postural challenge (Mathias, 2006). Moreover, the loss of descending regulation of sympathetic activity is the initial and primary cause of AD (Figure 3A), which leads to the development of central and peripheral changes (discussed below) that exacerbate the hyper-reflexive episodes. It is still unknown, however, if alterations in supraspinal regions following SCI contribute to AD. Supraspinal plasticity has been reported to occur after SCI, as a neural adaptation to paralysis. Such plasticity could theoretically impact supraspinal vasomotor networks, making them more conducive for hyper-reflexive bursts or sympathetic disinhibition, thus facilitating AD. However, research on supraspinal plasticity within the autonomic regions and its potential contribution to AD is certainly warranted.

**Pelvic afferent fiber sprouting**

Both pelvic myelinated and unmyelinated afferent fibers are upregulated after SCI, however only the unmyelinated C-fibers, which highly express neuropeptide calcitonin gene related peptide (CGRP) (Keast and De Groat, 1992), play an exclusive role in eliciting AD (Hou et al., 2008). C-fiber
sprouting in the dorsal root ganglia is instrumental for the development of AD following SCI. Compared to their myelinated counterpart, C-fibers are smaller in diameter, unmyelinated and are primarily involved in conveying thermal and nociceptive signals to supraspinal centers (Keast and De Groat, 1992). Notably, since CGRP-fibers express the high nerve growth factor (NGF) affinity receptor, TrK (Averill et al., 1995), elevation in NGF content following SCI substantially exacerbates CGRP-axonal sprouting (Korschning and Thoenen, 1985; Lindsay and Harmar, 1989) which exaggerates the degree of noxious sensory input.

Experimental mid-thoracic SCI causes considerable enlargements in CGRP terminal arbors within the dorsal horn, which represents increased sprouting of unmyelinated C-fibers within sensory neurons (Krenz and Weaver, 1998b; Krenz et al., 1999; Marsh et al., 2002) (Figure 3B). This has also been demonstrated in clinically relevant models of SCI (Weaver et al., 2001). The proliferation of CGRP-fibers within the dorsal roots exaggerates transmission of sensory inputs from peripheral sources, which over-excite the SPNs and consequently results in an augmented hyper-reflexive sympathetic response. Although CGRP-fibers undergo similar degrees of sprouting in all spinal segments following SCI (Krenz and Weaver, 1998b; Ondarza et al., 2003), sprouting in the lumbar sacral region, specifically, plays a chief role in eliciting AD (Cameron et al., 2006; Rabchevsky, 2006; Hou et al., 2008). This is likely because lumbar sacral segments contain afferent neurons innervated by the pelvic organs, which convey the most sensitive noxious stimuli for AD (bladder and colon distension). Moreover, elevated CGRP immuno-reactivity in the dorsal horn occurs 2 weeks post injury (Krenz and Weaver, 1998b; Wong et al., 2000; Weaver et al., 2001), which is when AD becomes fully established (Krenz and Weaver, 1998a; Krassioukov et al., 1999). Correlational observations show a strong relationship between CGRP-fiber distribution in the dorsal horn and the magnitude of CRD-induced AD following increased NGF release after SCI (Krenz et al., 1999; Cameron et al., 2006; Rabchevsky, 2006). More direct evidence shows that neutralizing intraspinal NGF with a NGF-antibody or a TrK antagonist prevents sprouting of CGRP-fibers and consequently mitigates the hypertensive response during CRD (Krenz et al., 1999; Marsh et al., 2002). Conversely, experimental overexpression of NGF further increases CGRP-fiber sprouting and exacerbates CRD-induced AD, while abrogating CGRP-fibers with Semaphorin 3A mitigates hyperreflexia (Cameron et al., 2006). These studies provide strong evidence that NGF-induced CGRP sprouting likely elicits AD by enhancing sensory input to the SPNs.

**Plasticity of propriospinal neurons**

Although there is a paucity of literature regarding the relationship between propriospinal neurons (PN) and autonomnic dysfunction following SCI, some evidence suggests that PN plasticity may facilitate AD. A PN is defined as an interneuron of which the cell body is located in the spinal cord and its axon terminals project to different spinal segments (Flynn et al., 2011). Anatomically, PNs are considered either long or short based on the length of their axons. Short PNs are those whose axons span over one to six spinal segments, whereas long PNs stretch over more than six segments (Contana, 2009). Anterograde tracing revealed that PNs extend along the entire length of the spinal cord via lamina X/dorsal gray commissure (Matsushita, 1998; Petkó and Antal, 2000). In motor function, this anatomical orientation serves as a basis...
for the reciprocal connection between cervical and lumbar motor circuitry to enable synchronous activity between upper and lower limbs during ambulation (Juvin et al., 2005).

Similar to C-fiber sprouting, PNs also undergo similar alterations following SCI that contribute to the genesis of AD (Figure 3B). This was initially hypothesized by Cameron et al. (2006), who employed anterograde tracing from the lumbosacral spine to reveal increased PN projections around the thoracic SPNs at 2 weeks post SCI, the time-point when AD was evident. These findings were later corroborated by studies reporting elevated lumbosacral PN axonal density around the dorsal gray commissure after SCI (Hou et al., 2008).

Sacral PNs convey noxious inputs from the CGRP-fibers rostrally towards SPNs in the thoracolumbar segments, which causes them to produce a reflexive sympathetic discharge (Hou et al., 2008). Furthermore, intermittent CRD caused a marked increase in c-fos levels around the lumbosacral dorsal gray commissure, indicating activation of lumbosacral interneurons during AD (Hou et al., 2008). This is in agreement with previous reports that showed a 3-fold increase in the amount of c-fos labelled neurons in the lumbosacral cord after similar treatments (Landrum et al., 2002). These findings suggest that plasticity of lumbosacral NPs may relay the increased sensory signal input towards thoracolumbar SPNs to elicit a dysreflexic episode.

### Morphological changes in SPNs

Following SCI, SPNs in the IML undergo morphological alterations that are pivotal for the development of AD. At 1 week post-injury, SPNs caudal to the injury become severely atrophied, as evidenced by reduced somal size as well as loss and retraction of neurite dendritic arborizing (Krasiooukov and Weaver, 1995, 1996; Llewellyn-Smith et al., 2006). Such morphological decaying is not evident in the SPNs rostral to the injury, suggesting that loss of supraspinal input plays a key role in mediating such maladaptive plasticity after SCI. By 2 weeks post-injury, SPN atrophy is completely reversed, as somal size and dendritic density are regained, while dendritic projections are restored towards their normal terminal points (Krasiooukov and Weaver, 1996; Krenz and Weaver, 1998a). These temporal alterations in the SPNs are also confirmed by human studies (Krasiooukov et al., 1999). Interestingly, re-establishment of SPN size at 2 weeks post-injury coincides with the time point of AD manifestation. At 1 week post-injury when SPNs are atrophied, CRD does not elicit AD, however when SPNs regain their size at 2 weeks post-injury, CRD results in dramatic hypertensive episodes (Krasiooukov and Weaver, 1995; Krenz and Weaver, 1998a). This implies that as SPNs regain their normal size and dendritic arborization, new inappropriate synapses are formed which instigate reflexive sympathetic responses to noxious sensory input.

It is unknown how new intraspinal connections that mediate AD are created, however upregulation of neural regulatory signals following SCI may account for their formation. For instance, synaptophysin is a presynaptic vesicle phosphoprotein involved in fiber outgrowth and synaptogenesis (Masliiah et al., 1991) and is highly expressed around caudal SPNs 1 week post SCI (Krasiooukov and Weaver, 1995). Although this is the time point prior to restoration of SPN morphology and development of AD, it suggests that neurotrophic factors that form new unfavorable synapses are activated well before the establishment of AD, which could provide a window of opportunity for early neuroprotective treatments (Krasiooukov and Weaver, 1996). Moreover, growth associated protein-43 (GAP-43) is another phosphoprotein involved in nerve regeneration and new neurite path formation (Neve et al., 1998) that may be implicated in AD. Following SCI, GAP-43 is over-expressed around the SPNs in the IML and extends throughout the intermediate gray matter, suggesting sprouting of new intraspinal axons that are possibly implicated in the initiation of AD (Weaver et al., 1997). Additionally, despite disruption of supraspinal input to spinal autonomic regions, SPNs caudal to the injury sustain detectable amounts of glutamate, GABA and catecholamines, all of which may provide anatomic substrates for exaggerated sympathetic reflexes during AD (Cas-sam et al., 1997; Llewellyn-Smith et al., 1997).

### Peripheral vascular alterations

In addition to central neural plasticity, the vasculature also undergoes adaptive alterations following SCI that are highly implicated in AD (Figure 3C). Mathias et al. (1976) was the first to report changes in vascular function following SCI, where individuals with SCI demonstrated greater increases in blood pressure compared to able-bodied individuals after administration of an α-receptor agonist. This invoked the idea that after SCI, α-adrenoceptors may become hypersensitive to sympathetic stimulation, thus augmenting vasoconstriction and hypertension during AD. These findings were later confirmed by a series of studies, which confirmed that α-adrenoceptors, on the receptor level, become hyper-sensitive to sympathomimetics in systemic (Krum et al., 1992a, b) and local blood vessels (Arnold et al., 1995) after SCI. There is currently no evidence suggesting an upregulation or increase in the amount of vascular receptors after SCI. Hyper-responsiveness of α-adrenoceptors following SCI is thought to be a physiological compensation to the sustained low levels of plasma nor-adrenaline following sympathetic denervation (Krum et al., 1992a, b). However, this postulate is somewhat contentious, as β2-adrenoceptors are also subjected to low levels of catecholaminergic stimulation following SCI, but do not demonstrate such hyper-excitability (Krum et al., 1992b). Similarly, rats with SCI exhibit super-sensitivity to angiotensin II agonists, despite upregulation of this hormone (Groothuis et al., 2010; Al Dera and Brock, 2015) and its enzyme precursor, renin (Mathias et al., 1976). Therefore, attenuated sympathetic tone following SCI may not completely explain the reason behind α-adrenoceptor hyper-sensitivity.

Recent in vitro studies propose different potential mechanisms for vascular super-reactivity after SCI. These studies typically reported enhanced and/or prolonged vascular contractions in response to peripheral nerve stimulation (Yeoh et al., 2004; Brock et al., 2006; Rummery et al., 2010; Tripovic et al., 2011) or α-adrenoceptor agonists (Yeoh et al., 2004; Brock et al., 2006; Laird et al., 2008). However, such vascular
responses are attributed to altered smooth muscle morphology (Yeoh et al., 2004), impaired neural re-uptake of norepinephrine (Brock et al., 2006; Laird et al., 2008), or disruption in the relative proportion of α-adrenoceptor subtypes (Laird et al., 2008). In addition, there still remains much discrepancy regarding the location (Laird et al., 2008; Rummery et al., 2010) and type of blood vessels (McLachlan and Brock, 2006) that become super-sensitive following SCI. It is noteworthy to mention that elevated vascular reactivity to sympathetic stimulation provides a secondary mechanism that exacerbates AD, whereas central plasticity is the primary cause. As such, reversing these vascular alterations could reduce the severity of hypertension during a dysreflexic episode, but would not completely eliminate it. Successful lasting treatments should focus on ameliorating central mechanisms, while peripheral strategies may serve as a temporary solution.

Applicable Treatments and Experimental Therapeutic Approaches for AD

Recent alarming reports show a substantial gap of knowledge regarding AD within medical emergency personnel (Jackson and Acland, 2011), individuals with SCI and even their caregivers (McGillivray et al., 2009; Schottler et al., 2009). It is therefore imperative that clinicians, individuals with SCI and those living with them to be educated on the necessary measures required to prevent, detect and manage AD. The best approach for managing AD is for SCI individuals to become well aware of the specific noxious stimuli that trigger an episode and to avoid such situations (Rabchevsky and Kitzman, 2011). There are currently no permanent effective treatments for AD, as the most commonly used interventions only have transient and fleeting effects. During a dysreflexic episode, non-pharmacological measures should be employed first in order to alleviate the symptoms and decrease the hypertensive spikes. If non-pharmacological measures are ineffective in doing so, pharmacological agents with rapid anti-hypertensive properties should be implemented (Consortium for Spinal Cord Medicine, 2002; Krassioukov et al., 2009). Which if are also unsuccessful in reducing blood pressure, then the individual must be taken to the hospital immediately.

Nonpharmacological management

A step-by-step protocol for acute and immediate management of AD is outlined in the Guidelines of the Consortium for Spinal Cord Medicine (Consortium for Spinal Cord Medicine, 2002) (Figure 4). First, prompt recognition of symptoms is a must, which can also be confirmed by obtaining a blood pressure measurement. Second, the individual must be kept in an upright position, as this could facilitate blood pooling in the lower limbs due to orthostatic gravitation. In addition, keeping a patient in supine during AD can increase the risk for cerebrovascular hemorrhage and/or hypertensive encephalopathy. The next step is to loosen any tight clothing or constricting devices caudal to the injury to improve lower limb blood pooling, but also, tight clothing may act as a noxious stimulus in overly sensitive individuals. This is followed by rapid investigative work to identify and remove the source of noxious stimulation triggering AD, however, in 85% of cases it is related to bladder distension or fecal impaction (Krassioukov et al., 2009). In this case, indwelling urinary catheters should be examined for possible blockages, urinary bags must be emptied and steps must be taken to facilitate voiding. Elimination of the noxious trigger usually eliminates AD immediately, however, if elevated blood pressure is sustained, then pharmacological interventions become necessary.

Pharmacological interventions

In a recent systematic review, Krassioukov et al. (2009) discussed in detail the most commonly used drugs to alleviate symptoms of AD. Nifedipine, a calcium channel blocker traditionally used to treat hypertension and angina, is the most widely used drug for immediate treatment of AD. It has been the preferred method by patients due to its instant effects on reducing blood pressure and ameliorating minor and major symptoms (Krassioukov et al., 2009). It is typically administered via a ‘bite and swallow’ method at a dose of 10 mg, which ensures rapid release and absorption of its contents. The same dose may be taken again within 30–60 minutes if blood pressure has not completely subsided back to normal (Ferguson and Vlasses, 1986). Nifedipine is also effective in reducing blood pressure spikes during noxious procedures such as cystometry (Thyberg et al., 1994), cystoscopy (Dykstra et al., 1987) and vire-avigation (Steinberger et al., 1990). Nitrates are the second most commonly used agents for acute treatment of AD in individuals with SCI (Krassioukov et al., 2009). In contrast to Nifedipine, nitrates are potent vasodilators that work directly on vascular smooth muscle, and are also primarily used for the treatment of angina. Sublingual administration of nitrates is the preferred method, as it has rapid onset of action and longer lasting effects compared to inhalation (Braddom and Rocco, 1991). Besides anecdotal observations and expert opinions, no studies have provided empirical evidence for the effectiveness of nitrates on AD. Although not validated in clinical trials yet, acute administration of neuropathic pain medication, gabapentin, was recently shown to alleviate CRD-induced AD in SCI rats (Rabchevsky et al., 2011, 2012). Gabapentin is thought to exert its positive effects by decreasing presynaptic glutamatergic release, as glu-
Capsaicin
Capsaicin is a neurotoxin extracted from red peppers and has a selective inhibitory effect on sensory C-fibers through their vanilloid receptors. Low doses of capsaicin initially excite and depolarize C-fibers in the dorsal root, while prolonged application eventually desensitizes and damages the sensory fibers, thus inhibiting transmission of noxious sensations (Lynn, 1990). As C-fiber sprouting plays an important role in the pathogenesis of AD (see mechanisms section), it is plausible that ablating them with capsaicin would reduce the severity of the hyper-reflexia. One study demonstrated elimination of AD during bladder distension following capsaicin treatment in patients with SCI (Igawa et al., 2003), while another showed exacerbation of AD during urodynamics after administration of BTA (Gallien et al., 1998; Schurch et al., 2000). In addition, more recent clinical trials reported decreased severity and frequency of AD during urodynamics after administration treatment with BTA, which was related to increased bladder volume, compliance and voiding threshold (Tsai et al., 2009; Fougeré et al., 2016). However, these results are not universal, there is a need to resolve literature dispute as one study showed exacerbation of AD in a subpopulation of SCI individuals following BTA injections (Chen and Kuo, 2012).

Doses of capsaicin must be administered in sufficiently high doses to eliminate C-fibers, since low doses could alternatively stimulate a hyper-reflexive event.

Anti-CD11d antibody
Anti-CD-11d antibody is an anti-inflammatory agent specific to the CD11d/CD18 integrin. It has a neuroprotective immunomodulatory effect by blocking the interaction between CD11d and vascular cell adhesion molecule 1 (VCAM), thus preventing pro-inflammatory cytokines from being released and further damaging the spinal cord (Weaver et al., 2015). Administration of CD11d antibody acutely after experimental SCI markedly reduced CRD-induced AD by at least 50%, which persisted for 6 weeks (Gris et al., 2004). These improvements were not related to changes in CGRP-fiber content, but possibly due to enhanced preservation of neural tissue over several segments caudal to the injury site (Gris et al., 2005). Moreover, CD11d administration within the first 6 hours of an injury substantially reduced the magnitude of the hypertensive reflex during CRD, suggesting an early window of opportunity for this form of treatment with clinical relevance, as humans typically get to a hospital after a SCI within 6–12 hours (Ditor et al., 2006).

Cell transplantation
Cell transplantation has been extensively studied for its therapeutic potential to restore sensory/motor function following SCI, however, little is known about its ability to improve autonomic deficits in this population. Only recently pre-clinical studies started to examine the effects of cell transplantation on cardiovascular autonomic function in SCI. In the first study to do so, Kalincik et al. (2010) showed that transplanting olfactory ensheathing cells (OEC) following SCI did not alleviate the severity of AD, but accelerated blood pressure recovery time during a hyper-reflexive episode by approximately 50%. Although OEC transplantation did not promote nerve regeneration across the graft, there was evidence for morphological alterations in the SPNs caudal and rostral to the injury site, which may have mediated the partial autonomic recovery. In contrasts, transplantation of neural stem cells (NSCs) may be a more promising strategy for restoring cardiovascular autonomic function after SCI. Recently, Hou et al. (Hou et al., 2013) transplanted embryonic rat brainstem neural stem cells into a complete T1 transection, which improved resting hemodynamics and dramatically reduced CRD-induced AD. These improvements were in conjunction with robust long-distance axonal growth and subsequent topographic reinnervation of caudal SPNs (Hou et al., 2013). Moreover, since spinal serotonergic depletion caudal to the injury contributes to the initiation of AD (Cormier et al., 2010), transplantation of serotonergic cells from fetal raphe nucleus reduced the frequency and magnitude of AD in rats with SCI (Hou, unpublished).

Future Perspectives and Considerations
It is clear that AD is a very complex disorder mediated by maladaptive central and peripheral reorganization. The multifaceted nature of AD pathophysiology makes it difficult to
develop focused and long lasting treatments. For example, this report provided evidence for collective plasticity within the SPNs, CGRP-fibers, PNs, and peripheral vasculature, all of which contribute to the exaggerated hypertensive sympathetic reflex. Therefore, successful interventions may have to implore a comprehensive approach to address all of these issues. So far, clinical interventions used to treat AD are temporary means as they only provide a “Band-Aid” solution to the problem. This is not unexpected, as much remains unknown about the pathology of AD, but also, we do not know how all of the separate components leading to AD conjugate with one another. The majority of our knowledge stems from animal studies in the acute or sub-acute stages of SCI, hence we also do not know how the purported mechanisms change or contribute to AD chronically after SCI. Therefore, examination of the putative causes underlying AD is warranted. Moreover, most pre-clinical investigations of AD are based on completely transected injury models. Although transection models provide a great deal of insight to understand SCI and are also more pleasant for experimental evaluation, they are not clinically relevant. Accordingly, studies may simulate preclinical models as closely as possible to clinical situations to better understand AD.

Animal studies show that intraspinal plasticity facilitates AD development within 2 weeks of SCI. However, trophic and inflammatory factors mediating such plasticity are typically activated immediately following SCI, preceding the initiation of AD. This implies that neuroprotective strategies to block these negative factors could potentially prevent formation of unfavorable pathways, thus inhibiting the development of AD. Therapeutic approaches aimed at reestablishing supraspinal autonomic control are certainly required in the chronic stages of SCI. Although very novel, recent evidence from our laboratory suggests that stem cell transplantation, using different types of cells, may be efficacious in improving disordered cardiovascular autonomic regulation and reducing the severity of AD. We hope that by further refining and enhancing cell transplantation methods, we could find a permanent and effective treatment for AD.

Conclusion
AD is experienced by the majority of individuals with high severe SCI, which could have detrimental and life-threatening outcomes. Although there have been considerable advancements in the field, much remains unknown about the pathology of AD, hence we still do not have lasting effective treatments for this disorder. Disrupted supraspinal regulation over sympathetic spinal centers results in the formation of new intraspinal circuitry, in concert with peripheral vascular alterations, which are key for the development of AD. As such, strategies aimed at permanently treating AD should focus on restoring supraspinal connection and regulation of cardiovascular sympathetic activity.

Author contributions: HS and SH both contributed to concept, design, definition of intellectual content, literature search, manuscript preparation, manuscript editing and manuscript review.
Conflicts of interest: None declared.
Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.
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Open peer reviewers: Stefania Forner, University of California, USA; Michael Ghali, Drexel University, USA.

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