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# Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management

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ABSTRACT

Traumatic spinal cord injury (SCI) has widespread physiological effects beyond the disruption of sensory and motor function, notably the loss of normal autonomic and cardiovascular control. Injury at or above the sixth thoracic spinal cord segment segregates critical spinal sympathetic neurons from supraspinal modulation which can result in a syndrome known as autonomic dysreflexia (AD). AD is defined as episodic hypertension and concomitant baroreflex-mediated bradycardia initiated by unmodulated sympathetic reflexes in the decentralized cord. This condition is often triggered by noxious yet unperceived visceral or somatic stimuli below the injury level and if severe enough can require immediate medical attention. Herein, we review the pathophysiological mechanisms germane to the development of AD, including maladaptive plasticity of neural circuits mediating abnormal sympathetic reflexes and hypersensitization of peripheral vasculature that collectively contribute to abnormal hemodynamics after SCI. Further, we discuss the systemic effects of recurrent AD and pharmacological treatments used to manage such episodes. Contemporary research avenues are then presented to better understand the relative contributions of underlying mechanisms and to elucidate the effects of recurring AD on cardiovascular and immune functions for developing more targeted and effective treatments to attenuate the development of this insidious syndrome following high-level SCI.

## 1. Introduction

In addition to motor and sensory deficits, traumatic spinal cord injury (SCI) causes a constellation of interrelated autonomic and cardiovascular abnormalities. Cardiovascular complications secondary to SCI are among the leading causes of mortality and morbidity in this population, underscoring the necessity to understand and properly manage resultant comorbidities (Cragg et al., 2013; Garshick et al., 2005; Myers et al., 2007; Sabre et al., 2013). In humans, SCI at or above the sixth thoracic (T6) spinal cord segment often results in the development of a potentially life-threatening syndrome called autonomic dysreflexia (AD). AD is clinically defined as acute hypertension generated by unmodulated sympathetic reflexes below the injury level that is often accompanied by baroreceptor-mediated bradycardia, which provides short-term control of blood pressure (Karlsson, 1999). In response to hypertension, the baroreflex system lowers blood pressure by reducing heart rate and decreasing activity of vasoconstrictor sympathetic preganglionic neurons (SPN) located throughout the thoracolumbar spinal cord that regulate peripheral vascular resistance. However, while vagal parasympathetic innervation of the heart remains intact after SCI, the disruption of descending vasomotor pathways to SPN produces an incomplete compensatory decrease in peripheral vascular resistance so that hypertension persists until the triggering stimulus is removed (see Section 3.1).

Typically, AD is precipitated by noxious visceral or somatic stimulation below the level of injury that activates a massive sympathetic reflex causing widespread vasoconstriction. While the most common triggers are over-distension of the bowel or bladder (Canon et al., 2015; Lindan et al., 1980; Snow et al., 1978), other noxious stimuli including skin lacerations, ingrown toenails, pressure sores, tight clothing and certain medical procedures such as bladder catheterization and cystometry are also reported to cause AD (reviewed in Karlsson, 1999). During an episode of AD, arterial blood pressure can reach devastating levels, with systolic values as high as 325 mm Hg (McBride et al., 2003), exemplifying that AD is a hypertensive crisis that requires immediate medical attention (Muzumdar, 1982; Showkathali and Antionios, 2007; Verghese, 1989). Severe cases that do not receive rapid and appropriate treatment can have serious consequences such as hypertensive encephalopathy, stroke, cardiac arrest, seizure and even death (Bjelakovic et al., 2014; Colachis and

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**Nomenclature**

| | |
|---|---|
| SCI | spinal cord injury |
| AD | autonomic dysreflexia |
| SCI-IDS | spinal cord injury-induced immune depression syndrome |
| SPN | sympathetic preganglionic neurons |
| IML | intermediolateral cell column |
| NE | norepinephrine |
| BTX | botulinum toxin |
| NDO | neurogenic detrusor overactivity |
| NGF | nerve growth factor |
| GABA | gamma-aminobutyric acid |
| GBP | gabapentin |
| CRD | colorectal distension |
| SNS | sympathetic nervous system |
| HPA | hypothalamic pituitary axis |
| GC | glucocorticoid |
| DREADD | designer receptor exclusively activated by designer drug |
| CNO | clozapine-n-oxide |
| DGC | dorsal gray commissure |
| CGRP | calcitonin gene related peptide |
| NMDA | *N*-methyl-D-aspartate receptor |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor |

Clinchot, 1997; Eltorai et al., 1992; Fausel and Paski, 2014; Jain et al., 2013; Valles et al., 2005). Bouts of AD can arise multiple times daily due to the noxious yet unperceived afferent stimulation produced by normal, intermittent filling of the bladder and bowels (Fougere et al., 2016; Hubli et al., 2015; Popok et al., 2016). In light of this, it is perhaps not surprising that eliminating AD is one of the highest priorities of the SCI population, based on a large national survey (Anderson, 2004) which reported that both quadriplegics and paraplegics prioritize the recovery of bowel/bladder function and elimination of AD over regaining walking movements, highlighting the need for research strategies to mitigate the development of AD altogether.

In this review, we provide a clinical description of AD along with its pharmacological management, and discuss the underlying pathophysiological changes that contribute to such dangerous, episodic hypertension after high-level SCI. We further describe recent studies revealing body-wide disturbances that result from chronic recurring episodes of AD, including vascular, cardiac and immunological dysfunctions. Contemporary research strategies will be considered to understand more comprehensively the underlying mechanisms, the full physiological impact of this syndrome that typically occurs multiple times daily, and potential therapeutic approaches to abrogate its development.

## 2. Clinical description of AD

### 2.1. Who is at risk for developing AD?

The T6 spinal segment is critical to the development of AD (Lindan et al., 1980; Mathias and Frankel, 1988; Snow et al., 1978), as damage at or above this level interrupts descending modulation of the thoracolumbar SPN that regulate vasomotor tone, notably in the extensive splanchnic vascular bed (Blackmer, 2003; Gao et al., 2002). These vessels are innervated by the splanchnic nerves arising from the T5-T12 levels (Loukas et al., 2010) and receive approximately 25% of the cardiac output (Greenway and Lister, 1974; Rowell, 1990), which can have a large influence on total peripheral resistance and blood pressure. There are, however, uncommon reports of AD occurring after lesions below T6 but the magnitude of hypertension and changes in heart rate tend to be relatively mild since some degree of control over splanchnic sympathetic outflow remains intact (Moeller and Scheinberg, 1973).

Not all individuals with SCI at or above the T6 level develop AD, with the prevalence reported between 48% and 91% (Curt et al., 1997; Lindan et al., 1980; Snow et al., 1978). This discrepancy is likely attributed to differences in the completeness of SCI, time elapsed since injury, and differences in the criteria used to confirm the presence of AD used among studies (Furusawa et al., 2011). Indeed, the clinical definition of AD is somewhat inconsistent (see Section 2.2). Interestingly, AD has been documented in cases of non-traumatic abnormalities of the spinal cord such as intramedullary astrocytoma (Furlan et al., 2003) and multiple sclerosis (Kulcu et al., 2009), indicating that disruption of descending vasomotor pathways in any manner may contribute to the development of this syndrome.

### 2.2. Characteristic features of AD

The magnitude of hypertension required to be considered AD varies across studies. Snow et al. (1978) classified AD in adults as an increase of 40 mm Hg systolic blood pressure whereas Popok et al. (2016) defined AD as an increase of 20 mm Hg systolic blood pressure. Others (Lindan et al., 1980) diagnosed AD as a sudden rise in both systolic and diastolic blood pressure of any magnitude. Veteran's Affairs guidelines recommend that AD in adults is considered following abrupt elevation in systolic blood pressure of 20–40 mm Hg above baseline, whereas in pediatric SCI an increase of 15–20 mm Hg systolic pressure warrants consideration (Canon et al., 2015; Consortium for Spinal Cord, M., 2002).

In addition to elevated blood pressure, individuals with an acute episode of AD can experience a diverse set of symptoms including debilitating headache, sweating, flushing of the skin above the injury level, piloerection, stuffy nose, blurred vision and anxiety (Karlsson, 1999). While these symptoms are not simultaneously present in all cases, headache and sweating above the lesion occurs 88% of the time (Lindan et al., 1980). Although the classical definition of AD is acute hypertension coincident with bradycardia (Erickson, 1980; Guttmann and Whitteridge, 1947; Trop and Bennett, 1991), the importance of heart rate in the diagnosis of AD is a matter of controversy. Lindan et al. (1980) reported an equal incidence of bradycardia and tachycardia (increase in heart rate) in documented cases of AD, whereas others report that tachycardia is more common (Hickey et al., 2004; Kewalramani, 1980; Scott and Morrow, 1978). Whether an episode of AD is concomitant with an increase or decrease in heart rate may depend on the injury level (Collins et al., 2006; Karlsson, 1999; Krassioukov et al., 2003). As suggested by Karlsson (1999), activation of sympathetic circuits in the spinal cord below a cervical injury may propagate rostrally towards cardiac-innervating SPN (i.e., T1–T4), explaining why tachycardia is frequently observed during AD. However, the correlation between injury level and the direction of heart rate change during episodes of AD has not been formally investigated.

### 2.3. Temporal development of AD after injury

AD most often presents in the chronic phase of SCI, with a majority of cases first occurring 3–6 months after injury in humans (Lindan et al., 1980). While it may also occur in earlier stages of injury, the incidence of early AD is relatively low, with only 5.7% of individuals with SCI above T6 having clinically documented AD within the first month post-injury (Krassioukov et al., 2003). Though uncommon, the manifestation of AD in the early stage of injury is significant considering that treatment of acute, high-level SCI often includes pressor agents to help combat the profound hypotension associated with such injuries (reviewed in Ploumis et al., 2010). In cases of acute AD occurring within days of injury, systolic blood pressure as high as 210 mm Hg has been reported (Silver, 2000), suggesting that concurrent vasopressor support may compound damage during episodic hypertension.