Cardiovascular Dysfunction Following Spinal Cord Injury

14

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Abstract

Cardiovascular issues following spinal cord injury (SCI) are of paramount importance considering they are the leading cause of death in this population. The disruption of autonomic pathways leads to a highly unstable cardiovascular system, with impaired blood pressure and heart rate regulation. In addition to low resting blood pressure, on a daily basis, the majority of those with SCI suffer from transient episodes of aberrantly low and high blood pressure (termed orthostatic hypotension and autonomic dysreflexia, respectively). In fact autonomic issues, including the resolution of autonomic dysreflexia, are frequently ranked by individuals with SCI to be of greater priority than regaining motor function. Due to a combination of these autonomic disturbances and a myriad of lifestyle factors, the pernicious process of cardiovascular disease is accelerated after SCI. Unfortunately, these secondary consequences of SCI are only beginning to receive appropriate clinical attention. Immediately after high-level SCI, major cardiovascular abnormalities present in the form of neurogenic shock. After

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subsiding, new issues related to blood pressure instability arise, including orthostatic hypotension and autonomic dysreflexia. The present chapter reviews autonomic control over the cardiovascular system before injury and the mechanisms underlying cardiovascular abnormalities after SCI, while also detailing the end-organ consequences including those of the heart, as well as the systemic and cerebral vasculature. The tertiary impact of cardiovascular dysfunction will also be discussed, such as the potential impediment of rehabilitation, impaired cognitive function, and limitations to exercise capacity. In the recent past, our understanding of autonomic dysfunction has been greatly enhanced; however, it is vital to further develop our understanding of the long-term consequences of these conditions, which give us insight to cardiovascular disease morbidity and mortality in this population.

14.1 Introduction

Spinal cord injury (SCI) is a devastating condition with the capacity to change the trajectory of life resulting in increased morbidity and earlier mortality. Due to a combination of major autonomic disturbances and the related cardiovascular dysfunction, as well as a myriad of lifestyle-altering factors, the pernicious process of cardiovascular disease is extremely accelerated after SCI [1, 2]. Even after controlling for major risk factors, the risk of heart disease is almost threefold higher in those with SCI, while the risk for stroke is almost fourfold higher compared to those without SCI [3].

Disruption of the neuronal pathways of the spinal cord is well known to lead to paralysis, but also leads to major alterations of the autonomic nervous system. Although the site of injury to the spinal cord is generally localized to a small region (including neurons, supporting cells, as well as ascending and descending neuronal pathways), the effect of this disruption is frequently associated with a wide array of dysfunctions due to malfunction of the autonomic nervous system (see chapter 2).

Alterations in autonomic function are often dominated clinically by changes in spinal sympathetic control [4, 5]. Specifically, those with SCI often suffer from unstable blood pressure, including low resting blood pressure, severe drops in blood pressure when moving to the upright position (termed orthostatic hypotension (OH), and/or aberrant life-threatening bouts of acute hypertension termed autonomic dysreflexia (AD) [6]. The effect of SCI on autonomic/cardiovascular dysfunction is well reported in a variety of human and lower-order animal models (i.e., rodents) [6, 7].

Autonomic issues, such as cardiovascular dysfunction, are most frequently ranked by patients with SCI to be of greater priority to them than regaining their motor function [8]. Clinically, the importance of cardiovascular dysfunction is often overlooked and poorly understood and presents as part of complex and challenging clinical scenarios. In light of this, and the consideration that cardiovascular disorders in both the acute and chronic stages of SCI represent the most common causes

of death in individuals with SCI [9, 10], it is imperative to understand the cardiovascular consequences of this condition. It is only during the last decade, that in addition to the assessment of motor and sensory deficits [11], newly developed international Autonomic Standards were developed for clinical evaluation and management of autonomic dysfunctions following SCI [12].

The present chapter is focused on delineating cardiovascular dysfunction after SCI. Specific areas to be reviewed include: autonomic regulation of cardiovascular function, the underlying mechanisms of cardiovascular dysfunction after SCI, major cardiovascular clinical conditions after SCI such as orthostatic hypotension and autonomic dysreflexia, changes in cardiovascular disease risk factors and end-organ maladaptation after SCI, as well as management recommendations for SCI patients in order to mitigate cardiovascular dysfunction.

14.2 Autonomic Regulation of Cardiovascular Function

Arterial blood pressure and heart rate regulation are under constant control of the autonomic nervous system, which is comprised of two primary divisions: sympathetic and parasympathetic (Fig. 14.1) [14, 15]. Activation of the sympathetic nervous system plays an excitatory role (i.e., fight or flight response) and results in an increase in sympathetic peripheral nerve activity leading to increased heart rate, increase in cardiac contractility, and generalized systemic vascular constriction; together leading to increased arterial blood pressure. On the other hand, activation of the parasympathetic nervous system typically is limited to reducing heart rate and cardiac contractility (via vagal nerve), and is widely accepted 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 [16–18].

Although some cortical areas and hypothalamic regions [4] with tonic and inhibitory influences on cardiovascular functions have been identified, it is medullary neurons within the rostral ventral lateral medulla that are considered to be the major sympathetic cardiovascular regulatory region responsible for maintenance and regulation of blood pressure [19]. These sympathetically active central neurons project to the spinal cord and travel primarily through the dorsolateral funiculus synapsing on the spinal sympathetic preganglionic neurons (SPNs), which are located predominately within the lateral horns of spinal gray matter in spinal segments T1–L2. The axons of SPNs (preganglionic fibers) exit the spinal cord via ventral roots and synapse on the sympathetic ganglionic neurons within paravertebral chain ganglia (ganglionic neurons) [20]. Finally, the postganglionic neurons innervate target organs such as blood vessels (adrenergic sympathetic innervation), sweat glands, and piloerectors (cholinergic sympathetic innervation) [20]. Both the central and peripheral autonomic nervous systems provide crucial coordinated regulation of the cardiovascular system in order to provide appropriate blood pressure throughout daily living including such activities as exercise and orthostatic challenges.

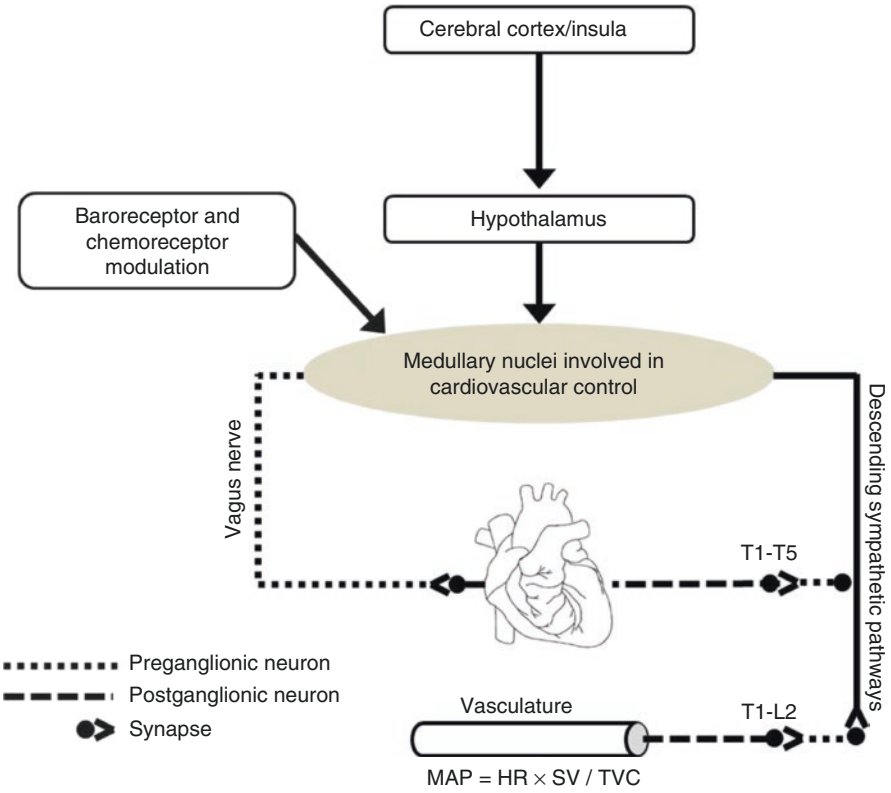


Fig. 14.1 Autonomic cardiovascular control. The cerebral cortex and hypothalamus project to the nuclei of the medulla oblongata, where autonomic cardiovascular control is coordinated and integrated with input from baroreceptors, chemoreceptors. Parasympathetic control of cardiovascular systems exits at the level of the brainstem via the vagus nerve. The preganglionic fibers of the vagus nerve then synapse with postganglionic parasympathetic neurons in ganglia on or near the target organ. Descending sympathetic pathways provide tonic control to sympathetic preganglionic neurons (SPNs) involved in cardiovascular regulation. Cell bodies of SPNs are found within the lateral horn of the spinal cord in segments T1–L2 and exit the spinal cord via the ventral root, and they then synapse with postganglionic neurons located in the sympathetic chain (paravertebral ganglia). Finally, the sympathetic postganglionic neurons synapse with target organs such as the heart and blood vessels. Considering Poiseuille's law, blood pressure is affected to the fourth power by arterial diameter and only linearly by increases in flow [heart rate (HR)-derived changes in cardiac output]. As such, it is not surprising that the vasomotor branch of the baroreflex is much more important than the vagal branch for the maintenance of mean arterial blood pressure (MAP). *TVC* total vascular conductance, *SV* stroke volume (Modified from Phillips et al. [13])

In terms of the parasympathetic division, the vagal nerve exits the central nervous system supraspinally and reaches target organs such as the heart and cerebral blood vessels without traversing the spinal cord. The parasympathetic division plays an important role in dynamically regulating the heart rate over very short time frames of 2–3 s [21], but does not play a major role in steady-state blood pressure

either in a supine or upright position [22]. Some sacral parasympathetic cell bodies of the parasympathetic division are located in the spinal segments S2–S4; however, they do not play a role in cardiovascular control. Both sympathetic and sacral parasympathetic preganglionic neurons receive supraspinal tonic and inhibitory nervous system control via spinal autonomic pathways that [23, 24], unfortunately, are frequently disrupted after SCI [25].

The baroreflex is the primary mechanism responsible for short-term regulation of blood pressure [13, 26] and also plays a critical role in long-term blood pressure regulation [27]. The baroreflex is comprised of two interdependent systems [28, 29] that work in concert as one reflex system. The first, a low-pressure system, is made up of cardiopulmonary stretch receptors located in the heart and lungs, which augments sympathetic nervous system activity in response to reductions in central venous pressure and volume [30]. The second, a high-pressure baroreflex system, consists of stretch receptors located in the tunica adventitia of the aortic arch and carotid bulbs [31]. These spray-like nerve endings generate a more rapid rate of depolarization and hence increase the frequency of action potentials in afferent nerves during periods of increased wall distension [30]. The signal is transmitted from the carotid bulb via the glossopharyngeal nerve (vagal nerve) and the aortic arch via the vagal nerve to the nucleus of the solitary tract in the medulla oblongata [14]. This transmission, which provides surrogate information on systemic blood pressure, is integrated with other afferent information (such as chemoreceptor afferent signals) in order to modulate efferent nervous activity transmitted through the vagal nerve and sympathetic system to target organs, with the aim of rapidly maintaining blood pressure around a set point (Fig. 14.1) [30]. For example, when a human moves from the supine to upright position, approximately 500 ml of blood is translocated away from the heart and brain and toward the blood vessels of the gut and legs [32]. Central baroreceptors detect reductions in stretch and respond by decreasing vagal tone to the heart and increasing peripheral sympathetic activity. The increase in sympathetic tone results in an increased heart rate and peripheral vasoconstriction that is responsible for maintaining stable arterial blood pressure [13]. After SCI, although the baroreceptors certainly detect reductions in central blood volume during orthostasis, disrupted descending sympathetic pathways precludes the capacity to vasoconstrict, often resulting in abnormal fluctuations in blood pressure with changing body position [13]. Our most recent understanding, as well as mechanistic insight, surrounding these episodes and other cardiovascular conditions after SCI will be discussed in the following sections.

14.3 Mechanisms Underlying Abnormal Cardiovascular Control Following SCI

We are just beginning to unravel the mechanisms underlying abnormal cardiovascular function after SCI. Due to the lack of a suitable animal model of OH, most mechanistic studies have focused on AD as the clinical condition of interest. The morphological changes within the spinal autonomic circuits after SCI have been

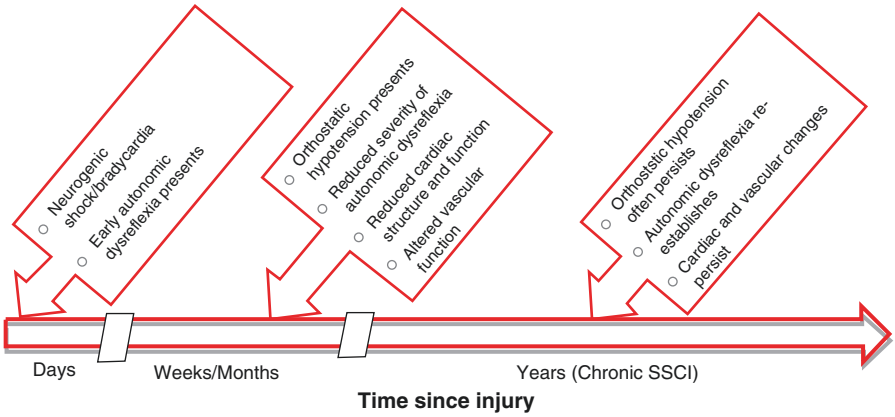


Fig. 14.2 Timeline of changes in autonomic and cardiovascular function after spinal cord injury

established relatively recently [33]. Furthermore, the role these changes are playing in the development of autonomic dysfunction has only just been solidified [34–36]. A variety of autonomic circuits have been highlighted that possibly contribute to abnormal cardiovascular control after SCI [6]. The disruption of descending spinal cardiovascular pathways leads to a minimum of six neuroanatomical changes that influence autonomic cardiovascular control:

1. Initial sympathetic hypoactivity due to loss of supraspinal tonic sympathetic excitation [37, 38].
2. Alterations in the morphology of sympathetic preganglionic neurons (SPNs) [20, 33].
3. Plastic changes of the spinal circuits (i.e., dorsal root afferent sprouting, potential formation of aberrant synaptic connections [39], or aberrant inputs to the spinal interneurons) [34].
4. Altered sympatho-sensory plasticity [35].
5. Altered peripheral neurovascular responsiveness [40].
6. Cumulative effect of tertiary factors. These factors will be discussed below.

Autonomic Pathways and SPN Plasticity It is now appreciated that in the acute stage after SCI, SPNs atrophy. However, over time, they regain somewhat normal morphology (similar soma size as pre-injury but more dendritic arbor and aberrant connections) [15]. It is most likely that the loss of descending projections of medullary neurons result in the initial atrophy of SPNs, as many of these are thought to synapse directly. In the very early phase after SCI, loss of descending inhibitory pathways predisposes individuals to early AD episodes, while, later atrophy of SPNs leads to an intermediate period where AD is less severe (Fig. 14.2) [15]. Disrupted descending pathways, as well as atrophied SPNs, likely contribute to the lack of sympathetic tone and very low resting blood pressure in the early phase of

injury as well as the extremely high prevalence of OH. As the phase of injury transitions into the more chronic stage, AD manifests again [6, 41]. For example, AD is most commonly documented during the subacute and chronic stages of SCI. AD often becomes clear within 2–3 months after SCI in those with SCI above the T6 spinal segment [42].

Dorsal Afferents and Intraspinal Plasticity Exaggerated sensory input to the spinal cord occurs caudal to the site of injury after SCI. For example, evidence from animal studies suggests that dorsal root afferents sprout along with an enlargement of soma size in the dorsal root ganglia after SCI [39, 43, 44]. 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 laminae II–V post-SCI) (see chapter 2) [45], accompanied by somal hypertrophy of the transient receptor potential cation channel subfamily V member 1 (TRPV1) in the dorsal root ganglia [35]. 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) (see chapter 2) [15]. Increased sprouting of primary afferents would generate new intraspinal circuits [34] and is a suspected mechanism for AD due to both similar time courses [34, 45–47] and its relation to AD severity [48].

Vasculature Peripheral Component An additional autonomic alteration associated with AD after SCI includes hyperresponsiveness of blood vessels to alpha-adrenergic stimulation. Specifically, it has been shown that the mesenteric artery is hyperresponsive to the pressor agent phenylephrine in rodents after SCI due to increased sensitivity secondary to impaired neuronal reuptake [49, 50]. Furthermore, a number of studies have shown exaggerated pressor responses to alpha sympathomimetic administration [51–53]. It has also been shown that sympathetically correlated spinal interneurons are hypersensitive to afferent stimuli after SCI [14, 15, 34]. Together, the combination of hyperresponsive interneurons and vascular smooth muscle, as well as the increased influence from primary afferents, creates a "perfect storm" of reorganization predisposing to episodes of transient hypertension in response to nociceptive or non-nociceptive afferent stimulation (i.e., AD). It is interesting to highlight however the multifaceted contributions to the presence of AD. For example, reductions in AD severity have been shown after interventions showing no reduction in blood vessel hyperresponsiveness [49], suggesting other factors such as altered sympatho-sensory plasticity may be playing a more central role.

Clearly, there are a number of factors after SCI that predispose to the frequent and widespread occurrence of AD and OH, which are major clinical conditions after SCI affecting both the quality and quantity of life in this population.

14.4 Cardiovascular Consequences Following SCI

Over the past 10 years, our knowledge regarding the underling pathophysiology of autonomic dysfunction after SCI has been enhanced greatly [5, 34, 41, 54]. The most prominent outcomes of mechanistic maladaptations described above are low

resting blood pressure [6] as well as extremely labile blood pressure characterized by frequent episodes of low blood pressure when assuming an upright position (OH) and episodes of high blood pressure in response to afferent stimuli below the level of injury (AD). These cardiovascular conditions will be discussed in detail throughout the next sections.

14.4.1 Low Resting Blood Pressure

In addition to hypotension during the acute period following SCI (neurogenic shock, see below) individuals with high thoracic and cervical SCI frequently experience low arterial blood pressure at rest that is notably lower than in able-bodied individuals [55]. Clinical evidence indicate that the extent and severity of hypotension, correlates well with the level and severity of SCI (Fig. 14.3) [41, 56–58]. Analysis derived from the non-SCI population has clearly illustrated that an inverted-U relationship exists in terms of resting blood pressure, whereas in addition to high blood pressure, there are significant clinical conditions associated with having a blood pressure that is too low [59–61]. This has recently been corroborated in the SCI population, where impaired cerebrovascular and cognitive function has been shown to be associated with low resting blood pressure [62]. In the SCI population, low resting blood pressure is also associated with a number of conditions, including cognitive impairment, exacerbated dizziness, and the development of syncope, as well as poor mood, lethargy, and fatigue [63–67]. Following this, low blood pressure should be appreciated and addressed in those with SCI.

14.4.2 Autonomic Dysreflexia

Episodes of AD are characterized by an acute elevation of systolic blood pressure of at least 20 mmHg, which may or may not be accompanied by a decrease in heart rate [68], and occurs in response to peripheral painful or non-painful visceral or somatic stimulation below injury, including a full bladder or bowel (see Fig. 14.4 for example of AD during bladder filling). It is now well appreciated that AD episodes can occur in both the acute and chronic phases of SCI [42, 69]. In fact, episodes of AD, where systolic blood pressure can rise above 300 mmHg, are now known to occur up to 40 times/day (average of 11 times/day) in the majority of those with high-level SCI above the T5 level [70]. Episodes of AD are often accompanied by a pounding headache, and flushing above the injury [6, 68, 71]. Left untreated, episodes of AD could result in life-threatening complications (Table 14.1) including cerebral hemorrhage, retinal detachment, seizures, cardiac arrhythmias, and death [152–154].

The most common stimuli to trigger AD include bladder and bowel distention, but can also be brought on by spasms, pressure sores, and even something as simple

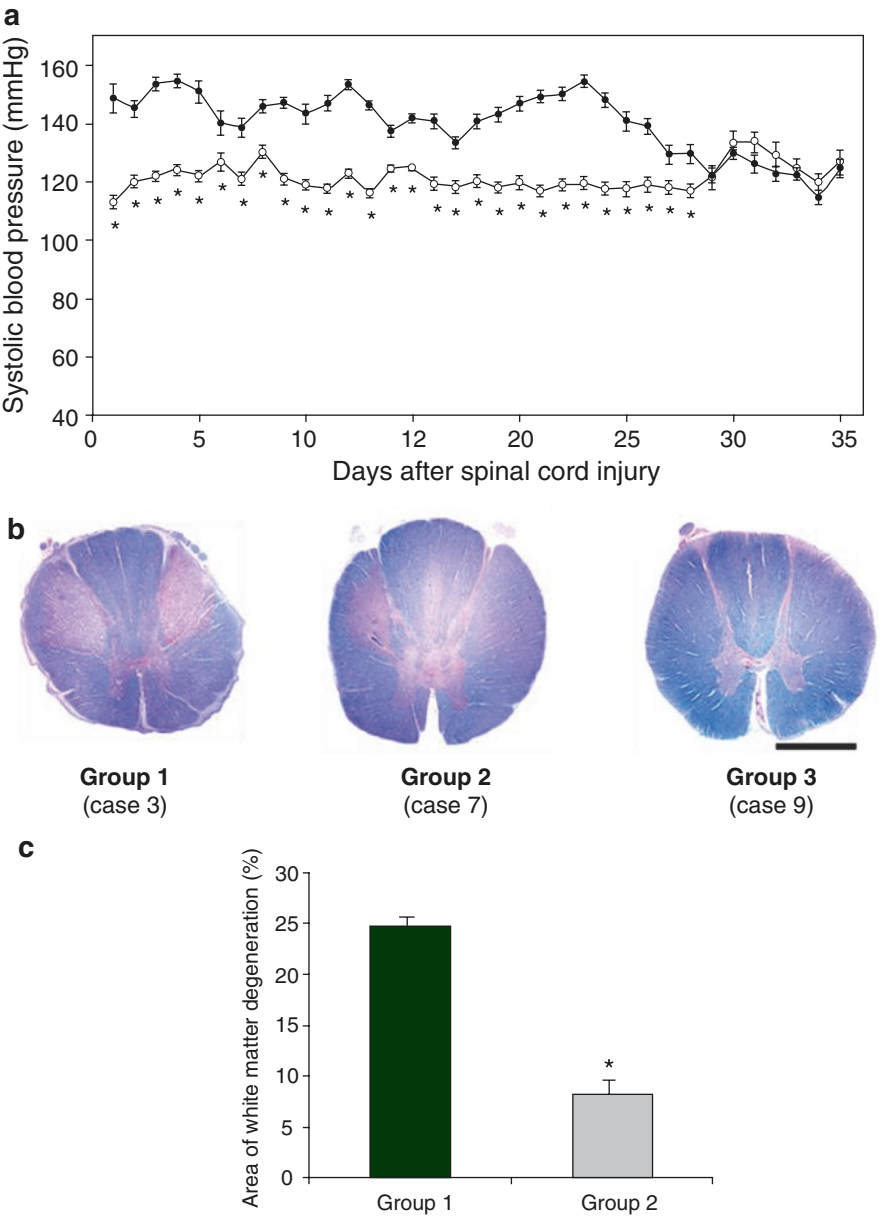


Fig. 14.3 Illustrating the effect of completeness of injury on blood pressure stability. Groups *1*, *2*, and *3* represent the same groups of participants from Parts (a), (b), and (c). Part (**a**): Daily mean ± standard error of systolic blood pressure from days 1 to 35 after spinal cord injury (SCI). Patients with severe cardiovascular complications (*empty circles*, Group *1*) were compared to those not developing major cardiovascular complications (*filled circles*, Group *2*) and were significantly different. Part (**b**): Sections of postmortem human spinal cord tissue stained for myelin with Luxol fast blue from representative cases of Group *1*, Group *2*, and Group *3* (non-SCI controls). Part (**c**): Areas of significantly more extensive axonal degeneration (pink areas within gray white matter) are present in individuals from Group *1* as compared to Groups *2* or *3*. *Represents $P < 0.05$) (Modified from Furlan et al. [25])

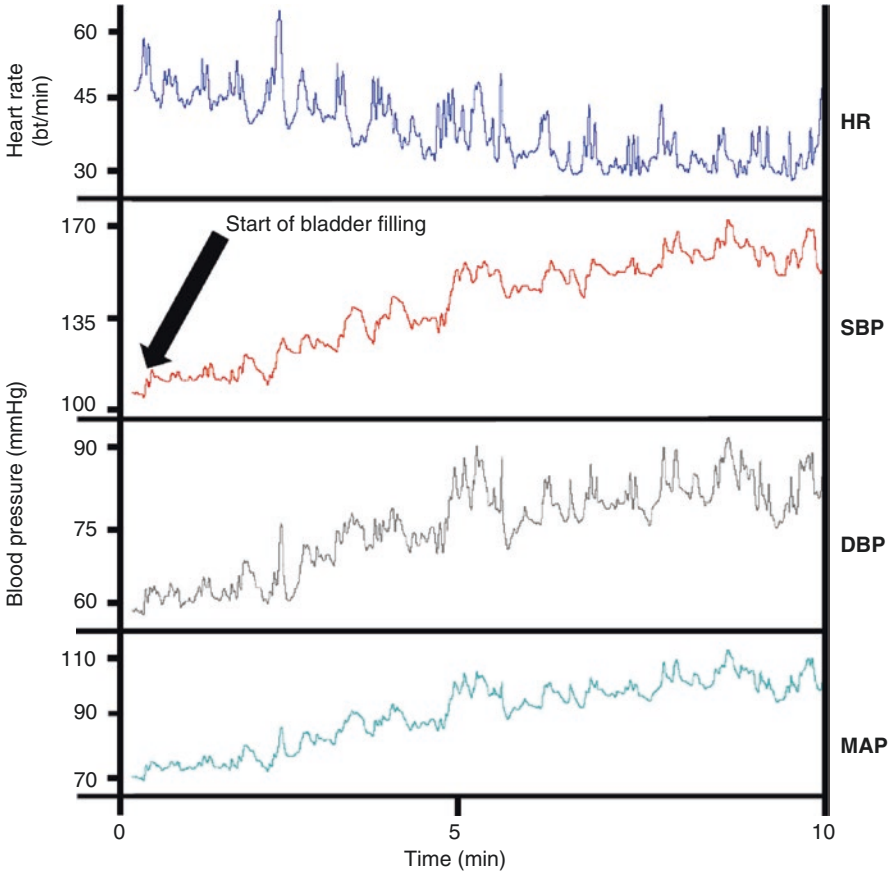


Fig. 14.4 Continuous beat-by-beat changes in heart rate as well as systolic, diastolic and mean blood pressure (*SBP*, *DBP*, *MAP*) during autonomic dysreflexia induced by urodynamic bladder filling in one male with a T2 motor complete (AISA) spinal cord injury. Clinical observation from our laboratory. Note that SBP increases by 70 %, up to 170 mmHg

as a tight shoelace [5]. Catheterization and manipulation of an indwelling catheter can also lead to AD, in addition to urinary tract infection, detrusor-sphincter dyssynergia, and bladder percussion. There are also a number of iatrogenic triggers such as cystoscopy, penile vibrostimulation or electrostimulation for ejaculation, as well as the electrical stimulation of muscles [89, 96, 155]. The intensity of AD episodes is variable, and not all episodes are severe, especially if the triggering stimulus is resolved promptly. In fact, many AD episodes are asymptomatic (i.e., patient does not recognize it even though blood pressure is increasing) or characterized by sweating and/or piloerection alone [156]. The level and completeness of the injury are the critical determinants for the presence of AD which is three times more common in complete versus incomplete quadriplegics [157] and typically occurs

Table 14.1 Triggers and conditions associated with autonomic dysreflexia

Urogenital system
Bladder distension [72–77]
Urethral distention [78–81]
Urodynamics/cystoscopy [72, 76, 78, 82–84]
Urinary tract infections [79, 85–87]
Epididymitis [88]
Renal calculus [89, 90]
Electroejaculation [91–93]
Coitus [94, 95]
Penile stimulation to obtain reflex erection [96–98]
Vaginal dilation [99]
Uterine contractions [77, 100–105]
Testicular torsion
Gastrointestinal system
Bowel distention [76, 106, 107]
Anal fissures/hemorrhoids [99, 108, 109]
Esophageal reflux [110]
Enemas [111]
Gastric dilatation [99]
Gastric ulcer [112]
Acute abdomen (peritonitis, cholecystitis, appendicitis) [112]
Skin/musculoskeletal
Cutaneous stimulation [113, 114]
Sunburns [115]
Pressure sores [116, 117]
Ingrown toenails [76]
Functional electrical stimulation [118]
Spasticity [119]
Bone fractures [120, 121]
Intramuscular injection [122]
Hip instability [123, 124]
Surgical procedures/conditions
Surgical procedures [125–130]
Radiologic procedures [131]
Unstable fusion [132]
Lumbar spondylolisthesis [133]
Miscellaneous
Pulmonary embolism [134]
Range-of-motion exercises [135]
Position changes [136, 137]
Medications [74]
Emergence in cold water [138]
Acupuncture [139]

(continued)

Table 14.1 (continued)

Advantages of autonomic dysreflexia (AD)
Self-induced AD (intentional boosting) [140–142]
Signal of onset of serious medical complications [99, 112]
Complications of AD seizures [88, 143]
Retinal hemorrhages [82, 88]
Intracranial hemorrhage [88, 125, 144–146]
Transient aphasia [147]
Neurogenic pulmonary edema [148]
Cardiac arrhythmias [71, 149]
Cardiac arrest [150]
Death [88, 125, 151]

primarily when the SCI is at or above the T6 spinal segment (see chapter 2) [5, 41]. As discussed previously in this chapter, changes in the autonomic circuits in the spinal cord are major contributing factors to the development of AD [34].

Finally, it should be noted that, although AD is certainly a life-threatening emergency [125] and known to be unpleasant [94], some individuals with SCI voluntarily induce AD in order to increase their blood pressure, as it may in some cases improve their athletic performance [140]. The inducement of AD is referred to as "boosting" and is considered unethical and illegal by the International Paralympics Committee Medical Commissions, leading to medical examinations before competitions. The occurrence of boosting in competition is a testament to the devastating functional and performance limitations imposed by the autonomic cardiovascular dysfunctions present after SCI.

14.4.3 Orthostatic Hypotension

Episodes of OH are characterized by substantial declines in blood pressure when assuming the upright posture (Fig. 14.5). After SCI, the interruption of sympathoexcitatory pathways from the brainstem to the SPNs impairs the efficaciousness of the arterial baroreflex to cause vasoconstriction and maintain blood pressure [158, 159]. Although the cardiovagal baroreflex is impaired after SCI, it is the sympathetic system that is primarily responsible for blood pressure maintenance following the first 2–3 s of orthostatic challenge (before which the cardiovagal response is important) [13]. The result is both low venous return secondary to blood pooling in the vasculature caudal to the site of injury, as well as low arterial blood pressure/vessel tone [13]. Additionally, there are low resting catecholamine levels after cervical SCI and no discernable increase with central supraspinal sympathetic activation induced by upright tilt [7]. The presence of stiffer central arteries (which are responsible for detecting changes in blood pressure) after SCI further impairs baroreflex sensitivity [1]. Orthostatic hypotension is most

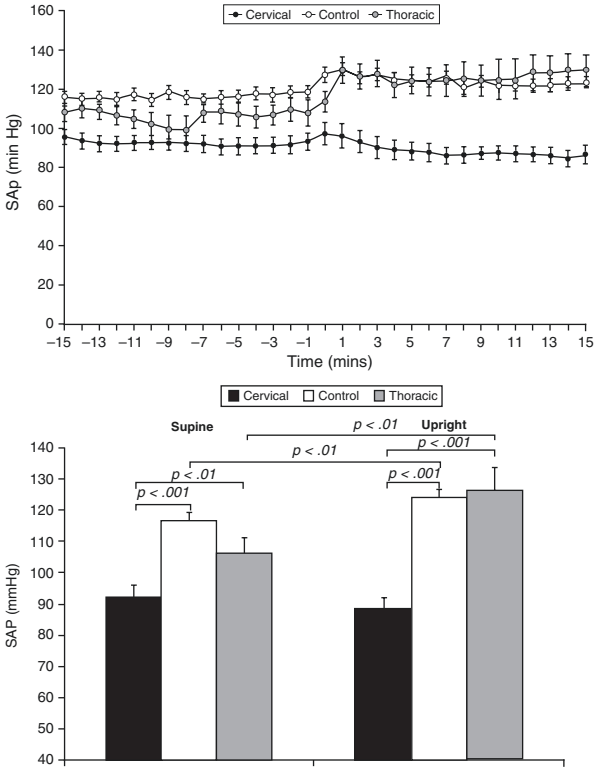


Fig. 14.5 Changes in systolic arterial blood pressure (*SAP*) during passive sit-up test in cervical SCI patients, non-injured controls, and thoracic SCI patients. *Top*: mean ± standard error SAP recorded every minute. The *black line* represents the upright portion of the sit-up test, while prior to that patients were supine. *Bottom*: mean ± standard error SAP averaged from the entire supine or upright portion of the sit-up test (Modified from Claydon et al. [63])

common and severe in the acute phase of SCI, but also can be observed in the chronic phase among individuals with high cervical injuries [66, 160]. Similar to resting blood pressure, the severity and level of injury to descending cardiovascular autonomic pathways is directly associated with OH (Fig. 14.5) [7]. Together, this indicates that the extent of cardiovascular instability after SCI is related to the completeness of injury to autonomic pathways within the spinal cord. Clinically, OH is defined as a decrease in systolic blood pressure of 20 mmHg or more, or a decrease in diastolic blood pressure of 10 mmHg or more, when assuming an upright posture from the supine position, regardless of presence of symptoms [161]. This definition was agreed upon by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology [161]. Presyncopal symptoms after SCI are no different from the able-bodied population [162]. These include light-headedness, dizziness, blurred vision, fatigue, nausea,

dyspnea, and restlessness [163, 164]. Orthostatic hypotension is extremely common in those with SCI. For example, one study showed that OH occurs in up to 74 % of individuals with SCI when performing orthostatic maneuvers during physical therapy and mobilization [67]. Similar to AD, OH does not always lead to presyncopal symptoms, and many individuals have asymptomatic OH. In fact, 41 % of those with SCI were asymptomatic during episodes of OH [7]. Recently, we have shown that often OH persists into the chronic stage of SCI; however presyncopal symptoms may partially subside [7]. In terms of prevalence, in the chronic phase of SCI, OH occurs in up to 50 % of cervical SCI patients and 18 % of thoracic patients; however, from this OH-positive group, presyncopal symptoms were only present in one third and one fifth of individuals [7]. This finding suggests that tolerance to low blood pressure and cerebral perfusion pressure may improve with time after SCI [65, 165, 166]. Considering the association between OH and an elevated risk of stroke in the able-bodied population [167], as well as the fact that stroke risk is 3–4 times greater after SCI, it is logical to posit that the presence of OH after SCI plays a contributing role [3, 168].

Other factors contributing to the presence of OH after SCI include reduced plasma volumes caused by hyponatremia [163], insufficient increases in the efficaciousness of the renin-angiotensin system to maintain blood pressure [51], and potential cardiac deconditioning [169–171]. A similar contribution from these mechanisms leads to low resting blood pressure after SCI as well [6].

To summarize, episodes of OH can lead to syncope, nausea, fatigue, and dizziness and significantly impede rehabilitation. Over the long term, OH likely contributes to an elevated risk of stroke after SCI. Resting hypotension also plays a role in cognitive dysfunction by exacerbating the severity and frequency of orthostatic intolerance. Approaches to combat the abnormal cardiovascular responses after SCI are only in the early stages of development and will be discussed below.

14.5 Cardiovascular Changes with Time Following SCI

Spinal cord injury results in a number of acute and chronic alterations in physiology and behavior that together contribute to cardiovascular decline over the life-span of individuals with SCI (Fig. 14.2). This section will discuss acute and chronic conditions after SCI and considerations related to cardiovascular decline that contribute to the high risk of developing cardiovascular diseases in this population.

14.5.1 Acute Cardiovascular Changes

It is clear at this point in the chapter that cardiovascular function itself is critically compromised by SCI. In the acute phase following high level of SCI, individuals present with severe hypotension and bradycardia [6]. These two issues are classic characteristics of the condition known as neurogenic shock [172]. Up to 100 % of

individuals with cervical SCI will experience severe hypotension in the acute phase after SCI, and roughly 50 % will require vasopressive therapy to maintain arterial blood pressure [6, 173]. Additionally, the majority of individuals with SCI will suffer from abnormal heart rates in the acute phase following SCI. Specifically, bradycardia has been reported in 64–77 % of patients with cervical SCI (being most severe for up to 5 weeks after injury) [82, 174–177]. When SCI occurs in the mid-thoracic region or caudally, bradycardia is typically less severe, secondary to partial preservation of supraspinal influences over cardiac sympathetic neurons. Neurogenic shock has the potential to significantly impact long-term recovery from SCI, by delaying acute surgical management of the injury itself [178], and the arrhythmias that present during this phase of injury can require the implantation of a cardiac pacemaker [176, 177].

It is important to differentiate the terms "neurogenic shock" and "spinal shock," both of which can occur during the acute phase of SCI, but represent two different conditions altogether [57, 179]. Although these terms are often used interchangeably, neurogenic shock describes the clinical outcomes of changes in autonomic blood pressure control after SCI, while spinal shock describes the clinical outcomes of changes in motor/sensory/reflex function after SCI (i.e., flaccid paralysis and areflexia) [179].

14.5.2 Long-Term Cardiovascular Considerations

14.5.2.1 Contributing Factors

It has been relatively recent that cardiovascular diseases were identified as the primary cause of death after SCI [10, 180]. In addition to the aforementioned lability in blood pressure (i.e., frequent episodes of AD and OH), we now appreciate that a number of interacting secondary conditions occur after SCI which likely increases the trajectory of cardiovascular disease progression throughout a patient's life-span, including widespread physical inactivity [181, 182], type II diabetes [183–186], increased inflammation [187], suboptimal cholesterol profile [188], and accelerated arterial stiffening [1, 2]. Comprehensively reviewing these conditions is beyond the scope of this chapter; however the following sections will highlight these issues and management recommendations.

14.5.2.2 Physical Inactivity

In addition to increased mortality, reduced physical activity is related to a myriad of conditions including accelerating cardiovascular disease progression [189]. Those with SCI, due to a spectrum of physical and psychosocial conditions and barriers, are less physically active when compared to able-bodied peers [1, 190]. A number of studies have highlighted that physical inactivity in those with SCI is a critical mediating factor related to the propagation of subclinical prognosticators for cardiovascular disease development [191]. Recent clinical guidelines for physical activity recommend for individuals with SCI to engage in aerobic

exercise twice weekly for a duration of at least 20 min, at moderate-to-vigorous intensity for health improvements indicative of mitigated cardiovascular disease risk [192]. Previous to this, clinical guidelines from American College of Sports Medicine recommended 3–5 exercise sessions per week at 50–60 % of maximum aerobic capacity for 20–60 min [193].

14.5.2.3 Impaired Glycemic Control

Hyperglycemia is well known to lead to diabetes or prediabetes. These abnormalities are identified with elevated fasting glucose levels (≥7 mmol/L), an elevated routine (i.e., non-fasting) blood sugar with symptoms of diabetes (≥11.1 mmol/L) hemoglobin A1c (HbA1c ≥6.5 %), or with an abnormal glucose tolerance test (2 h post-75 g glucose ingestion ≥11.1 mmol/L; CDA, 2008). In those with SCI, the prevalence of abnormal glycemic control and diabetes itself is consistently higher than in the able-bodied population [186]. Exercise plays a role in mitigating glycemic abnormalities in those with SCI as well as able-bodied individuals. Although the majority of studies reported improvements in glycemic control due to exercise after SCI, the modalities employed required expensive equipment and experienced training personnel (i.e., functional electrical stimulation of paralyzed limbs, body weight-supported treadmill exercise of lower limbs) [194–196]. No well-established recommendations exist for the management of glycemic abnormalities after SCI, although effective monitoring and standard treatment are encouraged.

14.5.2.4 Inflammation

Chronic inflammation is a key propagating factor in cardiovascular disease progression [197]. The measurement of highly sensitive C-reactive protein (hs-CRP) can clinically quantify the presence and severity of inflammation, which is statistically speaking an independent risk factor for the development of cardiovascular disease [198]. There are frequent infections in the chronic phase of SCI, including urinary tract infections and decubitus ulcers [199]. Therefore, inflammatory markers may spuriously represent underlying infection and not chronic inflammation. It should be appreciated however that in those with SCI, hs-CRP as well as other markers of systemic inflammation are significantly elevated, even without acute infection [200, 201]. To date, there are no studies clearly linking chronic inflammation in those with SCI and the development of cardiovascular disease; however, considering the link in able-bodied individuals, it is highly likely that chronic inflammation plays an exacerbating role [197]. The current recommendations suggest close monitoring of inflammation in SCI; however, the management thresholds are not clearly established and likely should be based on able-bodied individuals in the absence of SCI-specific data.

14.5.2.5 Lipid Abnormalities

Following SCI, there is consistent evidence of lipid profile abnormalities, particularly reduced high-density lipoprotein, which is a well-established risk factor for cardiovascular disease development [188, 202, 203]. Most individuals require

pharmaceutical intervention in order to normalize suboptimal cholesterol profiles [204, 205], and the cardiovascular disease event reduction strategies have been adopted from other populations not suffering from SCI [205, 206]. A number of studies highlight that physical activity (either active lower body or functional electrical stimulation of the lower body) can play a role in normalizing lipid profiles in those with SCI [207–210]; however no clear guidelines exist.

Unfortunately, all of the above risk factors are exaggerated in those with SCI, and no specific guidelines exist for these risk factors (with the exception of physical activity). In light of this, in most cases, it is suitable to follow standard (i.e., able-bodied) monitoring and treatment for well-established cardiovascular disease risk factors [3].

14.5.3 Cardiovascular End-Organ Maladaptation

14.5.3.1 Arterial Dysfunction

A great deal of interest has stemmed recently from the assessment of arterial health (e.g., arterial pulse wave velocity, endothelial responsiveness), both from the perspective of measuring subclinical cardiovascular disease progression in research, as well as in clinical practice for the capacity of arterial markers to be powerful predictive tools for future cardiovascular disease events [191, 211]. Arterial health markers also incorporate cardiovascular disease risk that is not captured by standard clinical assessments such as Framingham scores [212, 213], suggesting that standard predictive tools do not accurately detect cardiovascular disease risk stemming from arteriosclerotic decline. A number of studies have examined arterial health and function in those with SCI [1, 2, 214, 215]. Currently, it appears that SCI elicits very little effect on endothelial function, although this is likely confounded by imprecise covariation for critical influencing factors such as a rapidly reducing arterial diameter post-injury, secondary to reduced metabolic blood flow requirements in downstream perfused tissue [216, 217]. Aortic stiffness, however, as measured using pulse wave velocity, is consistently elevated by 2–3 m/s in those with SCI as compared to able-bodied individuals [1, 2], which corresponds to a 28–45 % increased risk of age-, sex-, and risk factor-adjusted likelihood of total cardiovascular events, cardiovascular mortality, and all-cause mortality [191]. Additionally, increased central arterial stiffness is shown to be a major cause of cardiac dysregulation after SCI, with recent data suggesting vascular stiffening is the primary cause of cardiovagal baroreflex dysfunction in this population [214]. Although arterial stiffness is currently being strongly advocated for use in clinical practice [218, 219], there are no specific recommendations or guidelines for the treatment of arterial health after SCI; however, management should adhere to recommendations for the aforementioned risk factors.

14.5.3.2 Heart

Cardiovascular decline is apparent through a number of deleterious alterations in cardiovascular end organs, some of which occur at a remarkably rapid rate of mere

weeks after the SCI itself [216, 220–222]. Impairments in cardiac structure and function have been extensively reported in the literature in the recent past. Specifically, a number of studies in both rodents and humans have shown a reduction in cardiac size after high thoracic and cervical SCI, whereas those with lower thoracic injuries do not appear to undergo the same changes, despite reduced stroke volume [216, 222–224]. It has recently been demonstrated in the rodent model that high-level SCI (i.e., T3 complete spinal cord transection) results in marked reductions in cardiac size (i.e., end-diastolic/systolic volumes) after only 7 days [224]. These reductions in cardiac dimensions occurred in unison with decreased cardiac contractility as well as with increased relative wall thickness and myocardial fibrotic collagen expression in the left ventricle. Collectively, these changes are key tenants of cardiovascular decline and cardiovascular disease progression and indicate elevated risk for cardiovascular disease [225].

To date, very few interventions have been examined for the mitigation of cardiac decline after SCI. One of the most promising therapies to date involves passive exercise in the early phase after injury [224]. In rodents who started passive exercise only 5 days after injury, all cardiac impairments noted above were normalized to uninjured control levels after 1 month of intervention [224]. Volume unloading (i.e., incapacity to maintain sufficient venous return to the heart) seems to be the principle mechanism by which these cardiac changes occur after high-level SCI. Both rodent and human studies on prolonged bed rest support the idea that maintaining adequate venous flow back to the heart preserves normal cardiac dimensions and function [226–228] Certainly, human trials are needed and ongoing; however, careful attention should be paid to the critical role volume unloading plays on the heart, especially as it appears that early participation in lower-limb exercise after SCI completely abrogates the majority of cardiac-specific decline in this population.

14.5.3.3 Cerebrovasculature

Unfortunately, the end organ of paramount complexity and importance also suffers significant and critical alterations after SCI. Although we know little about changes in brain morphology after SCI, as mentioned earlier, we do know that cognitive function (i.e., memory, attention/processing speed, executive function) is significantly impaired, and stroke risk is 3–4 times greater in this population [229–237]. Both of these conditions are considered to be at least partially vascular in origin, and we are just beginning to understand the extent of changes in cerebrovascular function after SCI [238, 239]. For example, we do know that people with high-level SCI are less able to maintain cerebral perfusion when undergoing an orthostatic challenge [65], and when blood pressure is low, the cerebrovascular reactivity to cognition (i.e., neurovascular coupling, which describes the efficacious matching of blood delivery to cognitive/neuronal activation) is completely abrogated [240]. These cerebrovascular disorders are associated with declined cognitive performance in able-bodied individuals and those with SCI [62, 241]. It appears that low blood pressure is a major contributing factor to impaired cerebrovascular reactivity in those with SCI, which represents a similar causal factor as that which has been elucidated for cardiac decline

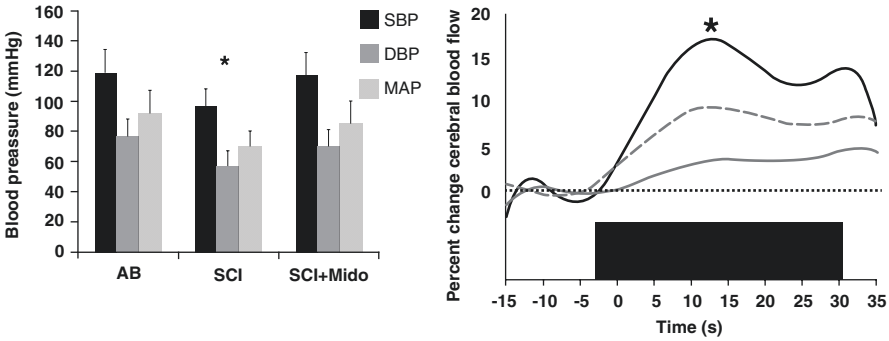


Fig. 14.6 Cerebrovascular reactivity after spinal cord injury. *Left panel*: Blood pressure in able bodied (*AB*), spinal cord injured (*SCI*), and spinal cord injured with normalized blood pressure using midodrine (*SCI + Mido*). *Right panel*: Neurovascular coupling of the posterior cerebral artery in AB (*black line*), SCI (*gray line*), and SCI + Mido (*gray dotted line*). *Thick black bar* denotes 30 s of eyes-open reading, preceded by 15 s of eyes-closed rest. Notice that normalizing blood pressure significantly improved neurovascular coupling. Improved neurovascular coupling as associated with increased executive functioning. *Represents significantly different from AB and SCI + Mido ($P < 0.05$) (Modified from Phillips et al. [62])

(i.e., reduced blood flow/loading) [62, 224, 227]. Please see Fig. 14.6 for detailed description of clinical findings leading to the above contention.

To date, very few studies have examined therapeutic interventions for improving cerebrovascular and cognitive function in those with SCI. Recently, normalizing hypotension by pharmaceutical administration of midodrine hydrochloride (10 mg tablet) was shown to improve cerebrovascular reactivity to cognition, and cognitive function in those with hypotension secondary to SCI [62]. It is important to note, however, that only a small component of cognitive function was measured in this study (i.e., verbal fluency), and although improved, pharmaceutical treatment did not completely normalize cognition as compared to able-bodied controls.

Taken together, systemic arteries, the heart, and cerebrovasculature are impaired in terms of health and function after SCI. These end-organ maladaptations contribute to a variety of clinical consequences such as increased risk of heart attack, stroke, orthostatic intolerance, and cognitive dysfunction. Both cardiac and cerebrovascular functions appear to be detrimentally influenced by reduced hemodynamic perfusion (i.e., low venous return and blood pressure), which can be improved by increasing circulation to the respective organ, such as passive exercise for increasing venous return to the heart and increasing blood pressure to increase blood flow to the brain.

14.6 Managing Cardiovascular Function Following SCI

As cardiovascular dysfunction exhorts such critical effects on morbidity and mortality, a number of strategies have been explored for the prevention and treatment of autonomic/cardiovascular instability after SCI. These have included a number of treatments to be implemented in the acute phase of injury with the goal of limiting

damage to autonomic pathways of the spinal cord as well as interventions designed to treat cardiovascular dysfunction once it has presented after SCI. These topics will be discussed in the following section.

14.6.1 Preclinical Experimental Therapies for Prevention of Cardiovascular Dysfunctions After SCI

As outlined above, cardiovascular dysfunction after SCI is largely the result of disruption of descending autonomic pathways and the subsequent decentralization of the spinal and peripheral sympathetic circuits, resulting in alteration of the autonomic/cardiovascular system. A number of therapeutic approaches have been developed and studied in order to regenerate or preserve descending sympathetic pathways and prevent the resulting cardiovascular dysfunction, although none of these approaches are currently approved for treating patients. These therapeutic approaches have been reviewed recently and will be highlighted below [242].

The preservation of descending supraspinal input using stem cells has been explored in a couple of interesting studies [243, 244]. Early work showed that olfactory ensheathing cells harvested from the animals themselves (and grafted into site of SCI) were able to improve AD (i.e., to reduce the duration of AD episodes) following SCI; however no improvements in resting blood pressure were observed. Unfortunately, when examining the underlying mechanisms, no discernible improvements in CGRP+ sprouting or reduction in injury size occurred making it difficult to ascertain what factors led to the improved autonomic cardiovascular function after SCI. A recent study using brainstem- and spinal cord-derived neuronal stem cell injection into the spinal cord reported a 50 % reduction in AD severity during colorectal distension, as well as a normalization of baseline blood pressure only when using brainstem-derived (but not spinal cord-derived) stem cells [243]. Mechanistically, brainstem-derived neurons led to catecholaminergic and serotonergic neuron axon growth and greater innervation of caudal SPNs, further illustrating the importance of central sympathetic tonic support in the prevention of autonomic cardiovascular impairments after SCI [243].

Another strategy tested to preserve spinal cord pathways after SCI has been the reduction of inflammation. A significant portion of spinal cord damage occurs after the original insult or primary injury due to ischemia, which is considered the secondary injury. The triggering of inflammation leads to the activation of well-established inflammatory processes such as macrophage migration, as well as neutrophil, microglia, cytokine, and matrix metalloprotease influx [245–248]. Together, along with the subsequent free radical generation and lipid peroxidation, neuronal tissue degradation occurs, including destruction of neural and glial cells [249, 250]. The most promising therapy targeting inflammatory processes involves inhibiting leukocyte migration across the blood-brain barrier and, thereby, preventing it from potentially attacking neuronal structures [251–254]. In general this therapy results in roughly a 50 % reduction of AD severity.

A number of studies, using a variety of therapeutic strategies, have specifically targeted the reduction of CGRP+ sprouting in the dorsal horn, which as mentioned is a primary mechanism underlying the development of AD after SCI [39, 45, 48, 251, 255, 256]. The majority of studies have shown that neutralizing the effect of nerve growth factor in the spinal cord after injury leads to improvements (i.e., 35–43 % reduction) in AD [45, 255]. This reduction in AD severity is directly related, albeit through modest coefficients of variation (i.e., r^2 = 0.36–0.64) [39, 48], to reductions in CGRP+ [255], sprouting, and inhibition of TRPV1 somal hypertrophy [35]. These modest coefficients of variation, combined with several studies showing improvements in AD (~50 %) without reductions in CGRP+ sprouting, suggest other major factors are influencing the development of AD after SCI, rather than just afferent sprouting alone [251, 256]. These studies represent preclinical animal models, and if any of these therapies are ever to be widely implemented into clinical practice, stringent human clinical trials are required. Considering the high priority of autonomic issues in those living with SCI, more rapid progress in this area could be achieved by the incorporation of cardiovascular outcome metrics into human trials examining stem cell/anti-inflammatory strategies for motor/sensory issues after SCI, which would provide further insight into the potential benefits of these therapies on autonomic function.

The preservation of descending sympathetic pathways would also provide significant benefit for OH after SCI, and therefore regeneration/anti-inflammation strategies would be suitable for this condition. Due to the difficulty in generating an animal model of OH after SCI, however, there remains limited specific data on therapeutic approaches for OH. In human models, there is a variety of cardiovascular adjustments that may occur after SCI to mitigate or prevent the severity of OH. These include the recovery of spinal sympathetic reflexes, the development of spasticity, increased muscle tone, increased activation of the renin-angiotensin system, maintained cerebral autoregulation and potentially increased tolerance to low cerebral perfusion pressure [5, 65, 166]. Although some of these factors may reduce the severity of OH and/or presyncopal symptoms, OH still is a major clinical problem after SCI, affecting the majority of this population.

14.6.2 Clinical Management of Abnormal Cardiovascular Control Following SCI

Managing episodes of AD and OH is critically important in the clinical setting, due to all of the aforementioned associated clinical outcomes such as heart attack, stroke, cognitive decline, and orthostatic intolerance. A number of interventions have explored pharmacological and non-pharmacological approaches to manage both of these conditions. Clearly, prevention is the first line of defense against episodes of AD and OH after SCI. Non-pharmacological and pharmacological options for management of blood pressure instability after SCI will be presented in this section.

The first component of effective prevention of episodes of AD should include education of patients, caregivers, and family members on proper bladder, bowel, and skin care as triggers originating from these organs (urinary tract infections, constipations, pressure wounds) are among the most common. Second, management of the developed AD event should initially include resolution of the trigger which most commonly will include bladder or bowel evaluation (although this may potentially initially exacerbate AD), but could also include mitigating a variety of noxious or non-noxious stimuli [257]. These immediate interventions should occur while the patient is in a seated position, or with the head elevated, in order to initiate orthostatically mediated declines in blood pressure and reduce the pressor effect of AD. Once an AD event is triggered, and is unresponsive to treatment attempts (blood pressure continued to be elevated above 150 mmHg), it may be required to intervene pharmacologically. Most commonly nifedipine (a short-acting calcium channel blocker), captopril (angiotensin-converting enzyme), or nitropaste (vasodilator) are recommended to mitigate this condition [258]. However, these drugs have been shown to also exacerbate low resting blood pressure [68]. This latter consideration is particularly relevant when considering treatment options for AD in those with SCI as they already suffer from low blood pressure [68, 259]. In an effort to overcome this side effect, the use of prazosin (alpha1 antagonist) has been explored. Recently, prazosin (1 mg oral tablet) effectively reduced AD severity (due to penile vibrostimulation) while exerting no effect on resting blood pressure, suggesting it may be a viable option for treating AD [259]. For detailed guidelines on management of AD, see [68, 257]. It is also possible that botulinum toxin A can reduce the frequency and severity of AD secondary to detrusor muscle overactivity [260, 261]. Typically, 200 units of botulinum toxin A is injected per procedure (diluted in 15 mL saline to 20 U/mL), where it is injected into the detrusor muscle at 20 sites (10U per site), sparing the trigone (see clinical vignette).

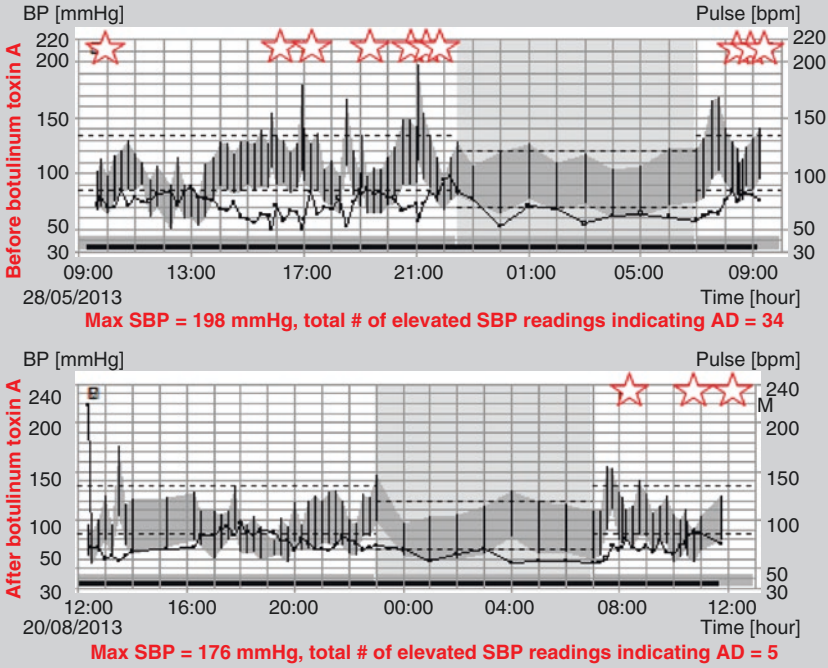
In addition to AD, individuals with SCI can experience episodes of OH on a daily basis, which will require management. The majority of activities of daily living require individuals with SCI to be seated in an upright posture in their wheelchair, which predisposes them to orthostatic instability, as a significant amount of blood accumulates in their abdomen and lower extremities (see above). The initial, most simple, preventative strategies of OH include the following: ensuring appropriate fluid intake; avoiding diuretics, large meals (postprandial hypotension), and heat stress; as well as wearing compression bandages/stockings and potentially engaging in a semi-upright sleeping position (i.e., 10–20° increase) [63, 262–265]. The assumption of a recumbent or semi-recumbent position during daily living can often resolve OH but can significantly influence the patient's quality of life. Pharmacological intervention may be required if these approaches are not effective at reducing OH. Typically these include volume expansion with fludrocortisone [264, 266] and/or increasing vascular tone with alpha1 agonist midodrine hydrochloride [65, 267, 268]. In fact,

maintaining cerebral blood flow using 10 mg of midodrine prevents OH and helps prevent presyncopal symptoms by preserving perfusion of the brainstem where discrete regions responsible for consciousness are located [269]. These approaches are most commonly used in combination, depending on the patient's responsiveness to each intervention, and the severity of autonomic cardiovascular disturbances.

14.7 Summary

Cardiovascular dysfunction in those with SCI is a leading cause of morbidity and mortality in this population and therefore requires careful clinical consideration. Disrupted autonomic pathways result in an unstable cardiovascular system characterized by impairments in blood pressure and blood flow regulation. The majority of those with SCI suffer from daily episodes of blood pressure fluctuation including episodes of AD and OH, resulting in rapid and substantial increases and decreases in blood pressure, respectively. In addition, resting blood pressure is often very low in this population. The clinical community has recently become aware that autonomic issues, such as cardiovascular control, are most frequently ranked by patients with SCI to be of greater priority than regaining motor function. The trajectory of the natural age-related increases in cardiovascular disease progression is increased in those with SCI, resulting in accelerated development of morbid cardiovascular conditions and mortality. Secondary consequences of SCI are only beginning to receive appropriate clinical attention. In the period immediately after high-level SCI, the first major cardiovascular abnormality presents itself in the form of neurogenic shock. After this, other autonomic cardiovascular conditions develop into chronic blood pressure instability. Other contributing factors to cardiovascular disease after SCI include widespread physical inactivity, impaired glycemic control, inflammation, and lipid abnormalities. Together, autonomic dysfunction and these other factors accelerate the decline of end organs, such as the central arteries, heart, and brain blood vessels. The clinical consequences of these conditions extend beyond the obvious mortality risk through heart attack and stroke to also include orthostatic intolerance, cognitive dysfunctions, and impediments to rehabilitation. Although our understanding of blood pressure abnormalities following SCI has certainly been greatly enhanced, we still do not understand the long-term consequences of these conditions and the full extent of their underlying clinical implications. Prevention/mitigation strategies for cardiovascular autonomic function due to SCI are still in their infancy having been explored mainly in animal models, while the majority of cardiovascular disease management guidelines are based off of recommendations developed for non-SCI populations with tenuous relevance.

Clinical Vignette (Patient): 60-Year-Old Male, C6/7, AIS B (34 Years Since Injury)
This SCI patient suffers from severe and frequent autonomic dysreflexia which was significantly impacting activities of daily living and leading to headache, confusion, and frequent sweating. The injection of botulinum toxin A into the detrusor muscle significantly reduced the severity and frequency of AD during urodynamics. Specifically, systolic blood pressure rose more than 70 mmHg during urodynamics in this patient before treatment, which was reduced to only 37 mmHg after botulinum toxin A injection. Furthermore, symptoms of AD reduced substantially, and as shown below the frequency and severity of AD, as assessed by 24 h ambulatory blood pressure monitoring, was drastically reduced. These data suggest that botulinum toxin A may be an effective strategy for treating AD due to detrusor overactivity in those with SCI. Red stars denote identified AD episodes.



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