Cardiovascular Control After Spinal Cord Injury

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Abstract: Spinal cord injury (SCI) leads to profound haemodynamic changes. Constant outflows from the central autonomic pattern generators modulate the activity of the spinal sympathetic neurons. Sudden loss of communication between these centers and the sympathetic neurons in the intermediolateral thoracic and lumbar spinal cord leads to spinal shock. After high SCI, experimental data demonstrated a brief hypertensive peak followed by bradycardia with escape arrhythmias and marked hypotension. Total peripheral resistance and cardiac output decrease, while central venous pressure remains unchanged. The initial hypertensive peak is thought to result from direct sympathetic stimulation during SCI and its presence is anaesthetic agent dependent. Hypotension improves within days in most animal species because of reasons not totally understood, which may include synaptic reorganization or hyper responsiveness of α receptors. No convincing data has demonstrated that the deafferented spinal cord can generate significant basal sympathetic activity. However, with the spinal shock resolution, the deafferented spinal cord (in lesions above T6) will generate life-threatening hypertensive bouts with compensatory bradycardia, known as autonomic hyperreflexia (AH) after stimuli such as pain or bladder/colonic distension. AH results from the lack of supraspinal control of the sympathetic neurons and altered neurotransmission (e.g. glutamatergic) within the spinal cord. Despite significant progress in recent years, further research is necessary to fully understand the spectrum of haemodynamic changes after SCI.

Keywords: Autonomic hyperreflexia; autonomic nervous system; blood pressure; heart rate; spinal cord injury

INTRODUCTION

Spinal cord disease results from diverse pathological processes, among the most common trauma. Irrespective of its pathogenesis, it leads to significant impairment of motor, sensory, or autonomic function, with variable incidence according to the spinal cord injury (SCI) etiology [1]. In the USA, traumatic SCI accounts for approximately 40 cases / million / year, or about 11,000 new cases / year. Currently, 183,000-230,000 SCI patients (721-906 people / million) are alive in the USA. Worldwide, SCI incidence is estimated at 15-40 cases / million [2-4].

In 1927, Harvey Cushing described an 80% mortality for World War I soldiers with SCI in the first few weeks because of infections from bedsores and bladder catheterization, with survival restricted to partial lesions [2]. Today, in well-organized spinal cord centers, 94% of patients survive the initial hospitalization [2]. Recent statistics in the USA show the cost of the care of patients with C1-4 tetraplegia at approximately $572,178 in the first year and approximately $102,491 for each subsequent year [5]. Estimated lifetime cost for high tetraplegia is $2,185,667 for 25-year-old individuals and $1,286,714 for 50-year-old individuals [5]. This amount does not include indirect costs such as loss of productivity, which vary with the educational background. Overall, lifetime costs range from $500,000 to $2 million, depending on the extent of injury and the location [5].

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Life expectancy is greatly decreased after SCI, although advances of medical management have prolonged survival. Therefore, since there are no current therapies to reverse the neuronal and axonal damage after trauma, physicians and health care professionals are left with the management of a constellation of complications [6]. This review will focus on the pathophysiology and management of the cardiovascular complications of SCI, translating results from recent studies in animal models to practical clinical applications. A summary of the cardiovascular changes following SCI is depicted in (Fig. **1**).

ACUTE HAEMODYNAMIC CHANGES FOLLOWING SCI

The term "autonomic nervous system" (ANS) was first coined by Langley to describe the portion of the nervous system whose cell bodies were located outside the CNS and involved in the regulation of visceral functions. This idea of "complete" autonomy can be understood, since only recently the mechanisms by which the CNS exerts control over the peripheral ANS started to be better understood [7].

The central ANS consists of a complicated network of structures, which are involved in the generation of patterns of neuronal activity (central autonomic pattern generators). Recent studies of functional neuroanatomy utilizing viral tracers have identified populations of autonomic pattern generation neurons in the ventrolateral medulla, rostral medullary raphe, periaqueductal gray matter and hypothalamus [7].

Acute and complete cervical or high thoracic SCI leads to a sudden disruption of the supraspinal control over the autonomic centers located at the thoracic/lumbar

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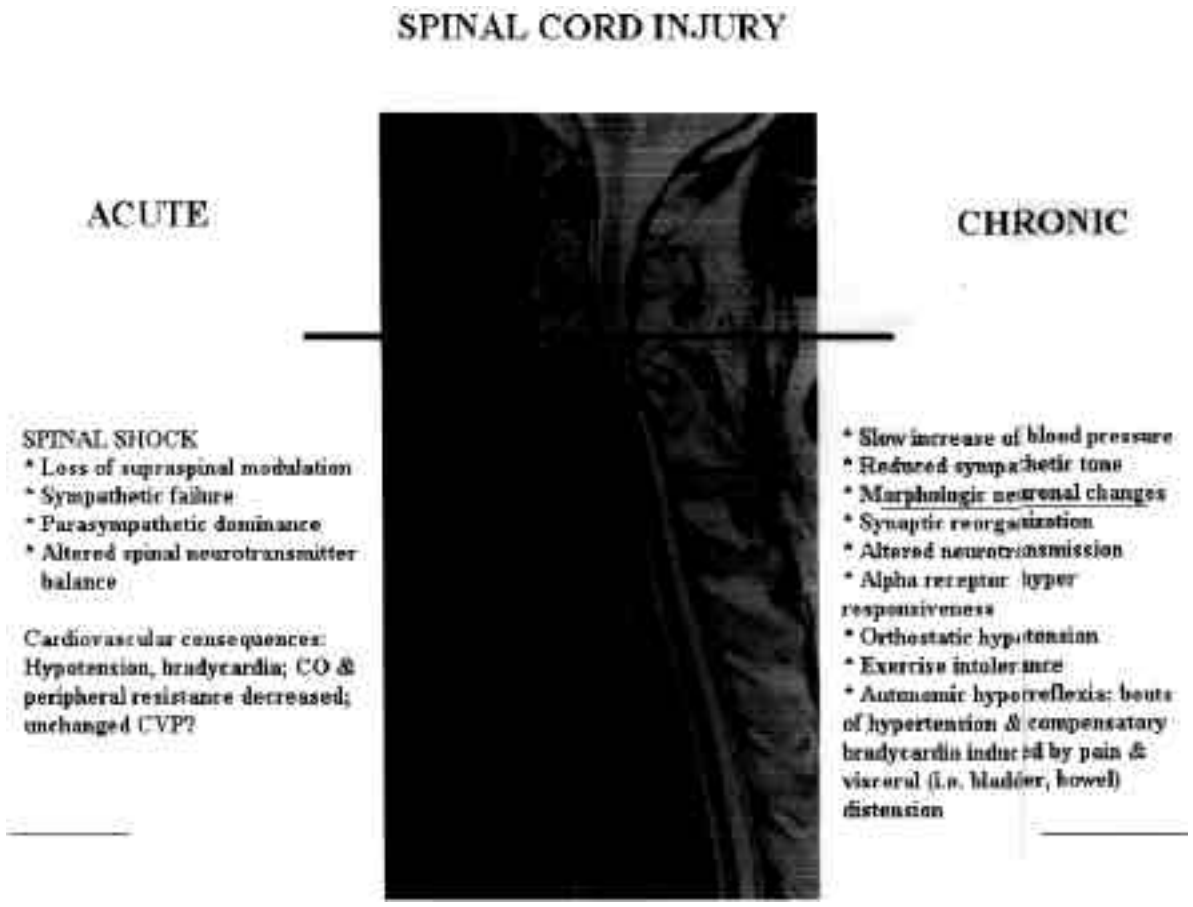

Fig. (1). Schematic summary of the cardiovascular complications in the acute and chronic phase of spinal cord injury.
CO: Cardiac Output
CVP: Central venous pressure

(sympathetic) and sacral (parasympathetic) spinal cord (Fig. **1**). In the acute phase, the classic syndrome of complete spinal cord transection at the high cervical level consists of respiratory insufficiency; quadriplegia with upper and lower extremity arreflexia; anaesthesia below the affected level; neurogenic shock (i.e. hypothermia and hypotension without compensatory tachycardia); loss of rectal and bladder sphincter tone and urinary and bowel retention. This constellation of symptoms is known as spinal shock. Despite more than a century since its first description, spinal shock remains not fully understood [8]. The lack of supraspinal modulation leads to transient shutdown of neuronal activity during the spinal shock phase, which may be ultimately secondary to altered balance of excitatory and inhibitory inputs [9]. Reduced sympathetic activity results in hypotension and bradycardia. There is pooling of venous blood in the lower extremities and abdominal viscera and therefore further administration of fluids does not correct hypotension and can lead to pulmonary edema [10-13].

Since the middle of the XX century, several experiments were performed to quantify the haemodynamic impact of SCI. The variety of techniques, protocols, anaesthetic agents and animal species occasionally lead to discrepant results, which still makes this subject a matter of controversy. Early experimental data in cats anaesthetized with chloralose demonstrated that pressure over the high spinal cord generates a great rise of blood pressure [14]. Eidelberg *et al.* 1973 confirmed in cats anaesthetized with methoxyflurane and chloralose that pressure over the high spinal cord generates a great rise of blood pressure, which could be abolished by the administration of α-blockers [15]. In a series of 4 papers published between 1978 and 1980, Tibbs *et al.* reported that cervical spinal cord transection initially (first 6-8 min) induced hypertension, increased systemic vascular resistance, increased left ventricular ejection fraction and bradycardia with escape arrthymias in dogs anaesthetized with pentobarbital [16-19]. Subsequently, prolonged hypotension with decreased systemic vascular resistance and decreased left ventricular ejection fraction replaced the initial phase. They also reported an initial increase peak of norepinephrine following transection, maintained cerebral blood flow and decreased coronary artery flow due to systemic hypotension. Guha *et al.* observed in rats anaesthetized with urethane and chloralose and later submitted to SCI by the clip compression injury model, that T1 SCI is accompanied by a brief hypertensive peak (lasting for 2-3 min) followed by prolonged

hypotension [20]. They observed significant bradycardia only 45 min post-injury. In addition, they also reported a 50% reduction of the cardiac output (which was speculated to be at least partially secondary to myocardic injury), reduced total peripheral resistance and unchanged central venous pressure. More recently, Bravo *et al.* observed in rats anaesthetized with ketamine+xylazine that T5-6 SCI leads to a marked immediate decrease in MAP and HR, followed by an abrupt increase of BP between 3 and 9 min post-injury, which resolved by 20 min [21]. They also observed that the fall of MAP and HR, as well as the overshoot increase in the MAP were abolished by atropine, NO synthase blockade with L-NAME and attenuated by cervical bilateral vagotomy. The latter findings suggest that in addition to a sudden drop of sympathetic activity after SCI, the acute haemodynamic imbalance after SCI maybe at least partially generated by parasympathetic nervous system hyperactivity. In addition, more recently [22], the same group observed that sympathetic blockade significantly improves cardiovascular alterations immediately after spinal cord injury in rats, which further reinforces that these changes were secondary to increased parasympathetic activity and a sympathetic withdrawal. Despite of modest HR changes after SCI documented in the rat model [20, 21], Greenhoot *et al.* [23, 24] observed in dogs anaesthetized with pentobarbital, that SCI is followed by an initial increase in HR and BP due to increased sympathetic activity, followed by a variety of cardiac arrhthymias due to parasympathetic activity. Possible explanations for this discrepancy are the fact that Greenhoot *et al.* monitored HR by ECG, while the other authors did not. Other possible explanations include different animal species and anaesthetic agents employed. Greenhoot *et al.* also found fuchsinophillic degeneration of myocardial cells, the same type of lesion produced by increased intracranial pressure, which suggests that the hyperadrenergic state in the initial SCI may lead to cardiac ischaemia [23, 24]. Overall, the different models, animal species and anaesthetic agent employed can explain the discrepancies described above. The latter explanation attracted our attention when we studied the effect of cervical spinal cord transection in rats anaesthetized with ether [25 and unpublished results]. Immediate hypotension, without a hypertensive peak was observed when SCI was performed in rats anaesthetized with ether (Fig. **2A**), in contrast to chloral hydrate anaesthesia (Fig. **2B**), where the hypertensive peak could be easily observed preceding the hypotension (Fig. **2B**). In fact, Maignan *et al.* measuring plasma noradrenaline (NA) concentration, spillover rate (SOR) and metabolic clearance rate (MC) in the rat, observed that different types of anaesthesia led to different changes of sympathetic activity [26]. NA-SOR was significantly reduced during anaesthesia with either sodium pentobarbital or chloralose, plasma NA concentration was not changed because NA-MC was also reduced. Ketamine did not reduce NA-SOR and ether increases both NA-SOR and plasma NA concentration, while NA-MC remained unchanged.

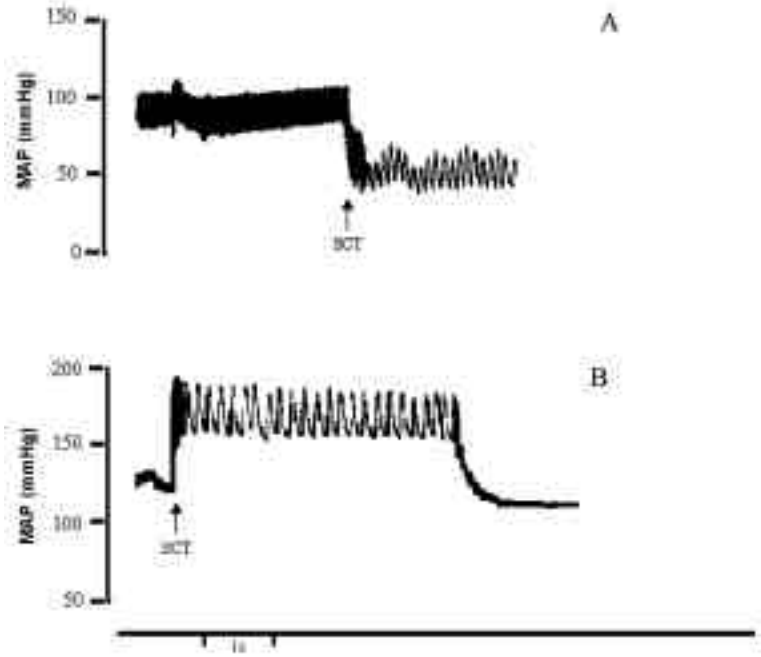

Fig. (2). Effect of acute spinal cord transection (SCT) in anaesthetized rats.

Part A demonstrates the acute drop in mean arterial pressure (in mmHg) in animals anaesthetized with ether, which is not preceded by a hypertensive peak.

Part B demonstrates that a hypertensive peak precedes the acute drop in mean arterial pressure (in mmHg) in animals anaesthetized with chloralose.

Note that the speed of the tracing was accelerated immediately after spinal cord transection (from 1 mm/s to 1 cm/s) to allow measurements of the heart rate changes and instability of mean arterial pressure following spinal cord transection (SCT) in rats.

Overall, taken together with clinical observations in humans, these findings show that our knowledge about the acute complications of SCI is still incomplete. Notwithstanding, an important principle to be followed in the acute management of hypotension in humans after SCI and multiple injuries is that whenever hypovolaemia due to blood loss caused by concomitant trauma is ruled out, one should avoid fluid resuscitation to prevent the development of acute pulmonary edema and therefore pressor agents should be the first choice [10-13].

SUBACUTE HAEMODYNAMIC CHANGES FOLLOWING SCI

Immediately after SCI plasma adrenaline, noradrenaline and their urinary metabolites are in the lower normal range [27]. The neuronal activity in the spinal cord neurons, including the neurons located at the intermediolateral aspect of the spinal cord, slowly returns after SCI. This process marks the end of the spinal shock phase and its mechanisms are not totally understood. Function returns at different times within the different levels and neuronal groups. The duration of the spinal shock phase depends on the phylogenetic complexity of the animal species: in rats neuronal activity has been documented within hours while in humans the spinal shock phase lasts for weeks, being more prolonged when the patient develops bed sores and infections [8, 9, 28]. Krassioukov *et al.* and Maiorov et al observed that by day 5 after T4-5 SCT, MAP and HR were similar to baseline levels [29, 30]. We have also observed the return of MAP and HR to baseline within 7 days after C7-T1 and T4-T5 SCT [31], which also coincided with the recovery of colonic function [32].

In mammals with intact neuraxes, most sympathetic activity is generated by the brainstem. In spinally intact rats, spinal interneurons do not play a major role in regulating sympathetic activity in intact rats [33]. Over the last 20 years, intense debate about whether deafferented spinal cord can generate significant basal sympathetic activity in awake rats or not has continued. In anaesthetized, acutely spinally transected rats, sympathetic outflow to abdominal organs (but not to skeletal muscle) was reported to be well maintained [34, 35], suggesting that SCI exerted a differential effect on the sympathetic activity of different organs [36, 37]. Osborn *et al.* also reported elevated renal activity after spinal transection in chloralose-anaesthetized rats [38]. The major criticism for these studies was that anaesthesia itself could have contributed to the generation of sympathetic activity. Therefore, several studies were performed to address this hypothesis in awake rats. Direct measurements of sympathetic activity were not possible or very difficulty to obtain in awake rats. By utilizing pharmacological blockers, Trostel & Osborn reported (by indirect evidence) that renal sympathetic activity was present in awake rats [39]. They observed that adrenergic blockade in rats 24h after cervical SCT still elicited changes in urinary sodium and potassium excretions. However, few years later the same group reported that natriuresis observed with phentolamine administration was due to imidazoline binding and therefore that there was no evidence for functionally significant spinally generated sympathetic nerve activity in awake cervical SCI rats [40]. Hong *et al.* measured renal sympathetic activity in intact and spinal rats [41]. They observed that despite the tonic modulation of sympathetic neurons by spinal neurons with excitatory aminoacid and cholinergic receptor activity, the sympathetic activity generated did not play a major role in maintaining arterial pressure in the conscious spinal rat. Therefore, despite the return of the neuronal activity, there is no convincing data to demonstrate that the deafferented spinal cord can generate significant basal sympathetic activity in awake rats. In fact, human studies utilizing microneurographic recordings have also reported decreased activity in the cutaneous and muscle postganglionic axons situated below the level of injury, at baseline or during bladder stimulation [42, 43]. These studies showed no evidence of arterial baroreflex modulation of muscle sympathetic activity in patients with traumatic lesions between C5-T8. A given stimulus induced sympathetic reflex discharges synchronously in muscle and skin nerve branches. Increases of intravesical pressure induced only weak increases of muscle sympathetic activity associated with marked hypertensive reactions [42, 43]. Resting catecholamines are decreased in patients with cervical SCI compared to controls and individuals with paraplegia [44].

CHRONIC HAEMODYNAMIC CHANGES FOLLOWING SCI

In the motor system, the resolution of the spinal shock is marked by the return of muscle tone and gradual overactivity leading to spasticity. Within the ANS, basal sympathetic activity will not return to normal baseline levels with levels above T6, but instead a propensity to autonomic hyperactivity, leading to the so-called autonomic hyperreflexia (AH) supervenes. In addition, several other important cardiovascular complications will persist in the chronic phase and will be discussed below (Fig. **2**).

A- Pathophysiology of the Cardiovascular Changes in the Chronic Phase of SCI

In patients with quadriplegia and bouts of hyperreflexia in the chronic phase of SCI, the amount of noradrenaline infusion in the dorsal foot veins necessary to cause vasoconstriction to half of the baseline level was 6-7 times less than in paraplegic patients [45]. Section of preganglionic nerves in animals also leads to hypersensitive responses to noradrenaline [46]. In addition, Mathias *et al.* reported enhanced pressor responses to noradrenaline in patients with quadriplegia and cervical lesions as compared to paraplegic patients [47, 48].

Overall, these findings suggested that hyper-responsiveness of α receptors occurs after high SCI. This hyper-responsiveness could result from 1. upregulation (due to reduced output), 2. increased number of receptors or 3. because of decreased presynaptic re-uptake of norepinephrine [44]. Mathias & Frankel [47] and Krum *et al.* [49] reported that this enhanced pressor response is not due to impaired noradrenaline clearance. Rodriguez *et al.* observed in individuals with cervical SCI a "trend" for lower α receptor density (as measured by competitive radioligand-binding assays in whole skin homogenates from skin biopsies) several years after injury as compared to early after

injury [50]. The latter findings suggested the presence of an increased number of receptors in the early phase of AH, but lack of statistical significance, small samples and assay errors preclude further interpretation. In addition, Osborn *et al*. later challenged the whole concept of α receptor hyper-responsiveness when they showed in rats with complete cervical SCI that there are no changes in pressor sensitivity to exogenous norepinephrine [28, 51]. Therefore, significant controversy about the exact nature of the mechanisms involved in α receptor regulation after SCI persists.

A more recent focus of research in this field has been the study of morphological, neurotransmitter and synaptic changes in the sympathetic neurons, in an attempt to explain the cardiovascular changes after SCI. Studies in animal models have shown initial signs of atrophy (dendrite retraction) in the acute stage of SCI, with subsequent regrowth of dendrites within 2 weeks of injury [9, 52, 53]. In addition, initial synaptic density decreased on choline acetyltransferase immunoreactive somata by 34% but increased on dendrites by 66% and almost half of the inputs to sympathetic preganglionic neurons lacked amino acids. By 14 days, the density of synaptic inputs to dendrites and somata decreased by 50% and 70%, respectively, in association with dendrite regrowth. Glutamatergic inputs also decreased by 40% and GABAergic proportion increased up to 60-68% [9]. The authors concluded that spinal sympathetic neurons participate in vasomotor control after SCI despite profound denervation and speculated that an altered balance of excitatory and inhibitory inputs explains injury-induced hypotension. In humans, a study in an individual who died within 2 weeks after injury showed a decrease in soma below the site of SCI, although another observation in an individual 23 years after SCI failed to demonstrate differences in sympathetic neurons [54].

A similar explanation (synaptic reorganization) has been invoked to explain the pathophysiology of hyperreflexia. After SCI, dorsal root afferents (and possibly interneurons) sprout and spinal neurons have the initial lost synaptic connections replaced by newer ones [55, 56]. Krenz & Weaver observed that the exaggerated reflexes present in rats 2 weeks after SCI are mediated by attenuation of N-methyl-D-aspartate (NMDA) receptor function [56]. Additional evidence about the role of glutamatergic neurotransmission on autonomic hyperreflexia was reported by Maiorov *et al.* [57] and will be discussed in the next section.

B- Autonomic Hyperreflexia (AH)

AH is referred as massive paroxysmal reflex sympathetic discharge in response to noxious stimuli (cutaneous or visceral, such as bladder and colonic distension), which occurs in patients with spinal cord injuries (complete and incomplete) above the splanchnic sympathetic outflow. It was first reported by Hilton [58] and Bowlby [59]. The classical features of the effect of bladder distension in soldiers were reported by Head & Riddoch, but initially sweating changes were the main focus of the attention [60]. Subsequently Guttman fortuitously realized that the blood pressure was raised [61] and in 1947, a more complete description of its clinical features and pathophysiology were reported [61, 62]. Although it has been reported after lesions above the foramen magnum and after spinal forms of multiple sclerosis [63], it is significantly more common after traumatic SCI. As a general rule, the higher the level and the more complete the SCI is, the greater the autonomic dysreflexia, although it has been reported after lesions as low as T8-10 [64]. Roche *et al.* also reported neurogenic hypertension in adolescents with lumbosacral paraplegia, but this finding remains to be confirmed [65].

Clinically AH consists of a constellation of complaints, which can include headache, cephalgia, "cutis anserina" (goose flesh), flushing, sweating, pilomotor activity, tachycardia or bradycardia, chest pain, paresthesias, shivering, nasal obstruction, anxiety, malaise, nausea, visual changes and paroxysmal hypertension. If left untreated, it can lead to severe neurological complications, such as retinal [66], subarachnoid and intracranial haemorrhage [67, 68], ischemic strokes [69], seizures and episodes of transient aphasia [70, 71], recurrent cardiac arrest [72] and ultimately death [73]. For more details about the clinical presentations, several reviews are suggested [73-76].

Objectively, massive increases in systolic and diastolic blood pressure are the most reliable clinical sign, although a continuum from mild to massive BP increase can occur. As part of the response to counteract the BP increase, baroreceptor-mediated bradycardia and vasodilation above the level of the injury occur. Tachycardia is also common, especially if part of the cardiac innervation is spared by the lesion [76]. A minimum 20% increase of BP combined with visualization of signs of vasoconstriction below the lesion level were suggested criteria by some authors [74].

The magnitude of the BP change indicates the involvement of a large vascular bed. Vasoconstriction of the skin and skeletal muscle below the level of the injury were proposed mechanisms [62] but an inability to dilate the splanchnic vascular bed by central command or even active splanchnic vasoconstriction are more plausible explanations [74]. Most researchers agree on the active role of the sympathetic nervous system [77]. Microneurographic recordings of the sympathetic nerve fibers below the lesion failed to demonstrate significant changes during hyperreflexia, despite changes in the skin [43]. This again points to the participation of the splanchnic vascular bed. Different mechanisms leading to AH have been postulated over the years and include upregulation of vascular catecholamine receptors, increased neural release of catecholamines, loss of baroreceptor reflex and loss of tonic inhibitory input to the spinal neurons [78]. Since loss of baroreceptor reflex and loss of tonic inhibitory input to the spinal neurons are present immediate after injury and AH develops in humans after few weeks or months and in rats after several hours, the idea of neuronal changes leading to AH was an attractive explanation and therefore explored in the experimental models of AH [79]. Since the 80s, several animal models of AH have been developed and provided important clues about the mechanisms involved in AH. Osborn *et al.* described a rat model of AH after bladder distension [28]. Krassioukov *et al.* described a rat model of AH induced by colonic distension [29] and Sansone *et al.* reported a female rat model where AH was induced by vaginocervical stimulation, therefore simulating AH in

women during parturition or sexual intercourse [80]. More recently Jacob *et al.* 2001 reported a mice model where AH was produced by colonic distension [81].

Vascular hyper-responsiveness was also well documented in a recent study in rats. Upper body exercise made the response of spinal rats to phenylephrine (α agonist) similar to intact rats and decreased the intensity of AH by 50% [82]. Renal sympathetic activity is also increased during episodes of AH in rats and further points to the involvement of the splanchnic circulation [51]. Neuronal reorganization after SCI leading to AH could involve afferent, interneurons or preganglionic sympathetic neurons [83]. The loss of bulbospinal input decreases synaptic input to sympathetic preganglionic neurons by 50-70% and is not replaced by synapses with spinal interneurons [9]. These synapses do not increase, but increased excitation of sympathetic preganglionic neurons coming from interneurons, through temporal summation has been advocated [84]. Therefore, excessive response of interneurons to afferent input could indicate that input is greater after SCI [79].

These animal models of hyperreflexia have significantly increased our knowledge about the mechanisms responsible for AH. Based on these models, synaptic reorganization has been invoked to explain the pathophysiology of both spinal shock and hyperreflexia. Maiorov *et al.* also observed that the intrathecal administration of alpha-amino-3-hydroxy-5-methyl-4- isoxazole propionate/kainate (AMPA) and N-methyl-D-aspartate (NMDA) antagonists attenuated the AH induced by colonic distension in rats [57]. These findings were among the first experimental evidence pointing to synaptic reorganization as a possible mechanism of AH. More recent works have reinforced this hypothesis. After SCI, dorsal root afferents (and possibly interneurons) sprout and spinal neurons have the initial lost synaptic connections replaced by newer ones [54, 57]. Krenz *et al.* observed that neutralization of nerve growth factor in the spinal cord minimized AH induced by colonic distension in rats [84]. Increased nerve growth factor (NGF) in the injured cord leading to stimulation of small-diameter primary afferent fiber sprouting and to magnification of spinal sympathetic reflexes were the proposed mechanisms. Krenz & Weaver also observed that the exaggerated reflexes present in rats 2 weeks after SCI are mediated by attenuation of N-methyl-D-aspartate (NMDA) receptor function [66]. A more recent review by Weaver *et al.* provides a detailed discussion about the mechanisms of synaptic reorganization in experimental models of AH [79].

Initial management of AH in humans is focused on the removal of the offending stimuli. The patient should be moved from the supine to the sitting position and clothing and constrictive devices should be loosened. Bowel impaction and bladder distension should be checked and indwelling catheters should be checked for obstruction. The threshold for treatment is not established since no prospective studies have established which level of elevated BP is dangerous. The Consortium for Spinal cord medicine recommends treatment of systolic BP greater than 150 mmHg as hypertensive urgency since SCI patients are commonly hypotensive or have a BP at the lower normal level [85]. If AH persists despite these measures, an anti-hypertensive should be administered. Traditionally AH has been treated with sublingual nifedipine. Because of the risk of an abrupt BP drop leading to complications such as angina, its use has been discouraged. Anecdotal reports have described the efficacy of nitroglycerin, diazoxide, phenoxybenzamine, prazosin, hydralazine and clonidine [86]. A recent 1-year, prospective, open-label study with captopril documented its efficacy and safety [86]. In this trial, 25 mg of captopril was administered sublingually. If BP remained elevated after 30 min, rescue therapy with 5 mg of nifedipine was used. Despite the positive results, randomized trials are warranted to further establish the best approach to the pharmacological management of AH.

C- Other Cardiovascular Complications in the Chronic Phase

Low BP occurs both during the acute and chronic phase. Frankel *et al.* observed an inverse relationship between the level of SCI and resting BP in 461 patients with traumatic SCI [87]. In addition, SCI patients also experience a wide range of cardiovascular complications. Orthostatic hypotension (OH) is common in patients with quadriplegia and paraplegia. It results from pooling of blood in the viscera and dependent extremities, due to the loss of mobility of the lower extremities and decreased sympathetic activity, leading to blood sequestration in the lower extremities and reduced heart filling [88-90]. Symptoms are worse in the acute phase, when autonomic instability may lead to massive drops of BP and bradycardia with postural changes [89]. Patients complain of lightheadedness, faintness and nausea. The true incidence of OH in SCI patients is unknown but Illman *et al.* observed BP changes indicative of OH occurred during 73.6% of mobilization treatments during physical therapy [91]. Signs and symptoms of OH were noted on 58.9% of mobilization treatments. However, these symptoms limited physical therapy in only 43.2% of occasions. Cariga *et al.* found OH in 57.1% of patients with varied SCI types [92]. Neck pain was reported by 53.6% of subjects and by 75% of subjects with OH and 25% of subjects without OH. Pain also exhibited positive correlation with upright posture and exercise, and relief when lying flat, indicating a positive association between neck pain and OH, similar to that reported in primary autonomic failure with OH. Unlike primary autonomic failure, the ingestion of food does not seem to consistently induce hypotension or exacerbate OH [93]. Anedoctal case reports have proposed successful management with midodrine [94]. Functional neuromuscular stimulation may also minimize cardiovascular changes during postural orthostatic stress in individuals with acute spinal cord injury [95].

Despite of the decrease in sympathetic activity, studies of heart rate variability in humans have demonstrated that the sympathovagal homeostasis persists in the chronic phase because of a parallel decrease in parasympathetic activity [96]. In rats submitted to T4-5 SCI, heart rate variability studies have shown an initial disruption and subsequent adaptation of the BP and HR relationship [97]. The occurrence of non-baroreflex sequences (opposite, linearly related changes in systolic BP and R-R interval) is also significantly lower in tetraplegic than in paraplegic patients

[98]. These findings are in agreement with Krum *et al*. [99] and point to decrease diurnal variation of BP in individuals with SCI. The overall reduction in sympathetic efferent activity also leads to exercise intolerance and general deconditioning, which are commonly reported by SCI patients [88].

CONCLUSIONS

SCI leads to major cardiovascular complications, which are more prominent after traumatic SCI and different according to the evolution of the SCI. Despite significant progress in recent years, further research is necessary to fully understand the spectrum of haemodynamic changes after SCI and develop more efficient therapies.

ABBREVIATIONS

AH = Autonomic hyperreflexia

ANS = Autonomic nervous system

BP = Blood pressure

HR = Heart rate

MAP = Mean arterial pressure

MC = Metabolic clearance rate

NA = Noradrenaline

OH = Orthostatic hypotension

SCI = Spinal cord injury

SCT = Spinal cord transection

SOR = Spillover rate

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