Medical University of Graz

Autonomic Functions and Cardiovascular Responses in Individuals with Spinal Cord Injury

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for the Academic Degree of
Doktorin der gesamten Heilkunde
(Dr.^{in} med.univ)

at the
Institute of Physiology
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Diploma Thesis
Graz, February 5, 2014

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Affidavit

I, hereby, declare that the following diploma thesis has been written only by the undersigned and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

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Abstract

Spinal cord injury, depending on its location, is known to affect cardiovascular responses as well as autonomic function. Several studies have reported these effects in humans. Additionally, the effects of exercise in spinal cord injury have been reported. The aim of this diploma thesis is to provide an overview of physiological basis of spinal cord injury and the associated effects at rest and during exercise depending on the level of injury (cervical, high-thoracic, low-thoracic and lumbar). Various cardiovascular complications are expected to occur depending on the time period following spinal cord injury. Following aspects are dealt with in some detail: neurogenic shock, orthostatic hypotension, cardiac dysrhythmias and autonomic dysreflexia. Beyond that, the effects of anti-G suit application on cardiovascular responses in spinal cord injured individuals during exercise are discussed. A literature review providing current state of the art knowledge with regards to the effect of spinal cord injury, at varying levels, on the autonomic function and cardiovascular responses as well as how different types of exercise affect these responses was carried out.

Keywords: *autonomic nervous system, cardiovascular responses, spinal cord injury, level of injury, paraplegia, tetraplegia, neurogenic shock, orthostatic hypotension, cardiac dysrythmias, autonomic dysreflexia, exercise, performance, postexercise hypotension, boosting, anti-G suit*

Zusammenfassung

Bekanntermaßen beeinflussen Rückenmarksverletzungen, je nach Läsionshöhe, kardiovaskuläre Reaktionen sowie autonome Funktionen. Mehrere Studien haben von diesen Auswirkungen beim Menschen berichtet. Zusätzlich wurde der Einfluss von Bewegung nach Rückenmarksverletzungen berichtet. Ziel dieser Arbeit ist es, einen Überblick über die physiologischen Grundlagen der Rückenmarksverletzung und den damit verbundenen Auswirkungen in Ruhe und bei Bewegung je nach Läsionshöhe (zervikal, hoch-thorakal, tief-thorakal und lumbal) zu liefern. Verschiedene kardiovaskuläre Komplikationen, abhängig von der Zeitdauer nach einer Rückenmarksverletzung, sind zu erwarten. In dieser Diplomarbeit wird auf folgende Aspekte näher eingegangen: neurogener Schock, orthostatische Hypotension, Herzrhythmusstörungen und autonome Dysreflexie. Darüber hinaus werden die Anwendung und Auswirkungen eines Anti-G- Anzuges auf kardiovaskuläre Funktion in rückenmarksverletzten Personen während Bewegung diskutiert. Es wurde eine Recherche über gegenwärtig vorhandene Literatur durchgeführt, welche die Effekte von Rückenmarksverletzungen, abhängig von der Läsionshöhe, auf die autonome Funktion und kardiovaskuläre Reaktion berücksichtigt. Dabei wurde beachtet, wie verschiedene Arten von Bewegung diese Reaktionen beeinflussen.

Schlüsselwörter: *autonomes Nervesnsystem, kardiovaskuläre Reaktionen, Rückenmarksverletzung, Läsionshöhe, Paraplegie, Tetraplegie, neurogener Schock, orthostatische Hypotension, Herzrhythmusstörungen, autonome Dysreflexie, Bewegung, Leistungsfähigkeit, Hypotension nach Bewegung, boosting, anti-G Anzug*

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I Background

1.1 ”Normal” regulation of the cardiovascular system

A stable and adaptable cardiovascular system is essential for our overall health and physical fitness. The cardiovascular system ensures adequate organ perfusion for the exchange of gases (oxygen, carbon dioxide), nutrients, metabolic products, electrolytes, hormones as well as heat between the cells and the environment [Klabunde, 2011, pp.1-2]. This is done appropriate to their involvement in the various activities that constitute the individuals daily life (e.g., sleeping, ingestion and digestion of food or high-performance sport). Whether at rest or during exercise, the cardiovascular system is subject to permanent specific reflex regulations. These are mediated by activity of the autonomic nervous system, both parasympathetic and sympathetic [Mai and Paxinos, 2011, p.1060]. The mechanisms that allow the stabilization of complex state variables in the cardiovascular system are based on the assumption of a sufficient filling and expansion of the vessels. We have to keep in mind that an adequate blood volume is a condition for efficient functioning of the circulatory reflexes. Before I will discuss the effects of the nervous system in relation to the cardiovascular system, I want to present a general view of some basic cardiovascular state variables and the autonomic nervous system.

1.1.1 Basic state variables of the cardiovascular system

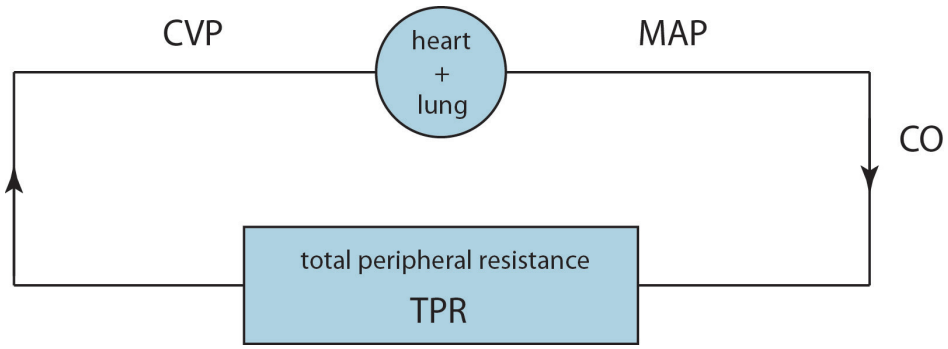

Figure 1: Simplified model of the cardiovascular system

The model (Fig.1) represents the physiological relationships of the cardiovascular system in a simplified form. It consists of a pump (the pulmonary circulation is integrated) and - as image of the circulatory system - the resistance. Driven by the pump, the blood flows from the high-pressure arteries through a point of resistance into the low-pressure venous reservoir (*pressure gradient* Δ p, equation 1) [Guyton and Hall, 2010, p.159].

$$\Delta p = MAP - CVP \tag{1}$$

The *cardiac output* (CO) is a measure of the volume of blood that the heart can pump out in a given amount of time [Guyton and Hall, 2010, p.229]. If the heart pumps more blood per beat, called *stroke volume* (SV), cardiac output will increase. It will also grow up, if the heart beats faster, meaning an increase of the *heart rate* (HR). Cardiac output is calculated by stroke volume times heart rate, as shown in equation 2 [Guyton and Hall, 2010, p.159]:

$$CO = SV \times HR \tag{2}$$

The *mean arterial pressure* (MAP) represents the balance between the inflow volume from cardiac output (CO) and the outflow volume past the *total peripheral resistance* (TPR). Arterioles account for most of total peripheral resistance [West et al., 2013]. Because central venous presseure (CVP) is usually at or near 0 mmHg, the interrelationship of pressure, flow and resistance is often simplified, as shown in equation 3 [Klabunde, 2011, pp.98].

$$MAP = (CO \times TPR) + CVP \quad \approx \quad CO \times TPR \tag{3}$$

As shown in equation 4, change in *central venous pressure* (Δ CVP) is equal to change in *venous blood volume* (Δ V) divided by the *compliance* (C_v) of the corresponding veins [Klabunde, 2011, pp.107].

$$\Delta CVP = \frac{\Delta V}{C_v} \quad \rightarrow \quad C_v = \frac{\Delta V}{\Delta CVP} \tag{4}$$

That means that the central venous pressure (CVP) increases as a result of increased total blood volume or by increased venous return, like during exercise (muscle contraction) and during head-down tilt [Klabunde, 2011, pp.110]. The compliance varies according to the filling level of the veins. As shown in equation 4, the venous compliance determines how strong the pressure increases per additional increase of volume. Basically, veins have a much higher compliance than arteries. Therefore, most of the entire blood volume is pooled in the low pressure system [Guyton and Hall, 2010, pp.167-168].

1.1.2 Autonomic nervous system: overview

Figure 2: Simplified diagram of the nervous system

A simplified diagram illustrates the three main components of the nervous system (Fig.2). *Sensory input* modulate via the *central nervous system* (CNS) the activity of the *motor output* [Guyton and Hall, 2010, p.5].

In this section I want to focus on the efferent pathways of the *autonomic nervous system* (ANS). The integrative role of the central nervous system as well as the sensory input are discussed later.

The autonomic nervous system is an important part of the nervous system. It is responsible for the adaption of the organism to the surrounding information fields to maintain the homeostasis of the body [Furlan and Fehlings, 2008]. The processes of the autonomic nervous system occur unconsciously and are often reflexive, meaning that they are extremely rapid. The increase of the heart rate to twice normal within seconds is only one example among many [Guyton and Hall, 2010, pp.5, 729].

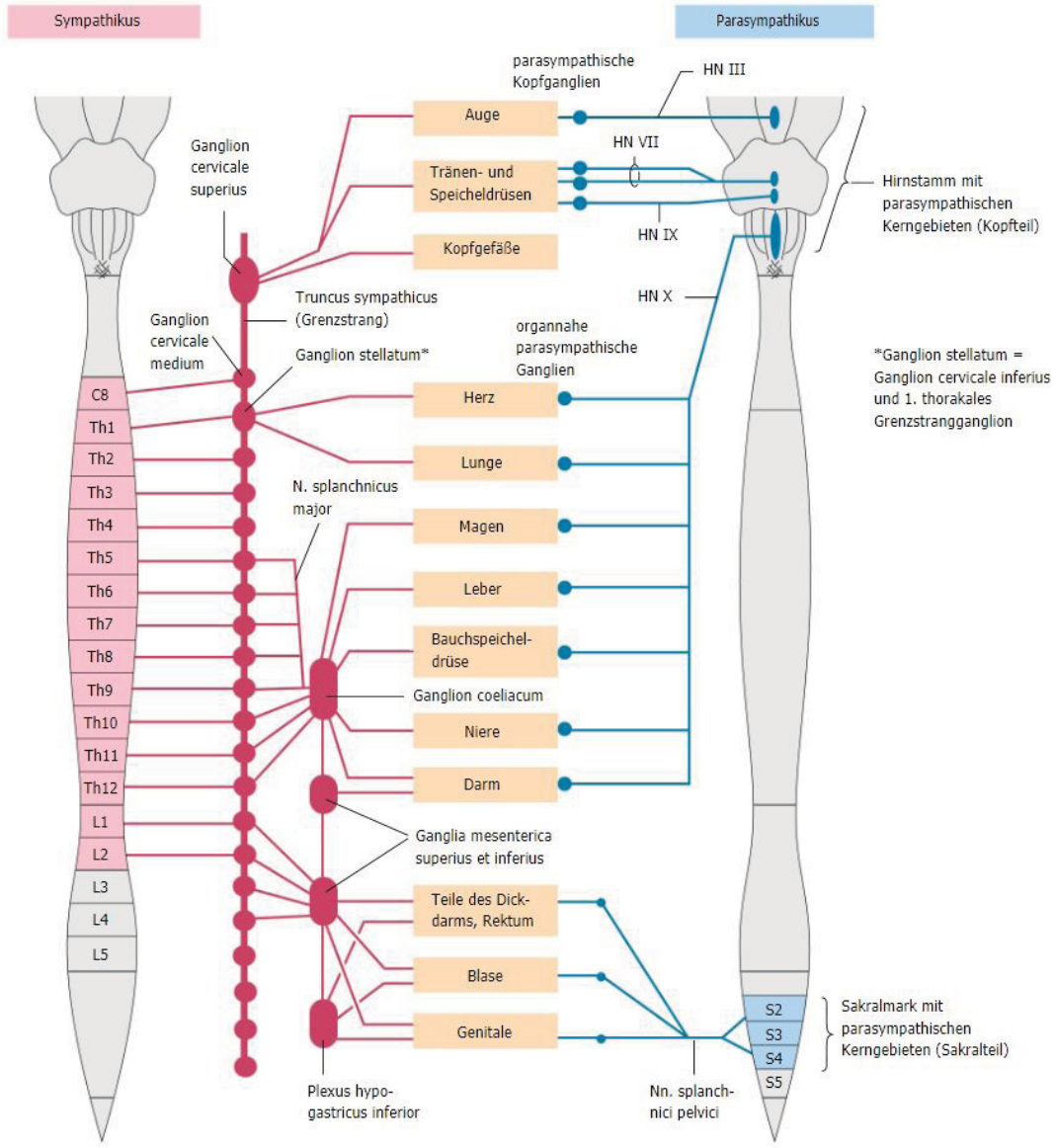

Figure 3: Overview of the ANS: sympathetic and parasympathetic. Taken from: [Schünke et al., 2006, p.316]

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Classically, the efferent pathway of the autonomic nervous system is divided into two subsystems: the *parasympathetic nervous system* (PNS) and *sympathetic nervous system* (SNS). Both divisions of the autonomic nervous system innervate almost all organs of the body, including the heart and vascular system [West et al., 2013], see Fig. 3.
In order to provide stable autonomic control, the PNS and SNS are differentially, depending on the physiological or pathophysiological demands [Mai and Paxinos, 2011, pp.143-144].

As shown in figure 4, the efferent pathways in both divisions consists of *pre- and postganglionic neurons*. The cell body of the preganglionic neurons originates in the CNS, that is: the gray matter of the brain or the spinal cord. The preganglionic neuron synapses with the postganglionic neuron at an autonomic ganglion. Postganglionic neurons innervate the effector organs such as the heart and vessels. The pre- and postganglionic neurons of the parasympathetic and sympathetic pathways are of different length. In fact, the sympathetic postganglionic neurons are longer than the neurons of the parasympathetic [West et al., 2013].

Anatomy of the Parasympathetic Nervous System The parasympathetic pathways are divided into two parts, depending on the origin of their preganglionic neurons: cranial and sacral parasympathetic pathways, Fig. 3 [Mai and Paxinos, 2011, p.143]. The preganglionic neurons of the cranial parasympathetic pathways originate in the

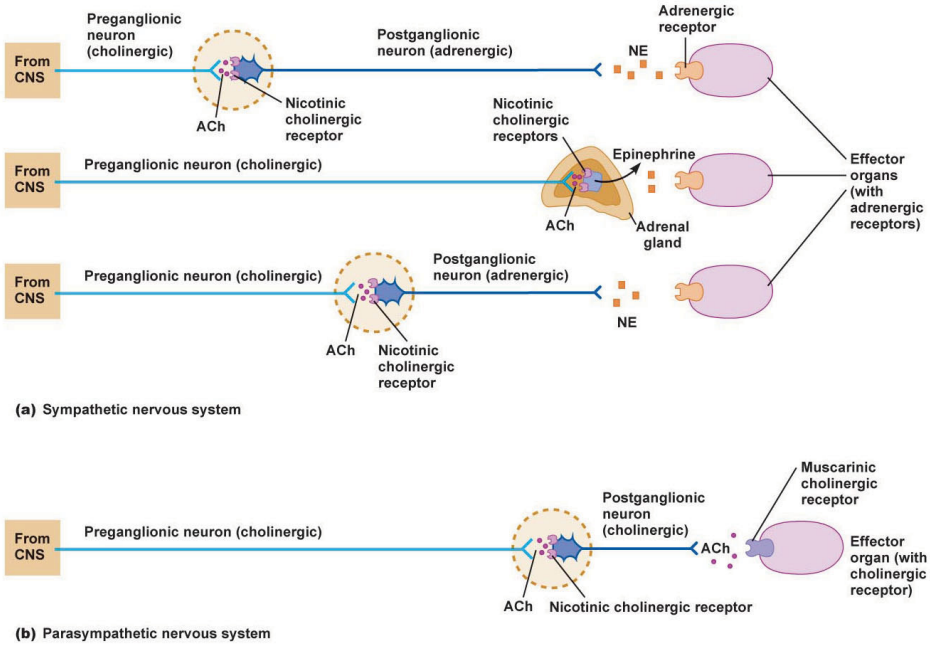


Figure 4: Overview of pre- and postganglionic neurons. Taken from: http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202007/figure_11_07_labeled.jpg [Accessed 21/06/13]

nuclei of following four cranial nerves, located in the brainstem: N. oculomotorius (third cranial nerve), N. facialis (seventh cranial nerve), N. glossopharyngeus (ninth cranial nerve) and N. vagus (tenth cranial nerve). The preganglionic neurons of the sacral parasympathetic pathway have its source within the sacral spine segments S2 to S4 [Hagen et al., 2012a]. The location of the synapse in order to transfer the information from the preganglionic to the postganglionic neuron takes place either near the effector organ or in the wall of the effector organ [Guyton and Hall, 2010, p.731]. The tenth cranial nerve (N. vagus) regulates almost all internal organs of the body, with the exception of the genitals, bladder, distal intestine and anus, due to the fact that they are innervated by the parasympathetic sacral nerves S2-S4 [Hagen et al., 2012a].

Anatomy of the Sympathetic Nervous System As shown in Figure 3, the preganglionic neurons are found within the intermediolateral horn [Hagen et al., 2012a]: thoracic (T1-T12) and lumbal (L1-L2) segments of spinal cord [West et al., 2013]. If we take the location of their ganglia into account, pre- and postganglionic neurons are arranged in following three patterns, Fig. 5:
(1) The spinal sympathetic preganglionic neurons (SPN's) leave the spinal cord through the ventral root. The ventral and dorsal root form the spinal nerve that passes through the spinal canal [Krassioukov, 2009]. The preganglionic neurons go via the white ramus to *paravertebral ganglia*. Paravertebral ganglia are situated on both sides of the spine and are connected with one another to form the sympathetic trunk. A single preganglionic neuron can synapse with many postganglionic neurons up and down the sympathetic trunk. Some postganglionic neurons leave the sympathetic through the grey ramus.
(2) Preganglionic neurons go via the white ramus to *prevertebral/collateral ganglia* where they synapse to the postganglionic neurons.
(3) As shown in Figure 4, long preganglionic neuerons innervate modified postganglionic cells (chromaffin cells) in the adrenal medulla. The chromaffin cells synthesise the hormones epinephrin and norepinephrin, in the ratio of 4 to 1 and release them into the blood [Guyton and Hall, 2010, pp.729-730].

Autonomic neurotransmitters and receptors on the effector organs Figure 4 shows that there are two main neurotransmitters within the autonomic nervous system: *acetylcholine* (Ach) and *norepinephrine* (NE). Fibers that release the transmitter acetylcholine are also referred to as cholinergic and those that release adrenalin as adrenergic [Guyton and Hall, 2010, p.731].
Preganglionic neurons, of parasympathetic as well as sympathetic system, are cholinergic. While all parasympathetic postganglionic neurons are cholinergic too, almost all postganglionic neurons of the sympathetic system are adrenergic. An exception are

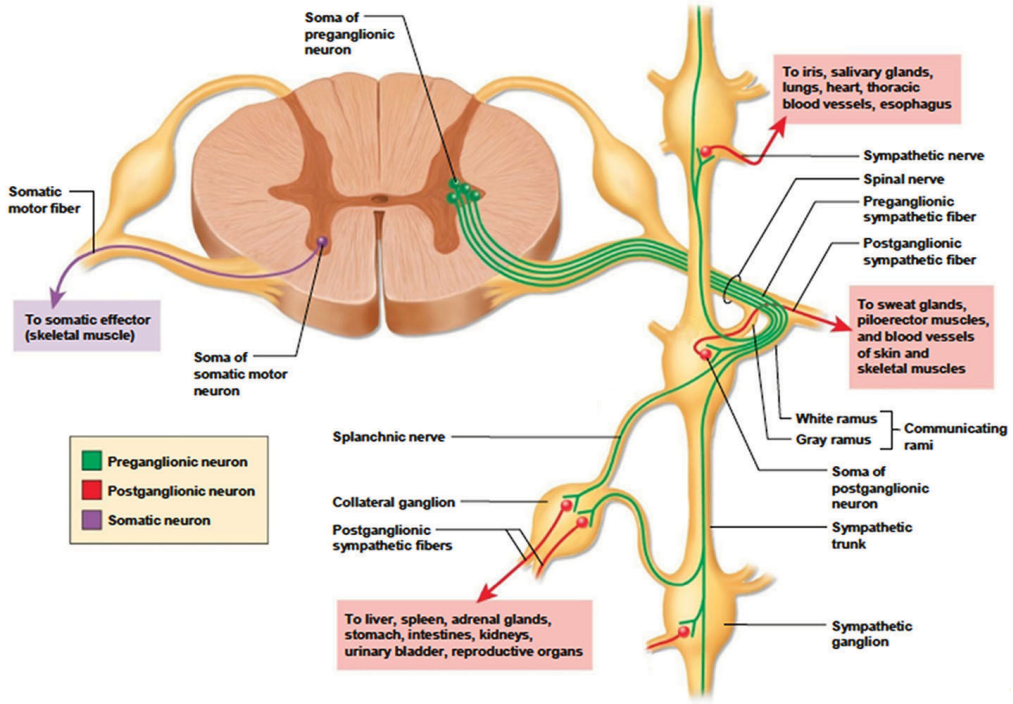


Figure 5: Organization of pre- and postganglionic neurons of the SNS. Taken from: http://classconnection.s3.amazonaws.com/636/flashcards/1088636/png/screen_shot_2012-03-10_at_100926_am1331402983393.png [Accessed 21/06/13]

sympathetic neurones that innervate the sweat glands and piloerector muscles of the hair. Those release acetylcholine (not shown in the figure) [West et al., 2013].
Adrenergic receptors are found within the sympathetic nervous system (except in sweat glands and piloreceptor muscles of the hair). Adrenergic receptors are divided into two main classes (α and β) and subclasses (α_1, α_2 and β_1, β_2, β_3). The parasympathetic system contains cholinergic receptors (muscarinic and nicotinic) [Guyton and Hall, 2010, p.733].

1.1.3 Effects of the ANS on the heart and vessels

Autonomic regulation and innervation of the heart and vessels In both parsymphatetic and sympathetic systems, the reflex pathways include sensory receptors, afferent pathways, integration centers in the central nervous system, efferent pathways and target organs, as shown in Figure 2 [Furlan and Fehlings, 2008].

In the short-term, the majority of blood pressure regulation is accomplished by *baroreceptors*. Baroreceptors obtain information about the pressure level in the arterial system. The baroreflex consists of two interdependent systems, a low-pressure system and a high-pressure system. The low-pressure baroreceptors are located within the cardiopulmonary system and are involved in blood volume regulation. If the central

venous pressure and volume drops, the sympathetic nervous system is strengthened in its function via cardiopulmonary stretch receptors. The stretch receptors of the high-pressure baroreflex system are situated within the aortic arch and carotid sinus. An increase in the mean arterial pressure leads to an increased depolarization of sprayed nerve endings. Hence the frequency of action potentials that are conducted to the nucleus tractus solitarius (NTS) of the medulla increases. Receptors of the aortic arch transmit the information vagal to the NTS and receptors of the carotid sinus transmit via the glossopharyngeal nerve. This triggers a reflex effect on the cardiovascular system through autonomic neurons. The medulla oblongata, located within the brainstem, is the prime site of autonomic control and contain the cell bodies of parasympathetic and sympathetic efferent nerves.
The baroreflex is affected by chemoreflex information and is thus influenced by respiration and arterial blood gases. Peripheral chemoreceptors sense arterial oxygen, carbon dioxid and pH level. Inspiration decreases and expiration increases the cardiovagal baroreflex response [Guyton and Hall, 2010, p.205] [Phillips et al., 2012].

As shown in figure 6, the medulla oblongata is subject to higher centers (cortex, hypothalamus) and connects the higher centers of the brain to the spinal cord. The medulla oblongata processes the various inputs [Krassioukov, 2009]. The processed information determines the activity of the efferent pathways of the ANS.

Having provided an overview of the efferent pathways of the ANS (section 1.1.2), I would now like to elaborate on the innervation of the heart and vessels. The segmental distribution of the sympathetic nerve fibers as well as the dual innervation (parasympathetic and sympathetic) of the heart are of prime importance in terms of the cardiovascular control in spinal cord injury patients [Krassioukov, 2009]. As shown in figure 6, the sympathetic innervation to the heart and the blood vessels of the chest and upper extremity originate from the spinal sympathetic preganglionic neurons (SPNs) of the cord segments T1-T5. However, the blood vessels of the splanchnic bed and lower extremity are innervated from the cord segments T6-L2 [Hagen et al., 2012a]. The heart is also innervated by the parasympathetic nervous system via the vagus nerves [Krassioukov, 2009]. Most peripheral blood vessels have no parasympathetic innervation, except the vessels that supply the pelvic organs [Hagen et al., 2012a]. Basically, peripheral blood vessels are only innervated by the sympathetic nervous system, while the cavernous tissue of the penis and clitoris only receive parasympathetic innervations [West et al., 2013].
A special importance attaches to the sympathetic nervous system in blood pressure regulation. As shown in table 1, the sympathetic system increases the activity of the heart and constrict the blood vessels. The parasympathetic nervous system affects

the heart in opposite direction as that by the sympathetic system and has minimal effect on the arterial blood pressure [Guyton and Hall, 2010, pp. 735-736]. This can be explained by the fact that most peripheral blood vessels have no parasympathetic innervation [Hagen et al., 2012a].

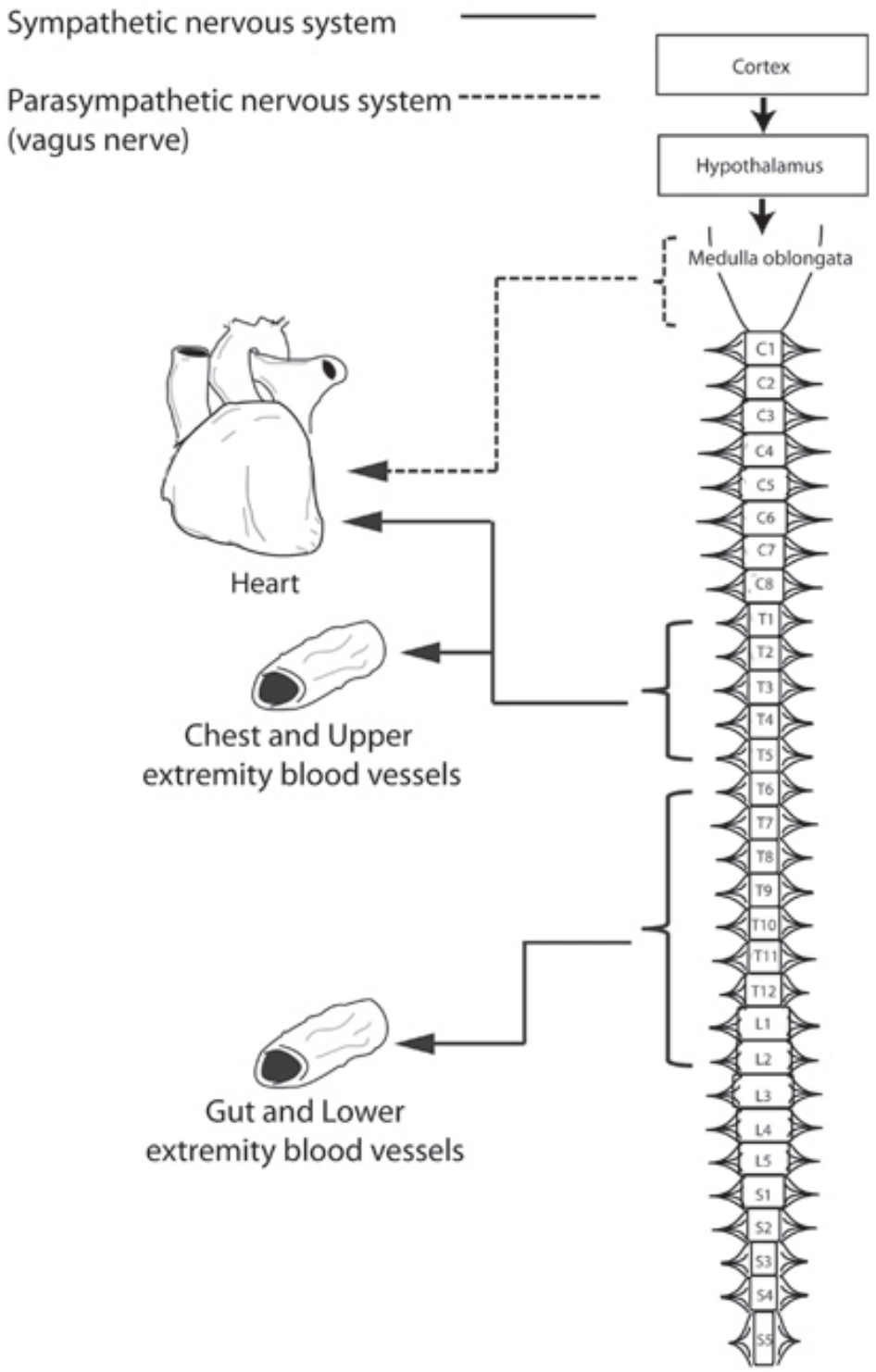


Figure 6: Schematic diagram of autonomic control of cardiovascular system. Taken from: http://www.nature.com/sc/journal/v49/n7/fig_tab/sc20112f1.html [Accessed 22/06/13]

1.1.4 Effects of hormones

As noted in section 1.1.3, short-term control of blood pressure come into effect through the autonomic nervous system by changing total peripheral resistance (TPR) and compliance, as well as on cardiac pumping activity. Long term control of blood pressure is done mainly via renal regulation of fluid volumes [Guyton and Hall, 2010, p.228]. Within this context, I would like to present hormones important for blood pressure regulation.

Perhaps most important system in blood pressure regulation is the *renin-angiotensin-aldosterone system (RAAS)*. Low blood pressure, decreased sodium delivery and increased sympathetic tone on the kidneys stimulate the release of renin into the circulation. *Renin* acts to convert angiotensinogen, which is secreted by the lever, into angiotensin I. That gets converted by angiotensin-converting enzyme (ACE) into *angiotensin II*. As shown in table 2, angiotensin II is a blood pressure increasing hormone. In addition to its effect on vasculature by vasoconstriction, it produces two other hormones that increase blood pressure: *aldosterone* and *anti-diuretic hormone (ADH)* [Guyton and Hall, 2010, pp.220-221] [Klabunde, 2011, p.137-138].
Atrial natriuretic peptide (ANP) is a counter-regulatory system for the RAAS. ANP is a hormone that the atria release in response to higher pressure and leads to natriuresis. It is one of the few hormones that lowers blood pressure [Guyton and Hall, 2010, p.376]. Circulation catecholamines, *epinephrin* and *norepinephrin*, originate from the adrenal medulla or from sympathetic nerves innervating blood vessels. These hormones stimulate the cardiovascular system via α- and β- receptors and have almost the same effects throughout the body as the effects caused by direct sympathetic stimulation [Klabunde, 2011, pp.136-137]. The essential difference is that the effects last longer because both of these hormones are removed from the blood slowly [Guyton and Hall, 2010, p.736].

Table 1: Actions of autonomic neurotransmitters on the cardiovasular system and the associated receptors. Abbreviations: M, muscarinic; SA, sinoatrial; AV, atrioventricular. Adapted from: [Klabunde, 2011, p.129] [Guyton and Hall, 2010, p.734] [Krassioukov, 2009]

Target organ	**Sympathetic**	**Receptor**	**Parasympathetic**	**Receptor**
Heart				
Cardiac muscle	pos. inotrop	$\beta_1 > \beta_2$	neg. inotrop	M2
SA node	pos. chronotrop	$\beta_1 > \beta_2$	neg. chronotrop	M2
AV node	pos. dromotrop	$\beta_1 > \beta_2$	neg. dromotrop	M2
Coronaries	dilatation, constriction	β_2, α	dilatation	M3
Blood Vessels	constriction	α_1, α_2	dilatation*	M3*

* This is true for arteries of the cavernous tissue of the penis and clitoris.

Table 2: Effects of hormones in blood pressure regulation. Abbreviations: TPR, total peripheral resistance; ADH, anti-diuretic hormone; ANP, atrial natriuretic peptide. Adapted from: [Klabunde, 2011, pp.135-142]

Hormones	Effects	Blood pressure
Angiotensin II	constricts resistance vessels → TPR ↑	↑
	release of aldosterone	↑
	relaease of ADH from pituitary gland	↑
	via renal tubules → Na^+ & H_20 reabsorption ↑	↑
	stimulates hypothalamus → thirst	↑
	enhances sympathetic activity	↑
	stimulates cardiac and vascular hypertrophy	↑
Aldosterone	enhance Na^+ & H_20 reabsorption	↑
ADH	increases water reabsorption	↑
	vasoconstriction (at ↑ plasma concentrations)	↑
ANP	leads to natriuresis	↓
	↓ renin releases	↓
Catecholamines	↑ heart rate, ↑ inotropy, vasoconstriction	↑

1.2 Spinal cord

As basic knowledge of spinal cord anatomy is essential for understanding spinal disorders, I will discuss briefly the spinal cord's anatomy and function.

1.2.1 Anatomy

As shown in figure 7, the spinal cord is surrounded and protected by the bony vertebral column and lies within the vertebral canal. It is attached to the brain stem. The spinal cord is a lot shorter than the vertebral canal. It begins at the exit from foramen magnum and continues down to conus medullaris that extends only up to approximately the second lumbar vertebra (L2) of the vertebral column, whereas the vertebral column continues down further. The conus medullaris merges into the filum terminale, a bundle of nerves called the cauda equina. The spinal cord is surrounded by the meninges: the pia mater, arachnoid mater and dura mater. Those circumscribe the subdural and subarachnoid space. The last-named contains the cerebrospinal fluid [Mai and Paxinos, 2011, p.187].

A spinal cord transverse section reveals the white and gray matter, Fig. 8. The gray matter is divided into a dorsal, lateral (only in thoracic and upper lumbar segments) and ventral horn. The intermediate lateral horn of the thoracic and upper lumbar segments contains preganglionic sympathetic neurons, Fig. 5. The cross bar of the gray

matter has within its center an opening, which is referred to as the central canal. It contains cerebrospinal fluid. The gray matter consists of neuronal cell bodies, whereas the white matter consists of longitudinally running axons that carry the information in so called columns (dorsal, lateral, ventral) up or down the spinal cord [Mai and Paxinos, 2011, pp.188-189].

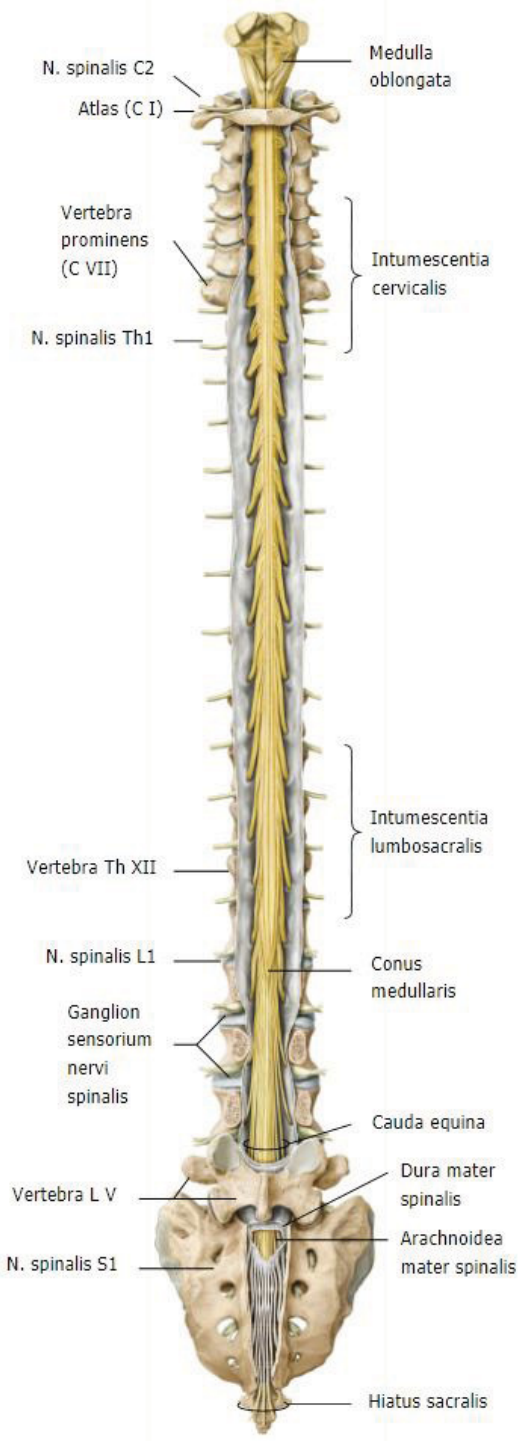


Figure 7: Location and external shape of the spinal cord. Taken from: [Schünke et al., 2006, p.269]

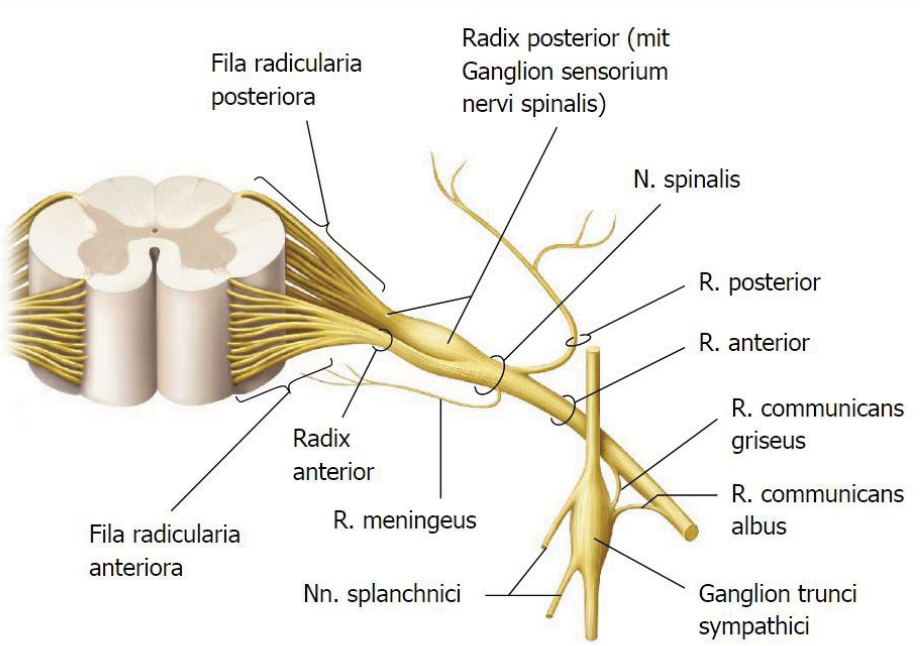


Figure 8: Structure of a spinal cord segment. Taken from: [Schünke et al., 2006, p.266]

The spinal cord consists of 31 segments, defined by 31 pairs of nerves branch off from the spinal cord, figure 9: eight cervical, twelve thoracic, five lumbar, five sacral and one coccygeal (not represented in the figure). In the cervical region the spinal nerves are named according to the vertebra below their exit point. From the first thoracic vertebra (Th1) downward, all spinal nerves are named after the vertebra above. As a result, there is an eighth cervical spinal nerve, even though there is no eighth cervical vertebra [Mai and Paxinos, 2011, p.190], Fig. 9.

Figure 8 represents the struture of one spinal cord segment. Neurons that are carrying sensory information from the body to the spinal cord via afferent fibers enter the spinal cord through the dorsal root (radix posterior). The cell bodies of these sensory neurons are located at the dorsal root ganglion. Motor and autonomic preganglionic neurons, innervating skeletal muscles and visceral organs, leave the spinal cord through the ventral root (radix anterior) via efferent fibers. Both, the dorsal and ventral roots, leave the vertebral column through intervertebral foramen and join with one another to form the spinal nerve. The spinal nerve itself branches into various nerves [Mai and Paxinos, 2011, p.190], as shown in figure 8.

1.2.2 Function

The exchange of information between the brain and body is guaranteed by the spinal cord. Many nerve pathways transmit essential signals up and down the spinal cord. Somatic motor pathways, running from the brain and spinal cord to the skeletal muscles,

are called efferent [ASIA, 2013a]. Motor pathways are divided into upper and lower motor neurons. The upper motor neurons begin in the prefrontal motor cortex and projects into the spinal cord. The lower motor neurons originate in the spinal cord and comprise the peripheral nerves [SCIInfoPages, 2013]. Each specific neurological segment (e.g. C5, T9 or L4) contributes to different muscles (myotome).
Somatic sensory pathways carry localizable sensations such as temperature, pain and touch by afferent nerves from the spinal cord to the brain. An area of skin supplied by a given spinal cord level is referred to as a dermatome. In addition to this, the spinal cord provides most sensory and motor information to and from organs as well as blood vessels by autonomic nerves [ASIA, 2013a], as described in section 1.1.2.
In order to properly interpret loss of function after SCI, it is necessary to know that some fibres decussate within the brainstem (fibers for motor control, proprioception and vibratory sensation) and others within the spinal cord at the level of injury (e.g. pain and temperature sensation) [Royden Jones et al., 2011, pp.346-347].

1.3 Spinal Cord Injury

1.3.1 Definition

A spinal cord injury (SCI) is a trauma or damage to the spinal cord. Compression, caused by bleeding, bruising, swelling or tumor-associated, lead to disturbance in the functions of the nerves so that messages that flow between the brain and the spinal cord are blocked. A spinal cord injury (SCI) affects sensory, motor and reflex messages below the site of the injury [Schweizer Paraplegiker-Vereinigung, 2013].

1.3.2 Epidemiology

SCI affects mainly young adults (>50% are male) between the ages of 16 and 30 [National Spinal Cord Injury Statistical Center, 2013]. SCI's are either of traumatic (most often) or of non-traumatic origin [Schweizer Paraplegiker-Vereinigung, 2013]. The most common traumatic causes of SCI are motor vehicle accidents, followed by falls (especially for elderly populations [Hagen et al., 2012b]) and acts of violence, including gunshot wounds and stabbing. Sports and athletic activities, as for instance American football, gymnastic, ice hockey, horse riding, account for about 10% of spinal cord trauma [National Spinal Cord Injury Statistical Center, 2013].Tumorous compression, spinal stenosis, vascular ischemia or inflammation and multiple sclerosis are examples for acquired non-traumatic causes of SCI [Schweizer Paraplegiker-Vereinigung, 2013]. The causes of SCI in children, e.g. car and pedestrian accidents [Hagen et al., 2012b], birth injuries, spinal cord injury without radiologic abnormality (SCIWORA) [Schottler et al., 2012] or spina bifida [Schweizer Paraplegiker-Vereinigung, 2013], are quite different compared to those of adults.

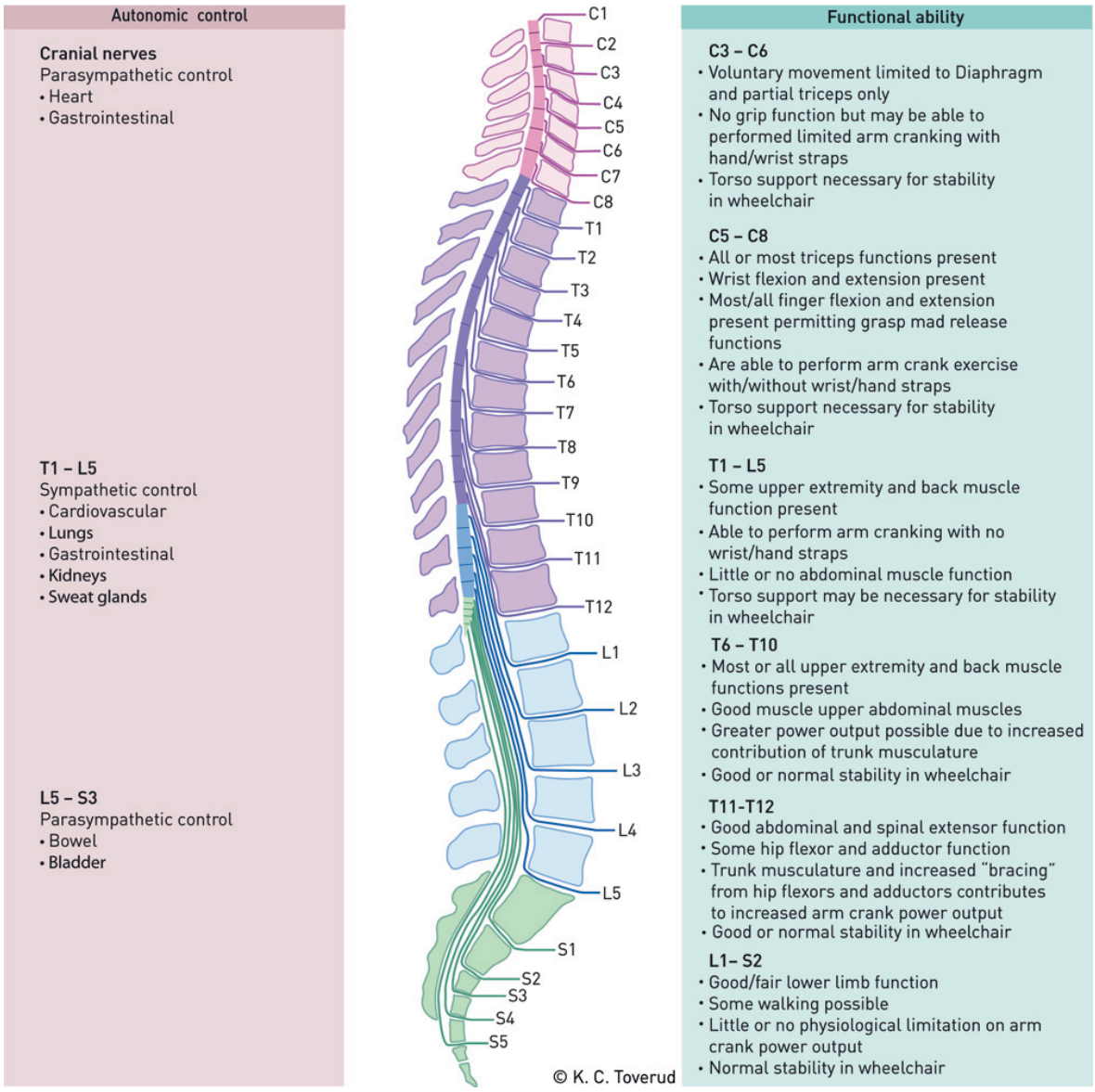


Figure 9: Spinal cord injury and its effects. Taken from: [Hagen et al., 2012a]

The most common neurological levels of injury are cervical (C4 to C7) and the thoracolumbar transition (T12 to L1) [National Spinal Cord Injury Statistical Center, 2013]. These epidemiological data vary greatly from one country to another [Hagen et al., 2012b].

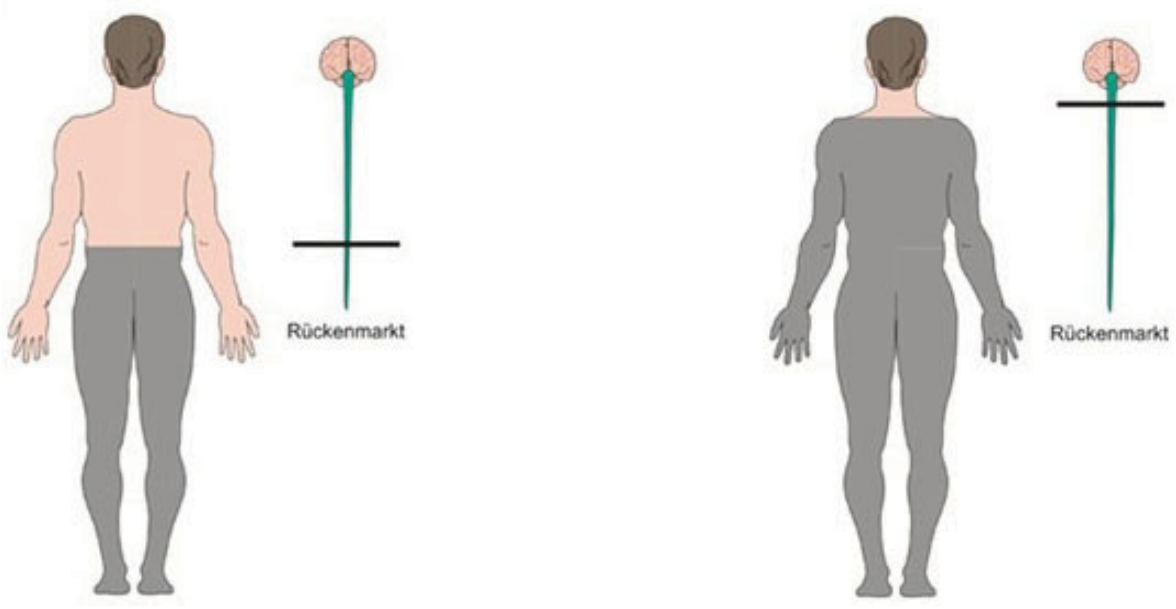
Spinal cord injured individuals have a significantly lower life expectancy than those with no SCI [National Spinal Cord Injury Statistical Center, 2013], even though individuals with SCI live longer than ever before. As a consequence, cardiovascular complications are increasingly becoming the leading cause of mortality in individuals with SCI [West et al., 2013]. Diseases of the respiratory system as well as of the cardiovascular system, each account for about one fifth of all deaths in individuals with SCI [National Spinal Cord Injury Statistical Center, 2013].

1.3.3 Spinal Cord Injury Levels and Classification

In this section discussed are the issues related to spinal cord injury levels, the terms para- and tetraplegia, the definition of ”complete” and ”incomplete” SCI, the zone of partial innervation, as well as the ASIA classification approach towards SCI.

Level of Injury SCI are classified according to motor, sensory and neurologic level of injury. The motor and sensory level of injury is defined as the lowest normally innervated either myotome or dermatome on both sides of the body [ASIA, 2013a]. Therefore, the neurological level of SCI is defined of the lowest spinal segmental level that has both intact sensation and muscle function [Hagen et al., 2012b]. It must be considered that due to the unequal growth of the spinal cord in relation to the vertebral column [Mai and Paxinos, 2011, p.187] (shown in figure 9), spinal vertebral (anatomical level) and spinal cord segmental levels are not necessarily the same. The anatomical level of injury fall into two main groups: high (cervical) and low (thoracic, lumbar and sacral) injuries [Hagen et al., 2012b].

Para- and Tetraplegie The following illustration (figure 10) shows the difference between para- and tetraplegics.
Paraplegia, as a result of injuries in the thoracic and lumbar levels, affects the lower



(a) paraplegic (b) tetraplegic

Figure 10: Para- and Tetraplegic. Gray area: Loss of motor and sensory function. Taken from: http://www.das-kontinenzzentrum.de/unterscheidung-der-plegie.html[Accessed 16/07/13]

limb (both legs) and the trunk.
Tetraplegia, also referred to as quadriplegia, results from injuries in the cervical level of the spinal cord. This means that the lower extremity, trunk as well as the upper extremity (both arms) are affected by SCI. The higher the lesion, the more arm muscles are affected [Schweizer Paraplegiker-Vereinigung, 2013].

Complete and Incomplete SCI may be further divided into either complete or incomplete. A SCI is considered complete if there is either sensory nor motor function in the anal and perineal region (S4-5), which represent the lowest parts of the spinal cord. It has to be taken into account that a complete injury doesn't necessarily mean that the spinal cord is transected. It simply indicates that no significant transmission of neural impulses pass through the injured spinal cord [ASIA, 2013a].
In terms of complete injuries, the zone of *partial preservation* is used to describe myotoms and dermatoms below the neurological level of injury, where partially motor and sensory innervation is still present [Schweizer Paraplegiker-Vereinigung, 2013].
An incomplete injury is meant that some functions are maintained below the primary level of injury.The incomplete spinal cord injuries are classified in five distinct syndromes, as illustrated in figure 11. Both, complete and incomplete SCI, can result in a damage to either the upper or lower motor neuron and its axons [ASIA, 2013a].

Classification of Spinal Cord Injury Severity - The ISNCSCI and the ISAF-SCI The International Standards for Neurological Classification of SCI (ISNCSCI), also called the ASIA ISCOS test, documents the neurological examination of individuals after SCI. It is a useful standardised test to define SCI, whereas only motor and sensory functions are examined. It includes the ASIA Impairment Scale (AIS) [Krassioukov et al., 2012].

The level of sensation is determined on both sides of the body on specific sensory key points with light touch and pin prick. The response is recorded on a three point scale (0 to 2). To determine motor level, ten different key muscles on both sides of the body are tested by using a 0 to 5 scale. Based on the sensory and motor index

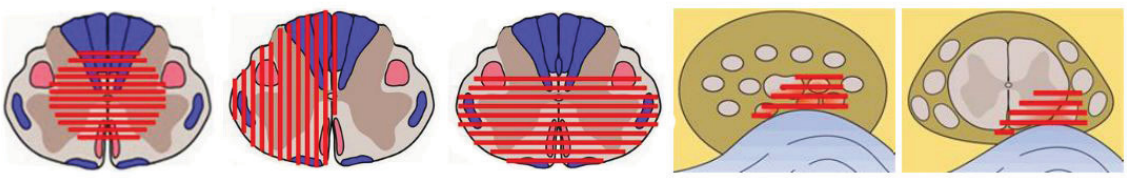


Figure 11: Incomplete SCI syndroms. From left to right: central cord syndrome, Brown-Sequard syndrom, anterior cord syndrome, cauda equina syndrom and conus medullaris syndrom. Taken from: [ASIA, 2013a]

score, the neurological level is defined. Next, the SCI is classified in either complete (zone of preservation) or incomplete. Then an injury grade is assigned according to the ASIA Impairment Scale (AIS). The AIS ranges from A to E to grade the various degrees of impairment on the basis of completeness of SCI [ASIA, 2013a]. However, this classification does not include the evaluation of autonomic function [West et al., 2012].

In addition to the ISNCSCI, the Autonomic Standards is used to document remaining Autonomic Function after SCI (ISAFSCI). The Autonomic Standard Assessment Form allows a anatomical classification into suproconal, conal and cauda equina. The Autonomic Standard Assessment Form consists of three different categories: the general autonomic function; lower urinary tract, bowel and sexual function; urodynamic evaluation. The assessment of these three categories is different in each case. The information is obtained through physical examination, observation, clinical history as well as self-reported history [Krassioukov et al., 2012].

The assessments of both, the ISNCSCI and the ISAFSCI, are useful in view of future rehabilitation, to monitor progress of SCI as well as a basis for planning of research projects [Krassioukov et al., 2012].

1.3.4 Effects and complications following spinal cord injury

Spinal cord injury at a particular level causes damage to the nerves that come out from the spinal cord at that level and below. That leads to temporary loss of sensory, motor, reflex and autonomic function occurring below a spinal cord injury, commonly known as *spinal shock* [Apparelyzed, 2013] [Krassioukov, 2009]. Loss of touch, pressure and temperature sensations, flaccid paralysis, areflexia and thermoregulatory disturbances are the consequences [Grigorean et al., 2009]. Injury to the spinal segments may also affect the autonomic control of various organ systems (see figure 9). Thus, SCI has wide ranging impacts, such as impairment in respiratory, bladder and bowel function. Abnormal temperature regulation, sweating dysfunctions [Hagen et al., 2012a] as well as changes in sexual function and fertility may occur after SCI, although to a variable extent [ASIA, 2013a].

Duration of spinal shock varies greatly and can last for days, weeks and months. The average duration is between four and twelve weeks postinjury [Popa et al., 2010] [Grigorean et al., 2009] [Furlan and Fehlings, 2008] [Krassioukov et al., 2003]. Ditunno et al. reported that spinal shock can be divided into four phases, as the following table 3 provides. As the spinal cord recovers from shock, hyperreflexia occurs. Local spasticity and clonus are the result [Ditunno et al., 2004] [Apparelyzed, 2013].

Table 3: The four phases of spinal shock. Adapted from: [Ditunno et al., 2004]

Phase	Period of time	Reflex response
1	0 - 24 hours	areflexia, hyporeflexia
2	1 - 3 days	initial reflex return
3	4 days - 1 months	early hyperreflexia
4	1 - 12 months	hyperreflexia, spasticity

Spinal shock is not to be confused with neurogenic shock. Neurogenic shock, usually occurs in individuals with acute severe cervical or high-thoracic SCI [Furlan and Fehlings, 2008], is accompanied by severe hypotension and persistent bradycardia following immediately after SCI [Krassioukov, 2009]. This is, however, discussed later on.

The loss of function after SCI depends on the severity of the injury and the location of the affected spinal segment. Figure 9 shows that higher the location of spinal cord injury, more the functional disability [SCIInfoPages, 2013].

Spinal cord injuries may result in a number of secondary complications, such as neuropathic pain, pressure sores, increased susceptibility to infections (especially of the respiratory and urinary tracts), partly due to the lack of physical activity and reduced muscle mass osteoporosis or, only rarely, syringomyelia [SCIInfoPages, 2013]. Due to the associated lack of physical acitivity/reduced muscle mass, lipid disorders, metabolic syndrome and diabetes may occur. All these are risk factors for atherosclerotic diseases [Hagen et al., 2012a] [Grigorean et al., 2009].

The effects of SCI are very varied. SCI affects the injured patient both physically and psychologically. Not only is spinal cord injury associated with increased morbidity and mortality (see section 1.3.2), loss and changes in normal activities in daily life are a major challenge for the affected and his/her family members [National Spinal Cord Injury Statistical Center, 2013].

1.3.5 Management and Treatment

In order to maintain the best possible function and prevent complications following spinal cord injury, immediate trauma care and timely transfer to a specialized SCI rehabilitation center are mandatory. First of all the medical status (airway, breathing and circulation) of the patient must be stabilized. Surgery has to be taken into consideration either with the view to relieve the compression of the spinal cord or to correct the spinal malalignment. The halo-body-jacket or Gardner-Wells tongs represent

conservative therapeutic options [Royden Jones et al., 2011, pp.565-568].

Professional and targeted rehabilitation carried out in specialized centers is the most important after SCI. Individually tailored treatment strategies aim to maximize functional recovery, prevent secondary, etc. complications as well as to assist the patient in returning to his/her socio-cultural environment. Therefore the patient has to be attended not only by a rehabilitation expert, but also by doctors of other medical fields, physio- and ergotherapist, psychologist and social workers.

Numerous drugs [ASIA, 2013b] and assistive devices [Royden Jones et al., 2011, p.570] may support the patient's rehabilitation as well as the activities of daily living.
Many research groups throughout the world have focused on stem cell therapy [ASIA, 2013b] [Balgrist, 2013] [SCIInfoPages, 2013] and Nogo antibody treatment for spinal cord injured [Balgrist, 2013].

Another factor not to be underestimated in this context is adaptive sports activity, see also chapter entitled "Importance of physical activity in spinal cord injured individuals" (4.4.1).
All the benefits associated with physical activity are applicable also for spinal cord injured individuals. Prevention of secondary complications following SCI by physical activity plays an important role. In addition, spinal cord injured individuals benefit from enhancing self-esteem and coping with individual psychosocial problems and obstacles [Kawanishi and Greguol, 2013].

II Objectives

Depending on its location, the impact of spinal cord injury on the autonomic nervous system causes various cardiovascular complications that can also be associated with life-threatening conditions. Such individuals have a much higher morbidity and mortality risk due to autonomic dysfunction than able-bodied individuals. Knowledge about clinical consequences and the underlying mechanisms following spinal cord injury is important for prevention, rehabilitation and therefore improving the individual's quality of life. This diploma thesis provides an overview of physiological basis of cardiovascular complications following spinal cord injury and the associated effects at rest and during different types of exercise, as well as how an intervention of an anti-G suit affects these variables. For this purpose, a systematic literature search was conducted in the bibliographic databases PubMed, Web of Knowledge and google scholar (in each case, coverage up to 1992).

III Material and Methods

The subject of my diploma thesis is "Autonomic functions and cardiovascular responses in individuals with spinal cord injury". I chose this because my particular interest is directed towards neurological, autonomic and cardiovascular functions, as well as sport and exercise science. While I spent time getting involved with those topics, I came across spinal cord injury and autonomic functions. When I realized that cardiovascular complications tremendously affect the lives of spinal cord injured individuals, it seemed advisable to me to focus my thesis on individuals living with spinal cord injury. That led me to the question of how autonomic cardiovascular functions and control is affected in individuals with spinal cord injury, depending on the level of injury and period of time, as well as how different exercise interventions affect these. For this reason, I set out to search the existing literature.

To construct my search strategy that would help me in obtaining systematically the relevant literature, I used keywords that were identifying the essential subject (using free text terms):

- Autonomic function
- Cardiovascular system
- Spinal cord injury
- Exercise
- Anti-G suit

Then I tried to find possible synonyms for these words as well as related words:

- "autonomic function": autonomic nervous system, autonomic physiology, sympathetic nervous system, parasympathetic nervous system
- "cardiovascular system": circulatory system, cardiovascular responses, cardiovascular control, heart, blood vessel, vascular system
- "spinal cord injury": paraplegia, tetraplegia, quadriplegia, level of injury
- "exercise": physical fitness, activity, performance, Paralympics, athletes, training, workout
- "anti-G suit": pressure suit, lower body positive pressure

Finally, I used the MESH database to see which of these words/ terms were represented in PubMed. Using these controlled vocabulary of a database - such as PubMed - that

is relevant to my topic of the diploma thesis helped me to obtain most of the relevant papers. Once the terms were identified, I was ready to build my search.

Limiting the search criteria: This is a critical aspect as the judicious use of "AND" or "OR" or "NOT" helps to ensure that appropriate articles are obtained. For example, including "AND" between words helps me to focus my research. Therefore, I used the following combinations:

- Autonomic function AND Cardiovascular system
- Autonomic function AND Spinal cord injury
- Cardiovascular system AND Spinal cord injury
- Spinal cord injury AND Exercise
- Spinal cord injury AND Anti-G suit

In addition, putting on quote ("") on the words also helps to ensure that specific articles related to these topics come up during the search. Therefore, I also used the following combinations:

- "Autonomic function" AND "Cardiovascular system"
- "Autonomic function" AND "Spinal cord injury"
- "Cardiovascular system" AND "Spinal cord injury"
- "Spinal cord injury" AND "Exercise"
- "Spinal cord injury" AND "Anti-G suit"

Where - in what databases/sources - did I search? And why?
PubMed is a tool I use quite regularly throughout my studies, as it provides a comprehensive archive for journal articles in e.g. medicine. Even though PubMed covers most of the published articles, there are still some articles that are not on PubMed. Therefore, along with PubMed, I use the **Web of Science** database. This is quite a good database as I can a get a lot of information about the authors. For example, what is the h index of the authors. Another important aspect of using Web of Science is that it is easy to see how many times the paper has been cited. This is particularly important as most of the citing articles are more current (newer) than the original article and either confirm or refute the findings of the paper. In addition, what I find particularly useful is the reference list of the articles and the associated articles. Sometimes the original article may not be very useful but the references provide therein or the citing

articles (or their references) are more helpful.

How did I choose the literature to be included?
The literature to be included was decided on the following criteria:

1. How relevant was it to my question?
2. I examined articles written in the last 25 years only (again this is an element that was placed in refining search criteria)
3. Literature was written in English and German. My knowledge of other languages is rather patchy and I would not want my research to be lost in translation (again this is an element that was placed in refining search criteria)
4. I included all primary literature (electronic) that were peer reviewed (abstracts + full texts)
5. I included secondary literature such as books as well
6. I included articles from all countries (as long as the literature was in English or German)

Abstracts of all articles that had a relevant title were reviewed to identify relevant literature. Available full texts were either downloaded or ordered in the library of the medical university of Graz. In addition to that, the references of each full text were checked to identify more relevant articles. Just mentioned steps were repeated. Furthermore, relevant literature was searched by using the author's name of already as relevant identified literature.

How the references were saved?
The references were saved to RefWorks. For this reason, I attended the course "Reference management with RefWorks" offered by the Medical University of Graz. I imported relevant references directly from PubMed and Web of Science to my RefWorks. As I used the text processing program LaTeX to design my diploma thesis, I used BibTeX format to output and present my references.

IV Current Literature

SCI results in cardiovascular short and long term disturbances, which affects the quality of the patient's life [Popa et al., 2010] [Kawanishi and Greguol, 2013]. The development and the extent of cardiovascular complications depend on the level of injury on one hand and severity of the SCI (complete or incomplete) on the other. Increasing age, accompanying disease such as obesity, lipid disorders, metabolic syndrome and diabetes as well as lack of physical fitness also play a major role in the development of cardiovascular diseases [Hagen et al., 2012a] that can result in acute or chronic health risks and even death [Grigorean et al., 2009] [Popa et al., 2010].

In the following section, first of all I want to present possible mechanisms that may occur after SCI that can be held responsible for abnormal sympathetic cardiovascular control following SCI. Below I will go into more detail on the impact on the cardiovascular system in regard to the level of injury as well as cardiovascular responses dependent on the period of time after SCI (acute and chronic). Finally, the effects of physical stress, orthostasis, Anti-G-suit and microgravity on the cardiovascular system will be demonstrated.

4.1 Abnormalities of autonomic cardiovascular control following SCI

Spinal cord injury entails dysfunction to the flow of information between the brainstem and spinal cord. As a consequence of disruption of descendent spinal involuntary autonomic pathways, stable autonomic control is no longer assured. The autonomic nervous system, which plays a crucial role for the cardiovascular control (as indicated in section 1.1.3), is impaired in its function. The extent of functional loss is determined by the level of injury (see section 4.2). Sympathetic hypoactivity and unopposed vagal tone are the cause of several cardiovascular disturbances, as described in the following sections. [Grigorean et al., 2009]
If the spinal cord below the level of injury functions independent of supraspinal control, as in a complete high-level SCI, it is referred to as "decentralization" of the SNS [Teasell et al., 2000].

Table 4 provides an overview of possible mechanisms responsible for abnormal sympathetic cardiovascular control following SCI. I would like to deliberately mention at this point only briefly those mechanisms, as I will go into further detail in the corresponding sections.

Table 4: Possible mechanisms responsible for abnormal sympathetic cardiovascular control following SCI. Adapted from: [Teasell et al., 2000] [Claydon et al., 2006b].

Loss of supraspinal regulatory (excitatory and inhibitory) control
Reduced sympathetic activity below the level of injury
Low catecholamine levels
Morphologic changes in sympathetic preganglionic neurons (SPN's) after SCI
Plasticity within spinal circuits
Hyperresponsiveness of peripheral *alpha*-adrenoceptors

First of all, SCI causes loss of supraspinal sympathetic regulatory control, whereby the extent of loss of sympathetic control correlates to the level and severity of injury. Hence, reduced activity of the sympathetic nervous system below the level of injury occurs. This can be linked to the fact that catecholamine (adrenaline and noradrenaline) plasma levels are low. Further on, atrophy of sympathetic preganglionic neurons (SPN's) reveals in the acute stage of SCI, followed by axonal sprouting that is assumed for new but impaired synaptic connections. The hyperresponsive of peripheral *alpha*-adrenoceptors below the level of injury correlates with the reduced plasma catecholamine levels. The possible reasons for this may be upregulatory or denervation supersensitivity mechanisms [Teasell et al., 2000] [Claydon et al., 2006b].

4.2 Cardiovascular complications depending on the level of injury

The level and severity of SCI to descending spinal voluntary motor and involuntary autonomic pathways concludes a variety of autonomic dysfunctions (see section 1.3.4) and thus naturally, dysfunctions of the cardiovascular system. The extent of cardiovascular dysfunctions depend on the altered supraspinal control of SNS and PNS [Krassioukov et al., 2012] [Hagen et al., 2012a] and includes modulation of coronary blood flow, heart contractility, heart rate and blood pressure [West et al., 2012].

As mentioned previously in section 1.1.3, the segmental distribution of the sympathetic nerve fibers to a variety of vascular beds as well as the dual innervation (parasympathetic and sympathetic) of the heart are of prime importance in terms of the cardiovascular control in SCI individuals (SCII), particularly in understanding of basal blood pressure (BP) and heart rate (HR), as well as cardiovascular responses following cervical, high-thoracic and low-thoracic SCI [Krassioukov, 2009] [Krassioukov et al., 2012].

At this point I would like once again to draw on the figure 6, as it is helpful to understand table 5. As outlined in table 5, T5 and above injuries are considered to be crucial for

Table 5: Impairment in cardiovascular control following SCI related to level of injury. Abbreviations: SSC, supraspinal symapathetic control; OH, orthostatic hypotension; AD, autonomic dysreflexia; APR, acute periode of rehabilitation. Adapted from: [Krassioukov, 2012] [ASIA, 2013a].

Level of injury	**Potential cardiovascular outcomes after SCI**
cervical	Loss of SSC of the heart and blood vessels
	Intact parasympathetic (vagal) control of the heart
	Low heart rate and resting blood pressure
	Prone to OH and AD
high-thoracic (T5 or above)	Similar to cervical lesions
	Loss of SSC to the major splanchnic vascular bed
	Prone to OH and AD
low-thoracic (T6 to T12)	Preserved SSC and vagal control of the heart
	Loss of SSC of the blood vessels below SCI level
	Less pronounced cardiovascular dysfunctions
lumbar (L1 and below)	Loss of only a small portion of SSC
	Intact autonomic control of the heart
	Normal resting blood pressure
	No episodes of AD
	OH mostly in APR due to deconditioning

the development of significant cardiovascular dysfunctions in individuals with SCI.

The level-dependent cardiovascular dysfunction coincides with loss of physical efficiency due to cardiovascular deconditioning and the limited ability to participate in exercise cause abnormal cardiovascular control compared with healthy able-bodied individuals.

West et al. conducted a meta-analysis to examine the effect of injury level on cardiovascular parameters in individuals with SCI, both, in the supine and seated position. They compared systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) between four groups, which were classified according to the level of injury: cervical (C) SCI (C4-C8), high-thoracic (HT) SCI (T1-T6), low-thoracic lumbar (LTL) SCI (below T6) and able-bodied (AB) controls.
The meta-analysis included 98 studies which provided data from 1968 individuals. Following participants inclusion criteria were applied: participants aged 16 years and over with chronic (> six weeks) SCI in stable medical condition as well as able-bodied (AB) individuals as controls. Participants with congenital SCI (see section 1.3.2), lower motor neuron injury, medically unstable cardiovascular outcome or during medical treatment known to affect the sympathetic nervous system were excluded.

The results of the meta-analysis are presented below in table 6. When looking at the results in supine position, it can be noted that all three cardiovascular parameters (SBP,

DBP and HR) were significantly lower in C compared to HT, LTL and AB ($p<0.05$). No significant differences were found in any of the three cardiovascular parameters between the groups HT, LTL and AB.
This is contrary to the assumption that, due to the loss of sympathetic control of the splanchnic bed, individuals with HT show also a significant lower SBP compared to LTL and AB. Since this was not the case, West et al believe that this can be explained by the relative small number of studies with a large between-study variance in the HT group. Since only two studies have examined the seated cardiovascular parameters in HT, this group is not used in the comparison. However, West et al. found that in seated position SBP and DBP were significantly lower in C than in the groups LTL and AB ($p<0.05$). A 15 mmHg lower SBP in individuals with C SCI was revealed in the seated compared with supine position. Due to baroreceptor induced sympathetically mediated vasoconstriction, blood pressure is maintained in individuals with LTL SCI and in the AB population during seated position.
A difference in heart rate was observed only between C and LTL.
Comparing the cardiovascular variables from the supine position with those from the seated position for all levels of injury, it is apparent that in the seated position SBP is significantly lower only in C ($p<0.0001$). No further relevant differences between the supine and seated cardiovascular parameters were observed for any dependent variable or group [West et al., 2012].

In summary, it can be seen, that impairment in resting cardiovascular parameters can be made dependent on the level of the lesion, whereby the higher the injury, the greater the extent of the cardiovascular dysfunction. That individuals with a C injury experience a significant lower resting blood pressure in seated position than in supine is of prime clinical importance, as it may result in symptoms characteristic of orthostatic hypotension [West et al., 2012].
In an article from 2001 Groah et al. shows the relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. They performed a historical prospective study that included finally 545 individuals, who survived at least 20 years with SCI. Those were categorized, based on the level of injury and ASIA Impairment Scale, into Tetra ABC, Para ABC and All D. The outcomes of CVD were obtained through medical record review and were classified into All CVD, coronary heart disease (CHD), hypertension, cerebrovascular disease (cerebrovascular accident and transient ischemic attack), dysrhythmia, valvular disease and "other CVD". CHD comprise myocardial infarction (MI), angina and coronary atherosclerosis. "Other CVD" referred to individuals with diagnosis of cardiomegaly, congestive heart failure, thrombophlebitis, endocarditis, deep venous thrombosis and venous insufficiency (VI) [Groah et al., 2001].

Table 6: Comparison between supine and seated cardiovascular parameters dependent on the level of injury: cervical (C), high-thoracic (HT), low-thoracic lumbar (LTL) and able-bodied (AB) controls. The values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) are indicated in mmHg, mean values and in brackets the confidence intervall. Heart rate (HR) is indicated in beats per minute (bpm). Adapted from: [West et al., 2012].

(a) Systolic blood pressure (SBP)

	Supine	Sitting
C	110 (107, 113)	96 (92, 99)
	31 Studies, n=345	11 Studies, n=124
HT	120 (114, 127)	100 (87, 112)
	6 Studies, n=86	2 Studies, n =16
LTL	122 (119, 126)	124 (121, 128)
	18 Studies, n=207	12 Studies, n=133
AB	121 (118, 124)	124 (120, 127)
	25 Studies, n=311	9 Studies, n=127)

(b) Diastolic blood pressure (DBP)

	Supine	Sitting
C	66 (63, 68)	64 (61, 67)
	27 Studies, n=284	11 Studies, n=124
HT	74 (68, 80)	64 (54, 74)
	6 Studies, n=86	2 Studies, n =16
LTL	71 (68, 75)	77 (74, 81)
	15 Studies, n=158	12 Studies, n=129
AB	72 (69, 75)	77 (73, 81)
	21 Studies, n=246	8 Studies, n=119

(c) Heart rate (HR)

	Supine	Sitting
C	64 (62, 67)	68 (65, 71)
	31 Studies, n=336	18 Studies, n=192
HT	71 (65, 78)	73 (63, 83)
	5 Studies, n=81	2 Studies, n =21
LTL	72 (69, 76)	76 (73, 78)
	11 Studies, n=131	18 Studies, n=195
AB	69 (66, 71)	69 (66, 73)
	27 Studies, n=294	15 Studies, n=181)

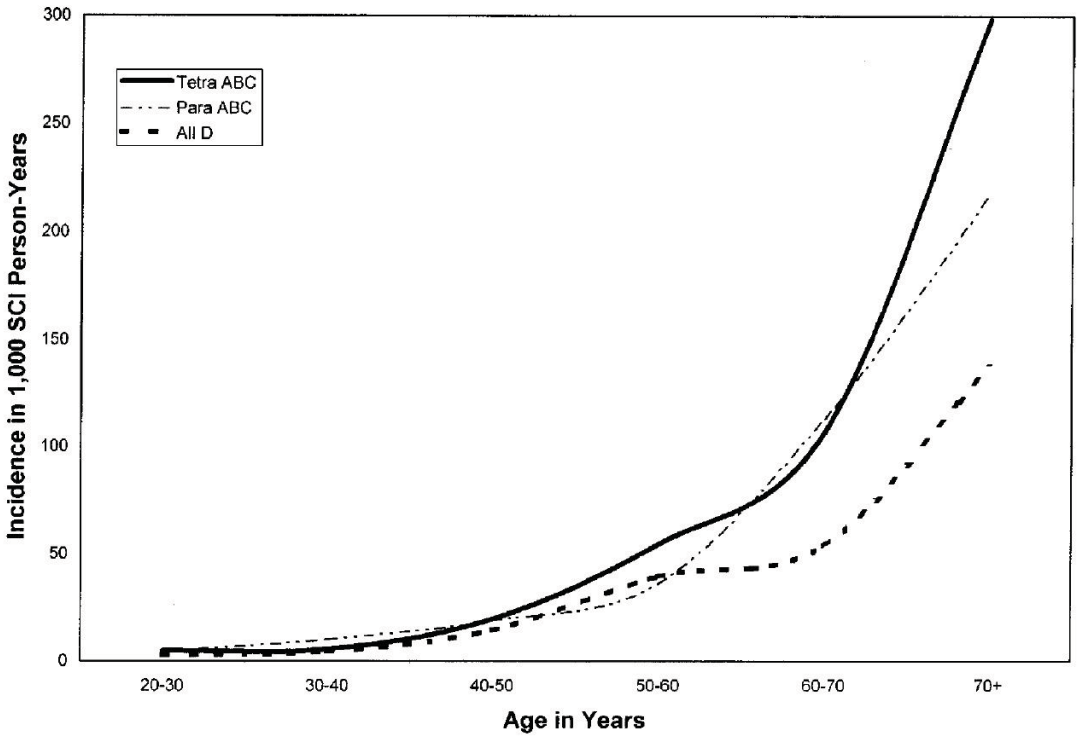


Figure 12: Incidence density of CVD by 10 year age group and neurologic category. Taken from: [Groah et al., 2001]

Groah et al. were thereby able to verify a positive correlation between the risk of CVD and age in all of the neurologic groups (Tetra ABC, Para ABC, All D), regarding to this see figure 12 [Groah et al., 2001].
24% of all CVD events were attributed to CHD, followed closely by hypertension with 21%. The table 7 below shows the distribution of all CVD events in individuals surviving at least 20 years with SCI [Groah et al., 2001].
The comparison between tetraplegics and paraplegics revealed that tetraplegic level bear a 16% higher age-adjusted risk of All CVD and a fivefold risk of cerebrovascular disease

Table 7: Distribution of all CVD events in individuals surviving at least 20 years with SCI. Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; VI, venous insufficiency (VI). Adapted from: [Groah et al., 2001]

Events of CVD	**Rate expressed as a percentage**
CHD	24
Hypertension	21
Dysrhythmias	16
Peripheral vascular disease	15
Congetive heart failure	8
Valvular diesease	2
Atrial fibrillation	2
Cardiomegaly, endocarditis, VI	~ 5

than paraplegic level. Another finding of the study was the fact that the higher the level of injury, the more cerebrovascular disease, dysrhythmia and valvular disease could be determined. In complete contrast to this are the diagnosis CHD, MI and hypertension, with an inverse association to the level of the injury. To quote one example, tetraplegics experienced 70% less CHD compared to paraplegics. A possible reason for such less CHD events in tetraplegics compared to paraplegics is due to a diagnostic bias, since individuals with SCI above T4 may not notice cardiac pain. Cardiac pain fibers travel with sympathetic afferent fibers and as a consequence of SCI both are affected in their function. However, hypotension in individuals with high-level injuries is frequently observed, as presented in section 4.3.2. Hence, Groah et al. noted that tetraplegics may be protected from CHD due to lack of hypertension.
They also found that severity of injury impacts the age-adjusted risk of CVD in individuals with SCI. A more complete SCI conferred greater risks of All CVD (44% higher risk), coronary atherosclerosis (43% higher risk) and dysrhythmia (two and half fold risk) [Groah et al., 2001].

As already mentioned in section 1.3.2, cardiovascular complications are increasingly becoming the leading cause of mortality in individuals with SCI [West et al., 2013], inter alia because of the fact that they survive to older ages [Groah et al., 2001] [West

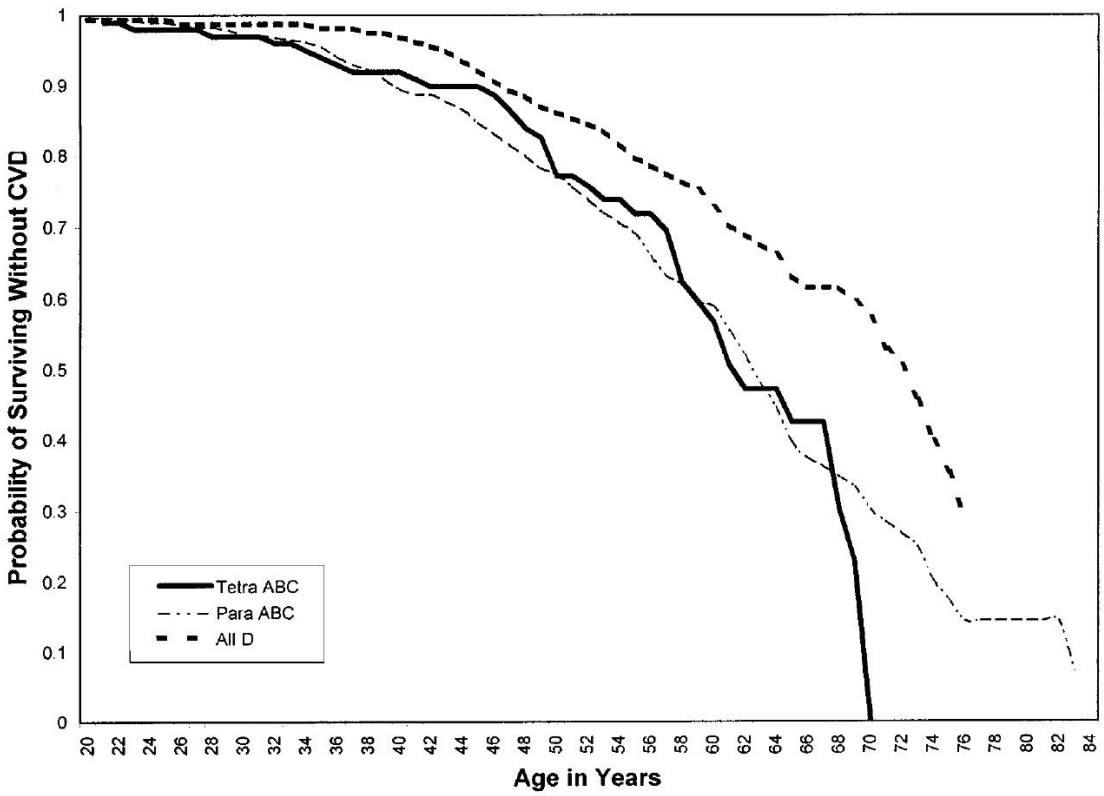


Figure 13: Probability of surviving without cardiovascular diesease (CVD) by age and neurologic group. Taken from: [Groah et al., 2001]

et al., 2013], although SCI individuals (SCII) have a significantly lower life expectancy compared to those with no SCI [National Spinal Cord Injury Statistical Center, 2013].

In this context, Groah et al. presented a survival analysis for CVD by age and neurologic category. As can be seen in figure 13, the All D group is more likely to survive without CVD than the groups Tetra ABC and Para ABC. This suggests that individuals with SCI are in need of a more intense surveillance for CVD and thus prevent secondary complications as well as mortality [Groah et al., 2001].

4.3 Cardiovascular complications depending on the period of time

Table 8: Overview of common cardiovascular complications following SCI during acute and chronic phase. Abbreviations: MI, myocardial infarction; ECG, electrocardiography; CV, cardiovascular. Adapted from: [Furlan and Fehlings, 2008] [Grigorean et al., 2009] [Popa et al., 2010] [Hagen et al., 2012a].

Acute phase
Neurogenic shock
Vasodilation and venous stasis
Deep vein thrombosis
Thromboembolism
Both, acute and chronic phase
Orthostatic hypotension
Cardiac dysrythmias
Cardiovascular deconditioning
Chronic phase
Autonomic dysreflexia
Impaired perception of chest pain →
Impaired transmission of cardiac pain (lesions above T4)
Loss of muscle mass in left ventricle
Pseudo-MI: Troponin ↑ with or without ECG changes without CV cause
Coronary heart disease
Systemic atherosclerosis

Table (table 8) offers an overview of possible cardiovascular complications divided into acute, both (acute and chronic) and chronic phase.
Acute phase means four to five weeks after SCI [Krassioukov et al., 2003] [Hagen et al., 2012a] [Furlan and Fehlings, 2008].
In the following I will focus on some selected, frequently cardiovascular complications, SCI individuals (SCII) are prone to.

4.3.1 Neurogenic shock

The first three to four minutes after a spinal cord injury, particularly injury to the cervical spinal cord, are characterized by a massive stimulation by the sympathetic nervous system and reflex activity of the parasympathetic nervous system [Grigorean et al., 2009] [Popa et al., 2010].
This can be attributed to release of norepinephrine from the adrenal glands on the one hand and hyperresponsiveness of α-adrenoreceptors on the other. This leads to a brief hypertensive peak and reflex bradycardia with escape arrhythmias [Gondim et al., 2004].
This initial phase of SCI is followed by a massive loss of activity of the sympathetic nervous system [Grigorean et al., 2009] [Popa et al., 2010]. Hence, spinal shock (see section 1.3.4) occurs below the spinal cord injury [Apparelyzed, 2013] [Krassioukov, 2009]. Autonomic nervous system malfunction or, to be more exact, lack of sympathetic activity despite intact parasympathetic activity, gives rise to neurogenic shock [Gondim et al., 2004].
Neurogenic shock is characterized by the sudden sympathetic decentralization following severe high SCI that implicates an abrupt relaxation of the smooth muscles in blood vessels. This manifests itself in vasodilatation and decreased blood pressure [Hagen et al., 2012a] [ASIA, 2013a]. The unopposed vagal activity results in bradycardia [Hagen et al., 2012a].
In this context, it should be considered that the vagus nerve is hypersensitive for about two to three weeks after SCI and bradycardia can be exacerbated by hypoxia and oral/nasal intubation. Individuals of severe high, complete injuries may suffer from this their whole life. The hypersensitivity of the vagal nerve in lower and/or incomplete spinal cord injured individuals usually recovers within four to five weeks [Hagen et al., 2012a].
But now back on the main subject of this section: neurogenic shock is characterized by severe arterial hypotension (resting systolic blood pressure below 90 mmHg) [Grigorean et al., 2009] [Popa et al., 2010] and bradycardia (mean heart rate for at least one day below 60 beats per minute) [Teasell et al., 2000].

As shown in figure 14, adapted from the paper "Descending Vasomotor Pathways in Humans: Correlation between Axonal Preservation and Cardiovascular Dysfunction after Spinal Cord Injury" published by the Journal of Neurotrauma in 2003, there are significant differences between individuals with severe and no/minor cardiovascular dysfunctions relating to (A) heart rate, (B) systolic and (C) diastolic blood pressures. Over a period of about 30 days (see figure 14), individuals with severe cardiac dysfunctions show in all three observed parameters (heart rate, systolic and diastolic blood pressures)

clearly lower values than in individuals with no/minor cardiac dysfunctions. As can be seen in figure 14 part B, systolic blood pressure is always above 90 mmHg, contrary to the definition of neurogenic shock. This is due to the fact that during the acute stage of SCI all patients received vasopressive therapy in order to maintain systolic blood pressure over 90 mmHg [Furlan et al., 2003].

Neurogenic shock requires commonly the application of vasopressor agents, as it represents a life-threatening cardiovascular complication in spinal cord injured individuals [Krassioukov, 2009] [Krassioukov, 2012] with cervical and high thoracic injury. Neurogenic shock doesn't occur in low thoracic injuries [Grigorean et al., 2009]. This can be explained by the fact that the sympathetic innervation to the heart as well as the blood vessels of the chest and upper extremity originate from the spinal sympathetic preganglionic neurons (SPNs) of the cord segments T1-T5 (high thoracic) [Krassioukov, 2009]. It is also worth noting that the timing of surgical decompression of the spinal cord after a traumatic injury plays an important role in the development of cardiovascular dysfunctions. Several studies have shown that a delay in the timing of surgical intervention correlates with the presence of neurogenic shock and delayed motor and sensory recovery. Further research is needed in order to clarify the possible impact of the timing of surgical intervention on the presence of hemodynamic instability [Popa et al., 2010].

4.3.2 Orthostatic hypotension

Definition of Orthostatic Hypotension? A decrease in systolic blood pressure of $\geq$ 20 mmHg or a decrease in diastolic blood pressure of $\geq$ 10 mmHg accompanied by orthostatic maneuvers as upright posture (standing, sitting) or head-up tilt of at least 60 degrees, regardless of whether symptoms occur or not are referred to as orthostatic hypotension [Popa et al., 2010] [Krassioukov, 2009] [Furlan and Fehlings, 2008] [Con, 1996].

The severity of OH is evaluated by performing a tilt test. In this case, the person is moved passively from a supine into an upright position. The individual is supported either by a footplate or a harness, as leg movements should be avoided. The individual is encouraged to remain as still as possible to avoid postural muscle movements [Claydon et al., 2006b].

Who suffers from OH? Whether a spinal cord injured person suffers from OH or not is determined by the level and severity of the injury. It is hardly surprising that OH occurs mainly following cervical and high-thoracic SCI [Popa et al., 2010] [Furlan and Fehlings, 2008] [Krassioukov, 2009] [Claydon et al., 2006b] [Sidorov et al., 2008] [West et al., 2012]. Compared to paraplegics, OH is increasingly present in tetraplegic indi-

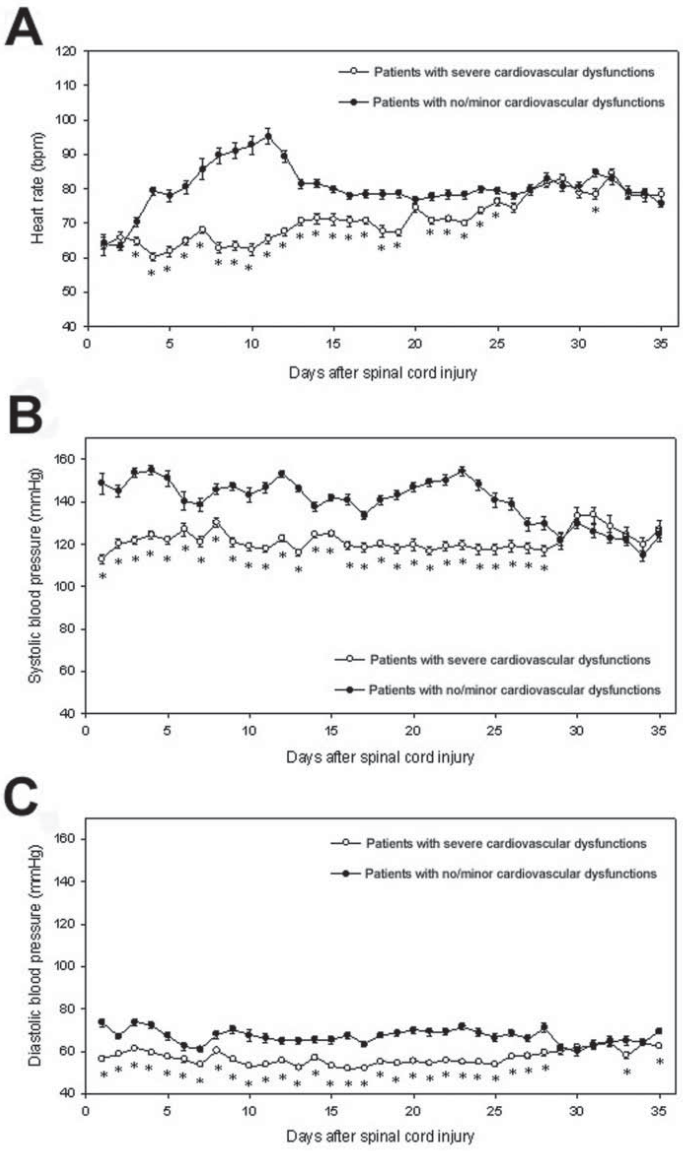


Figure 14: Neurogenic shock and associated hemodynamic parameters following acute traumatic cervical SCI in two groups of patients during a 5-weeks post-injury period. (A) heart rate, (B) systolic and (C) diastolic blood pressures. Abbreviation: Bpm, beats per minute. Adapted from: [Furlan et al., 2003].

viduals, who experience a greater blood pressure decrease induced by postural change, irrespective of whether the lesion was complete or incomplete [Sahota et al., 2012] [Claydon et al., 2006b] [Popa et al., 2010]. However, individuals with complete SCI are more prone to OH than those with incomplete SCI [Sahota et al., 2012] [Sidorov et al., 2008]. Furthermore, the risk of developing OH is higher after traumatic SCI than after non-traumatic SCI [Claydon et al., 2006b].

It is reported that, during orthostatic maneuvers performed during physiotherapy and mobilization, orthostatic hypotension is found in 74% of SCI individuals (SCII), even though only 59% of them experienced any symptoms and signs [Furlan and Fehlings, 2008] [Popa et al., 2010] [Krassioukov, 2009].

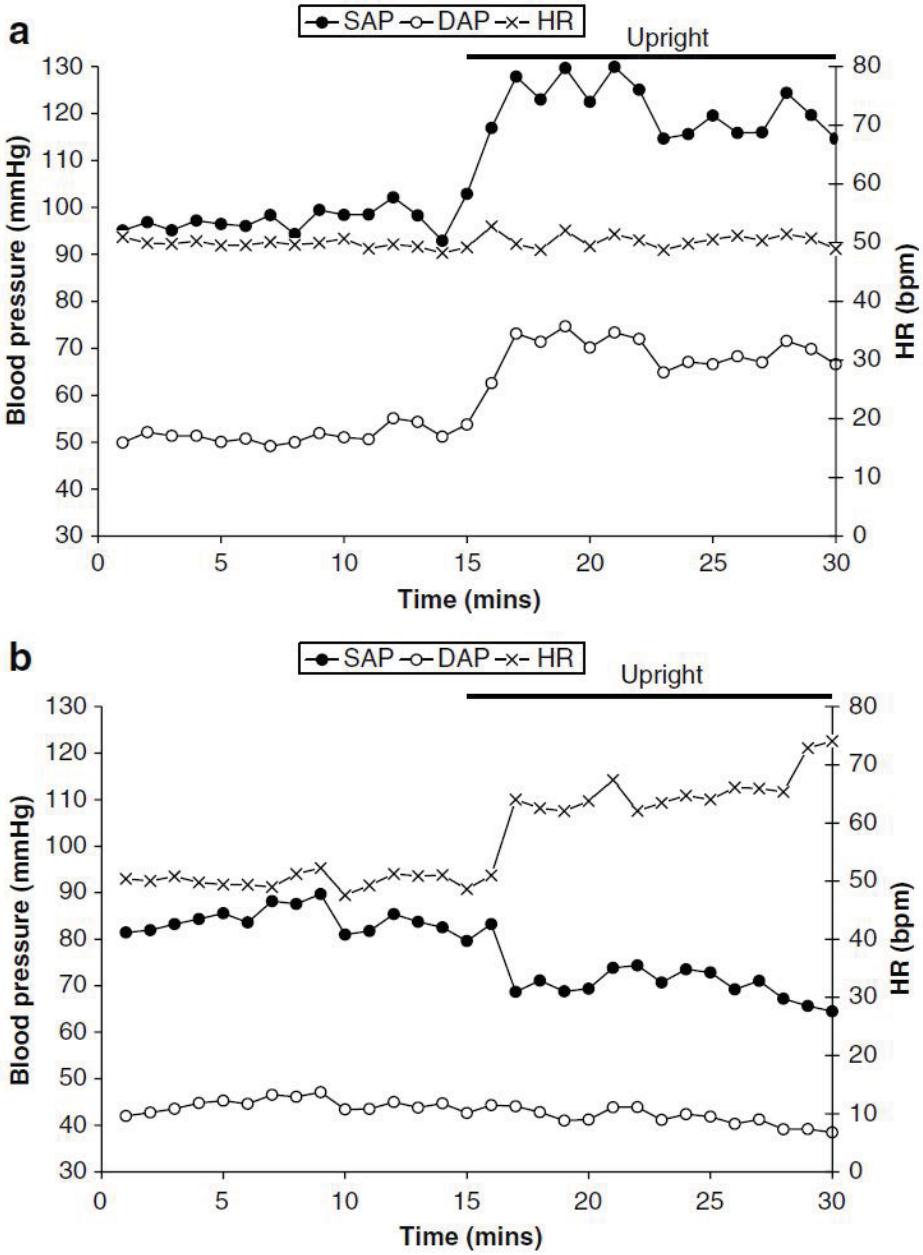


Figure 15: Orthostatic stress and associated blood pressure and heart rate responses in a healthy male control subject (a) and a man with chronic cervical SCI (b). Abbreviations: SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; bpm, beats per minute. Adapted from: [Claydon et al., 2006b].

Figure 15 compares the blood pressure and heart rate responses to orthostatic stress in a healthy male control subject (a) and a man with chronic cervical SCI (C5, ASIA B) with complete destruction of descending autonomic pathways (b).
Compared with the control subject, one conspicuous difference is that the SCI individual shows lower resting systolic (SAP) and diastolic (DAP) arterial pressure as well as heart rate (HR). The assumption of a passive upright seated position is indicated by the solid black line (at about 15 minutes). As can be seen, the control subject experienced a

Table 9: Common symptoms and signs of orthostatic hypotension. Adapted drom: [Con, 1996] [Popa et al., 2010] [Krassioukov, 2009] [Furlan and Fehlings, 2008] [Teasell et al., 2000].

Light-headedness
Dizziness
Feeling of faintness
Pallor
Fatigue or weakness
Ringing ears
Headache
Neck ache
Blurred vision
Dyspnea
Restlessness
Tremulousness
Nausea
Cognitive impairment (trouble focusing, thinking, reacting)
Heart palpitations (irregular heart beat)
Tachycardia
Loss of consciousness

significant increase in SAP and DAP with only very moderate change in heart rate following the orthostatic maneuver, due to intact autonomic cardiovascular control. Quite the contrary, the blood pressure, both SAP and DAP, of the SCI man decreases following the assumption of passive seated position as is characteristic of orthostatic hypotension. This is associated with a postural tachycardia of approximately 25 beats per minute (bpm) [Claydon et al., 2006b].

When does OH happen? Although OH occurs particularly in the acute phase following SCI, it also can continue beyond years after an injury [Furlan and Fehlings, 2008] [Claydon et al., 2006b]. Either the incidence and severity of OH diminishes [Popa et al., 2010] or, unfavorable, becomes worth in the course of time [Claydon et al., 2006b].

What causes OH? The definition, as previously said, anticipates that OH is caused by orthostatic maneuvers, such as the assumption of an upright posture from a supine position. Nevertheless, following precipitating factors should be taken into consideration at the moment of diagnosis: state of hydration, food ingestion, ambient temperature, time of day, recent recumbency, hypertension, postural deconditioning, medications, gender and age [Con, 1996].

Pathophysiology of orthostatic hypotension The exact mechanisms which are responsible for the development of orthostatic hypotension are not entirely clarified [Claydon et al., 2006b], but are likely to be multifactorial [Claydon et al., 2006b] [Claydon

Table 10: Orthostatic hypotension and predisposing physiological factors in SCI individuals. Adapted from: [Popa et al., 2010] [Claydon et al., 2006b].

(1) Impaired function of baroreceptors
(2) Lack of skeletal muscle pumping activity
(3) Cardiovascular deconditioning
(4) Altered salt and water balance
(5) Renin-angiotensin-aldosterone activity

and Krassioukov, 2006]. However, following factors predispose to orthostatic intolerance, as summarized in table 10.

First of all, I would like to refer to the catecholamines associated with orthostatic hypotension. As figure 16 reveals, supine catecholamine plasma levels, particularly noradrenaline, are low following cervical SCI, as compared with able-bodied individuals [Popa et al., 2010] [Claydon and Krassioukov, 2006] [Claydon et al., 2006b].
After the passive assumption of an upright seated position (90 degree), the plasma adrenaline in controls showed only a moderate increase. However, this could not be demonstrated in SCI individuals (SCII). In contrast to this, there was a marked increase of NA levels in the controls, attributed to the activation of autonomic circuits responsible for orthostatic stability in controls. As descending control is severely disrupted in individuals who sustained a cervical SCI, no change of NA levels in those occurred in response to orthostatic stress.
To summarize, during both, supine and upright position, NA levels were significantly lower in SCII than in able-bodied controls [Claydon et al., 2006b].

This is consistent with a study by Claydon and Krassioukov published in 2006 showing that supine NA levels were significantly lower in individuals with cervical SCI compared to individuals with thoracic SCI and able-bodied controls. They were thereby able to show that plasma NA levels increased in response to orthostatic challenge in thoracic SCI and in controls, with no change in cervical SCI [Claydon and Krassioukov, 2006].

As mentioned previously (see section 1.1.3), (1) baroreceptors occupy an important role in the short-term regulation of blood pressure.
If blood pressure increases, the baroreflex ensures an increased vagal tone and inhibition in the sympathetic nervous system. That results in decreased vascular tone, venous return, cardiac contractility and heart rate, whereas the opposite is true for reductions in blood pressure [Phillips et al., 2012].
It has become evident that baroreceptor responses are particularly impaired in patients with high-level, cervical and high-thoracic, injuries [Popa et al., 2010]. However, impair-

ment of baroreceptor control cannot be limited to individuals with high-level injuries only [Phillips et al., 2012] [Popa et al., 2010] [Claydon et al., 2006b], although baroreflex dysfunctions in individuals with low-level injuries are not as severe as in those with high-level lesions. This can be explained by the fact that individuals with low-level injuries can exert more physical activity as well as partially sympathetic vasomotor tone is preserved [Phillips et al., 2012].

It was found that baroreflex function was abnormal in individuals with lesions at T3 or above during orthostatic stress. Furthermore, in individuals with high-level lesions, the circadian blood pressure control is abolished, which emphasizes the baroreflex dysfunctions [Popa et al., 2010] [Claydon et al., 2006b].

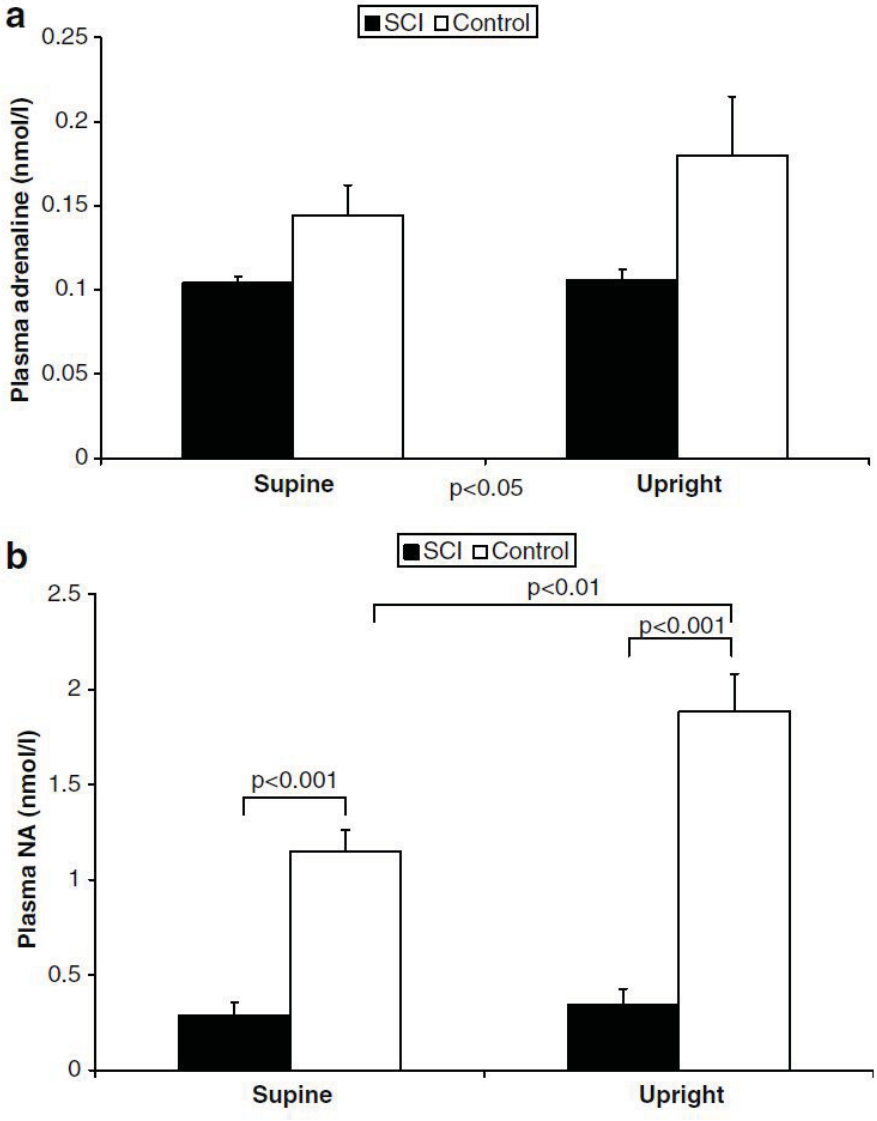


Figure 16: Plasma catecholamine levels, adrenaline (a) and noradrenaline (b), during an orthostatic challenge in control volunteers (n=7) and individuals with cervical SCI (n=7). Adapted from: [Claydon et al., 2006b].

Another factor which may predispose to orthostatic hypotension in SCI is the lack of skeletal muscle pumps during postural challenge (2). In able-bodied individuals, the skeletal muscle pumping effect during standing position leads to compressing of the veins and thus increasing the blood flow to the heart. This important mechanism in maintaining venous return in orthostatism lacks the SCII due to paralyzed limbs. Hence, stroke volume, cardiac output and blood pressure are lowered . Some investigations resulted in the fact that functional electric stimulation (FES) of the skeletal leg muscles during orthostatic maneuver prevents orthostatic hypotension in individuals with SCI [Claydon et al., 2006b].

Prolonged bed rest or exposure to microgravity lead to a number of physiological disorders that are summarized under the term cardiovascular deconditioning (3). Cardiovascular deconditioning is marked by profound orthostatic intolerance characterized by postural tachycardia and postural hypotension. It is supposed, that it is mediated via a diminished blood volume, decreased muscle or tissue pressure in the extremities because of reduced muscle mass or alterations in the sympathetic nervous system [Popa et al., 2010] [Claydon et al., 2006b] [Grigorean et al., 2009].

Vaziri from California found out due to a study that microgravity-adapted animals experience elevation of nitric oxide (NO) production in the kidney, heart, brain, and systemic arteries. Those findings were coupled with a significant decrease of NO production in the cerebral arteries. In addition, this study shows that cardiovascular deconditioning can be attributed primarily to the observed alteration of NO metabolism [Vaziri, 2003]. Since NO acts on the vascular smooth muscles to produce vasodilatation and it is also known as an endothelium-derived relaxing factor [Claydon et al., 2006b], alteration of NO metabolism induces peripheral vasodilatation and cerebral vasoconstriction . Drop in blood pressure and cerebral hypoperfusion are the consequences, both worsen orthostatic hypotension [Popa et al., 2010] [Claydon et al., 2006b] [Grigorean et al., 2009]. Orthostatic intolerance, due to combined effects of disruption of efferent sympathetic pathways and cardiovascular deconditioning following prolonged bed rest, complicates and delays recovery from acute SCI [Vaziri, 2003] [West et al., 2012]. It is not considered likely that cardiovascular deconditioning is responsible for orthostatic hypotension in chronic SCI, due to mobilization of individuals following SCI [Popa et al., 2010] [Claydon et al., 2006b] [Grigorean et al., 2009].

Another factor which may contribute to orthostatic intolerance is the salt depletion and the low plasma volume in SCII (4). Hyponatremia occurs commonly in acute and chronic SCII. Hyponatremie can be caused secondarily by increased ADH secretion with high sodium excretion, impaired sodium retention as well as by limited salt intake. In addition, limited water intake and the use of diuretics lead to low plasma volume. The combination of above mentioned factors would exacerbate episodes of orthostatic hypotension [Popa et al., 2010] [Claydon et al., 2006b].

The renin-angiotensin-aldosterone system (RAAS) represents a powerful mechanism for the maintenance of blood pressure (5) [Guyton and Hall, 2010, p.220], as indicated in section 1.1.4. The effects of angiotensin II, aldosterone and ADH on the blood pressure regulation are listed in table 2. Common to all of them however is the fact, that they cause a rise in blood pressure.
The plasmatic renin activity in individuals with SCI is higher than in able-bodied individuals. Furthermore, the renin levels rise rapidly and much higher following orthostatic posture or head-up tilt, independently of sympathetic nervous activity [Popa et al., 2010].

Common symptoms and signs of OH OH may be symptomatic (see table 9) and run in 41% of cases, asymptomatic, even though spinal cord injured individuals experience a marked decrease in arterial blood pressure [Popa et al., 2010] [Krassioukov, 2009] [Con, 1996].
It can be presumed that blurred vision, light-headedness, dizziness, fatigue, restlessness and dyspnea are caused by cerebral hypoperfusion occurring secondary to orthostatic drop in blood pressure [Furlan and Fehlings, 2008] [Sahota et al., 2012]. The symptoms of OH result in a significant deterioration in the quality of life and complicate participation in rehabilitation, work, exercise and other activities of daily living [Sahota et al., 2012] [Popa et al., 2010] [Claydon and Krassioukov, 2006].

Management and treatment of OH As summarized in table 11, there are pharmacological and non-pharmacological intervention strategies for the treatment of OH, whereas nonpharmacological interventions should be used as first-line therapy.
It may be pointed out only additionally that diuretics (alcohol and caffeine) and vasodilator stresses (heat stress and alcohol) must be avoided. The patient should be encouraged to take regular small meals to prevent postprandial hypotension. Desmopressin acetate and erythropoietin serve as supplementary medications in patients with more refractory symptoms.
But, whatever the case is, providing patient education about orthostatic hypotension, particularly of its precipitating factors and symptoms, will be the key step in the management of OH [Popa et al., 2010] [Claydon et al., 2006b].

4.3.3 Cardiac dysrhythmias

Some cardiac arrhythmias are life-threatening and may result in cardiac arrest. Although cardiac arrhythmias occur both in the acute phase and in the chronic phase, the risk of contracting cardiac arrhythmias or dying on it is much higher in the acute phase during the first few weeks. Nevertheless, cardiac dysrhythmias occurring in the

Table 11: Management of orthostatic hypotension. Adapted from: [Popa et al., 2010] [Claydon et al., 2006b]

Intervention → **Rationale**
Nonpharmacological management
Advice and avoidance of precipitating factors
→ Decreases noxious stimuli
Increased salt and fluid intake
→ Maintain plasma volume
Abdominal compression bandages and/or support stockings
→ Restricts venous pooling in the splanchnic region and limbs
Sleeping with the head of the bed elevated 15-20°
→ Increases plasma volume and orthostatic tolerance
Tilt training
→ Increase upright stance
Pharmacological management
Fludrocortisone
→ Expansion of plasma volume
Midodrine (*alpha*-adrenergic agonist)
→ Increases the peripheral vasoconstriction
Desmopressin acetate and erythropoetin
→ Expansion of plasma volume

acute phase can improve over time [Grigorean et al., 2009] [Furlan and Fehlings, 2008]. Bradyarrhythmias are the most occurring cardiac dysrhythmia in individuals following SCI [Furlan and Fehlings, 2008]. Nevertheless, tachyarrhythmias, as listed in table 12, have been found in SCII as well [Grigorean et al., 2009].

Bradyarrhythmias have a peak in frequency on the fourth day after injury [Grigorean et al., 2009] to a degree determined by the level and completeness of the spinal lesion [Furlan and Fehlings, 2008] [Furlan et al., 2003]. Bradyarrhythmias are more common in tetraplegics than in paraplegics [Furlan and Fehlings, 2008] [Grigorean et al., 2009] [Furlan et al., 2003], due to the fact that in individuals with injuries at the thoracic spinal cord a more balanced cardiac control is guaranteed, since the upper thoracic sympathetic neurons and the parasympathetic nervous system (vagus nerve) remain intact [Krassioukov, 2009]. Late asystole was found during the chronic phase in high cervical spinal cord injured individuals [Grigorean et al., 2009].

Above all, sinus bradycardia, defined by a heart rate of <60 beats per minute [Grigorean et al., 2009], is among the most occurring cardiac dysrhythmia in individuals with SCI in the acute phase at all. An example of sinus bradycardia is shown in figure 17, which

Table 12: Overview of possible cardiac dysrhythmias in SCI individuals, classified by rate. Adapted from: [Grigorean et al., 2009].

Bradyarrhythmias
Bradycardia
Asystolia, cardiac arrest
Tachyarrhythmias
Paroxysmal supraventricular tachycardia
Sinus tachycardia
Atria flutter
Atria fibrillation

represents ECG recordings on the first and fifth day after the accident [Furlan and Fehlings, 2008]. As can be taken from the cited paper, bradycardia can be divided into the following degrees of severity. A *mild bradycardia* occurs when the patient is asymptomatic and his arterial blood pressure maintains >90 mmHg without medication. A *moderate bradycardia* needs medical intervention in contrast, with a view to increase the heart rate and maintain an appropriate blood pressure. *Severe bradycardia* refers to asystolia [Grigorean et al., 2009].

Figure 17 presents that SCI can also cause non-specific ECG alterations. Inverted T waves, as marked by gray arrows, provides an example therefore, whereas other electrocardiographic findings like ST segment elevation, intraventricular conduction delay, bundle-branch block, repolarization changes and ventricular tachycardia have also been found [Grigorean et al., 2009] [Furlan and Fehlings, 2008].

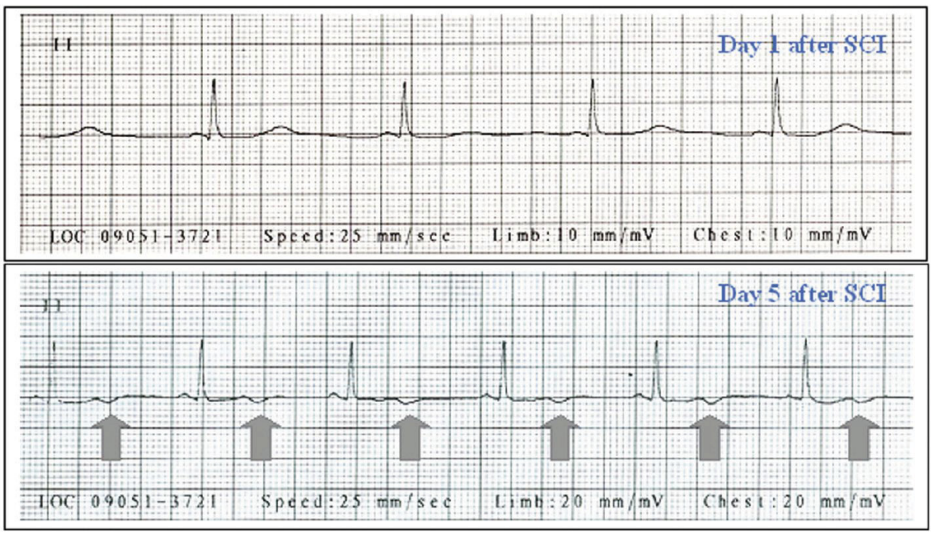


Figure 17: Sinus bradycardia and inverted T waves (gray arrows) in the acute phase following SCI. ECG recordings, leads II, at day 1 and 5 after accident. Taken from: [Furlan and Fehlings, 2008].

The pathophysiological background, which explains the development of bradycardia after SCI, has been discussed already in section "Neurogenic shock" 4.3.1. To put it briefly, mainly acute cervical injured individuals tend to hemodynamic instability, induced by hypotension and still intact parasympathetic outflow via vagus nerve [Grigorean et al., 2009].

In this section I would like to address the heart rate variability (HRV). The heart responds continuously to signals of the organism and the environment with finely tuned changes of the heartbeat period and heart rate. In this respect, the rhythm of the heartbeat is variable and not rigid. It is constantly changing and is determined by a variety of endogenous and exogenous factors. An optimal interaction of the sympathetic and parasympathetic nervous system is a precondition for the adaptability of the heart. Insofar the heart rate variability (HRV) can be regarded as a representation of the autonomic nervous system [Grigorean et al., 2009]. As already indicated in table 1, the sympathetic portion exerts an activating influence on the sinoatrial (SA) node, within the meaning of an increase in heart rate (positive chronotrop). The contrary is true for the parasympathetic portion (negative chronotrop).
Each person has an individual expression of heart rate variability, which decreases with increasing age. During a state of relaxation, the heart beats more variable than in the stressed condition. Studies could also show that physical activity influences the HRV. The variability increases with improved physical fitness.
Since, as just mentioned, the HRV has its origin in the function of the autonomic nervous system, thus, diseases can be identified which exert effects on heart rate [Julien, 2006]. The analysis of HRV can be used to measure quantitatively the varying influence of the two autonomic pathways on the cardiovascular system [Rimaud et al., 2012]. Some studies on HRV in SCII have already been carried out by means of autoregressive power spectral analysis.

The investigations revealed the existence of two major spectral components, low (0,05-0,15 Hz) and high (0,15-0,40 Hz) frequency, in healthy able-bodied individuals. Investigations using pharmacological blockade showed that vagal activity have influence on both components, low (LF) and high (HF) frequency, of HRV during supine and upright posture while sympathetic activity influences only the low frequency component during upright posture with little effect on heart rate at rest. In the majority of tetraplegic individuals only the HF component could be detected using the spectral analysis. Hence, the LF/HF ratio, representing the sympatho-vagal balance, was larger in tetraplegics individuals compared with the able-bodied ones. Those results can be attributed to the loss of sympathetic tone and intact parasympathetic tone in individuals with high SCI [Grigorean et al., 2009] [Furlan and Fehlings, 2008] [Popa et al., 2010].

Table 13: Severity grades of autonomic dysreflexia. Adapted from: [Popa et al., 2010].

	Severity grade	Increase in blood pressure
1.	mild/partial	$<$ 40 mmHg
2.	moderate	$>$ 40 mmHg, but systolic blood pressure is $<$ 180 mmHg
3.	severe	$>$ 180 mmHg

4.3.4 Autonomic dysreflexia

Definition of Autonomic Dysreflexia? The term "autonomic dysreflexia" (AD) refers to a condition characterized by a sudden increase in blood pressure accompanied by other signs and/or symptoms (see table 15) in response to a stimulus below the level of injury.

The systolic blood pressure value can be up to 300 mmHg [Hagen et al., 2012a] [Krassioukov, 2009] [Furlan and Fehlings, 2008]. Diastolic blood pressure values between 200 and 220 mmHg have been monitored as well [Hagen et al., 2012a].
It should not be forgotten that, due to the decentralization of the SNS, resting systolic and diastolic blood pressure in high-level injured individuals is lower than in able-bodied individuals [Furlan and Fehlings, 2008]. The resting systolic blood pressure is about 15-20 mmHg lower (on average 90 to 110 mmH) [Krassioukov et al., 2003] [Krassioukov, 2012]. Hence, a sudden increase in systolic blood pressure of 20 to 40 mmHg or, in other words, at least 20% above baseline associated with changes in heart rate and accompanied by at least one proper clinical symptom and/or sign as listed in table 15 can be regarded as an episode of autonomic dysreflexia [Krassioukov, 2012] [Furlan and Fehlings, 2008] and poses a life threatening situation to the patient [Gondim et al., 2004] [Krassioukov, 2009] [Hagen et al., 2012a] [Krassioukov, 2012].
Autonomic dysreflexia can be divided into mild, moderate and severe by means of the increase in blood pressure [Popa et al., 2010], as may be noted in the table 13 provided.

Who suffers from AD? Autonomic dysreflexia occurs mainly in individuals with a SCI at or above the level of T6 (cervical and high thoracic SCI) [Grigorean et al., 2009] [Popa et al., 2010] [Krassioukov, 2009] [Hagen et al., 2012a] [Krassioukov, 2012]. Very rarely, autonomic dysreflexia has been reported in individuals with lesions below this level [Grigorean et al., 2009] [Popa et al., 2010] [Krassioukov et al., 2003].
The greater the severity and the higher the injury of the spinal cord, the more often autonomic dysreflexia occurs. In individuals after complete injuries, autonomic dysreflexia is three times as frequently as in individuals after incomplete spinal cord injuries [Krassioukov, 2009] [Krassioukov, 2012].

When does AD happen? Autonomic dysreflexia is a cardiovascular complication that is typically encountered in the chronic phase of SCI with an incidence of 48% to 90% [Hagen et al., 2012a] [Krassioukov, 2012] [Krassioukov et al., 2003]. However, it should be kept in mind that autonomic dysreflexia also occurs in the initial period after SCI. Krassioukov et al. were able to show that autonomic dysreflexia occurs in 5,7 % of individuals with acute SCI above T6 already on the fourth post-injury day [Krassioukov et al., 2003]. The figure 18 below represents a 24-hours blood pressure and heart rate registration on the fourth day after accident of a 31 year old female who suffered a severe C2-3 fracture. The episode of hypertension is marked by an arrow and, as it can be seen, blood pressure increases up to almost 160/100 mmHg out of a baseline blood pressure of about 100/50 mmHg. This sudden increase in blood pressure was accompanied by headache and blurred vision. The episode of autonomic dysreflexia could be attributed to a full bladder, as the blood pressure clearly decreased after bladder emptying [Furlan and Fehlings, 2008].

Thus, more attention should be paid to the possible development of autonomic dysreflexia in the acute phase of SCI [Krassioukov et al., 2003], although it mainly develops during the first two to four months after SCI [Hagen et al., 2012a].

What causes AD? As in the case of those mentioned above, a full urinary bladder is responsible for the occurrence of autonomic dysreflexia in remarkable 85% [Hagen et al., 2012a]. Overall, 90% of autonomic dysreflexia are caused by processes initated by urinary bladder and bowel [Krassioukov, 2012].
Nevertheless, autonomic dysreflexia can also be triggered by a number of different noxious and non-noxious stimuli [Krassioukov, 2012] [Hagen et al., 2012a] [Krassioukov et al., 2003]. Following listed in table 14 are some of the more common potential causes.

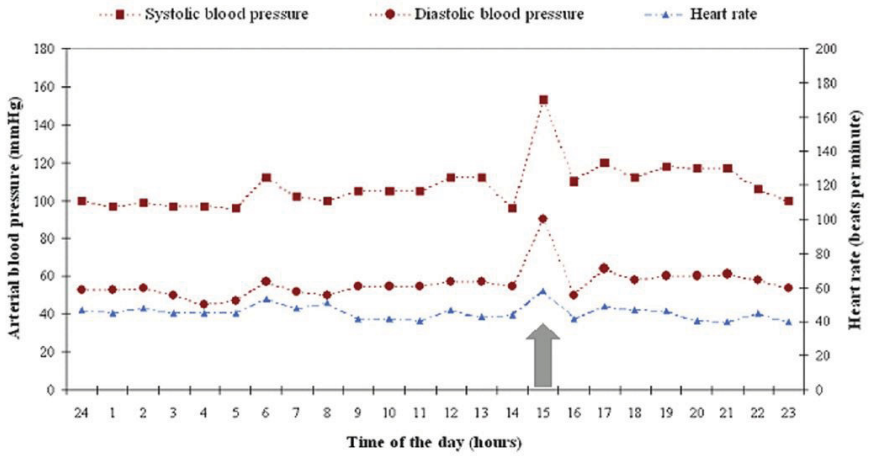


Figure 18: Autonomic dysreflexia: 24-hours blood pressure and heart rate registration on the fourth day. Taken from: [Furlan and Fehlings, 2008].

Table 14: Common triggers of autonomic dysreflexia episodes. Adapted from: [Krassioukov, 2012] [Hagen et al., 2012a] [Furlan and Fehlings, 2008] [Krassioukov, 2009].

Bladder distension
Bowel distension due to obstipation
Spasms
Pressure sores
Routine interventions:
Catheterization
Manipulation of indwelling catheter
Bladder percussion
Iatrogenic triggering factors:
Urological and endoscopic procedures (Cytoscopy, Cystometry)
Surgery, e.g. appendectomy and caesarean operation
Vibration or electrostimulation for ejaculation
Electrostimulation of muscles
Urinary tract infections
Anal fissures
Pregnancy
Childbirth
Sexual activity
Painful stimuli
Ingrown toenails
Or even something as seemingly trivial as tight or restrictive clothing

Pathophysiology of AD As already mentioned, autonomic dysreflexia occurs mainly in individuals with a SCI at or above the level of T6 or, to put it another way, above the major splanchnic sympathetic outflow (T6 through L2) [Popa et al., 2010] [Krassioukov, 2012], as illustrated in figures 6 and 3. The major splanchnic circulatory bed plays a key role in regard to the development of autonomic dysreflexia [Krassioukov, 2009] [Popa et al., 2010], as it provides the critical mass of blood vessels required to cause elevation of the blood pressure [Blackmer, 2003]. Thus, injury to the spinal cord at or above T6 affects the blood pressure homeostasis [Krassioukov, 2009].

Figure 19 serves to illustrate the following paragraph.
Via intact peripheral sensory nerves and neurons located in the intermediolateral thoracic and lumbar spinal cord, both, (1,2) a painful or non-painful stimulus below the level of injury triggers a sympathetic response [Blackmer, 2003] [Popa et al., 2010] [Krassioukov, 2009]. As a result of sympathetic hyperstimulation (3), vasoconstriction below the neurological injury occurs (4), due to the massive release of following neurotransmitters: norepinephrine, dopamine-β-hydroxilasis and dopamine [Popa et al., 2010] [Krassioukov, 2009]. These cause a massive increase in blood pressure (5) (hypertensive crisis) [Popa et al., 2010] [Blackmer, 2003]. Carotid and aortic baroreceptors are stimulated by the

hypertension and transmit the information via the glossopharyngeal (IX) and vagus (X) nerve to the brainstem (6) [Popa et al., 2010]. The attempt to lower the blood pressure can be divided into the following two compensatory mechanisms: (7a) Stimulation of the parasympathetic nervous system (vagus nerve) causes bradycardia, due to the fact that the cranial parasympathetic pathways, originating from the brainstem (see section 1.1.2), remains intact following SCI; (7b) Secondly, vasomotor centers above the SCI increases sympathetic inhibitory outflow which, however, are not able to be transmitted below the level of injury [Popa et al., 2010] [Blackmer, 2003].

Common symptoms and signs of AD Common symptoms and signs are summarized in table 15. Those may vary tremendously between the individuals and ranges from mildly uncomfortable symptoms to life-threatening crises [Krassioukov, 2012]. In general, reflex bradycardia occurs during an episode of autonomic dysreflexia. But in the course of autonomic dysreflexia, further cardiac responses can occur too (see table 15), ranging all the way through to cardiac arrest [Grigorean et al., 2009]. Headache, flushing, sweating and nasal congestion can be explained by vasodilatation,

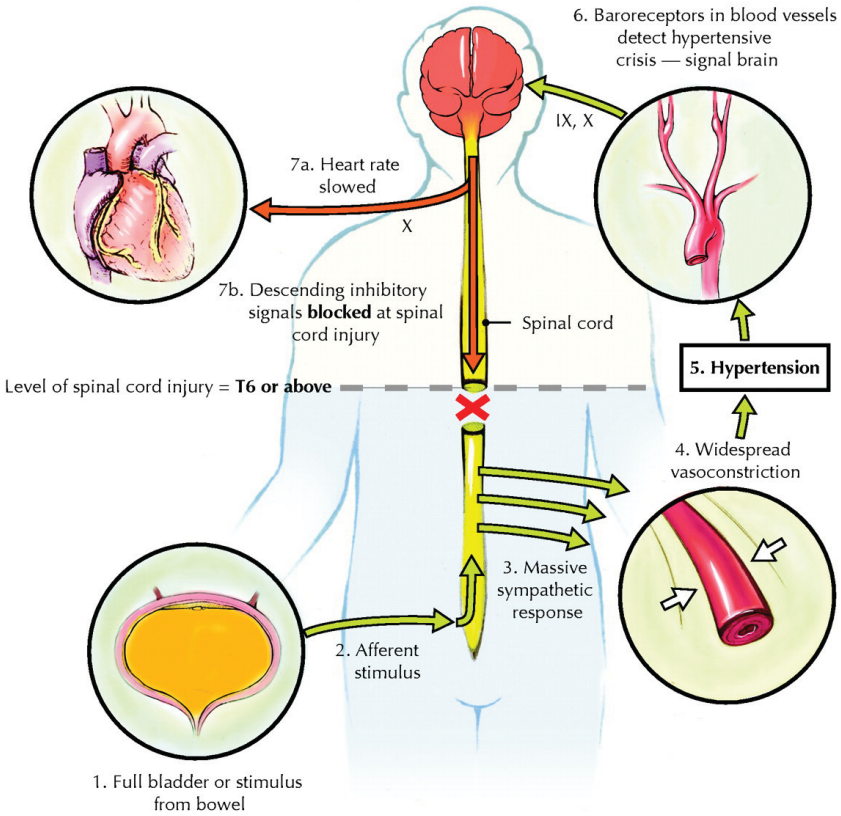


Figure 19: Pathophysiological model of autonomic dysreflexia. Cranial nerves are indicated as roman numerals (IX, X). Taken from: [Blackmer, 2003]

Table 15: Common symptoms and signs of autonomic dysreflexia. Adapted from: [Krassioukov, 2012] [Hagen et al., 2012a] [Grigorean et al., 2009] [Furlan and Fehlings, 2008] [Teasell et al., 2000].

Extreme hypertension (systolic blood pressures up to 300 mmHg)
Pounding headaches, especially in the occiput and frontal regions
Feellings of anxiety
Agitation
Shortness of breath
Bradycardia, cardiac arrhythmias, atrial fibrillation, cardiac arrest
Profuse sweating (above the level of injury)
Flushing of the skin (above the level of injury)
Piloerection (above or possibly below the level of injury)
Pale and clammy skin due to vasoconstriction (below the level of injury)
Goosebumps (above or possibly below the level of injury)
Blurred vision (spots in the visual fields)
Nasal congestion
Nausea

due to massive parasympathetic stimulation and lack of sympathetic tone above the level of the injury [Blackmer, 2003].

Consequences of AD Untreated massive increase in blood pressure may lead to hemorrhage (retinal, intracerebral or subarachnoid), retinal detachments, pulmonary edema, cardiac dysrhythmia, myocardial infarction, seizures, confusion and death [Hagen et al., 2012a] [Krassioukov, 2009] [Grigorean et al., 2009]. However, asymptomatic episodes of autonomic dysreflexia respectively simply characterized by sweating and piloerection are described too [Krassioukov, 2009] [Furlan and Fehlings, 2008].

Although autonomic dysreflexia is associated with unpleasant and/or life threatening complications, some disabled athletes induce such episodes voluntary by themselves before competition. This is referred to as ”boosting” and has the capacity to enhance athletic performance [Hagen et al., 2012a] [Krassioukov, 2009] [Krassioukov, 2012], but I shall return to this issue a little later (see section 4.4.6).

Management and Treatment of AD As banal as it may sound, autonomic dysreflexia can only be recognized and treated appropriately if it is known. Therefore, proper information to those affected but even so to clinicians, family members, friends and caregivers is of special importance. As autonomic dysreflexia is often unrecognized and misdiagnosed outside of specialized SCI rehabilitation facilities, education and empowerment of the SCI individual and closely related persons is mandatory, as education about autonomic dysreflexia constitutes a life saving tool. It appears from the review

Table 16: Management of autonomic dysreflexia. Abbreviations: SBP, systolic blood pressure; BP, blood pressure. Adapted from: [Blackmer, 2003]

Intervention → **Rationale**
1. Sit the patient upright → May cause an orthostatic decrease in blood pressure
2. Loosen any tight clothing or constrictive devices → Decreases noxious stimuli
3. Monitor the blood pressure every 2 to 5 minutes during the episode → Allows for rapid pharmacologic intervention where indicated
4. If no indwelling catheter is present, perform an intermittent catheterization → Bladder distension is the most common precipitant of AD
5. If an indwelling catheter is present, check it for obstructions and irrigate the catheter → Bladder distension is the most common precipitant of AD
6. If symptoms are still present and SBP is 150 mmHg or greater treat the BP pharmacologically → Risk of adverse sequelae increases when the SBP exceeds 150 mmHg
7. If symptoms are still present and SBP is less than 150 mm Hg, manually disimpact the bowel → Bowel problems are the second most common precipitant of AD
8. If symptoms persist, search for other precipitants → Other precipitants, as listed in table 14, must be found and treated appropriately to prevent further episodes
9. Consider admission or referral if symptoms persist or no precipitant is found → Patient is at risk of further episodes if no precipitant is found and should be monitored until the symptoms resolve and the blood pressure returns to normal

by Krassioukov et al. that education on the causes of autonomic dysreflexia, bladder and bowel routines and prophylaxis of pressure sores are the most important in regard to prevention of autonomic dysreflexia [Krassioukov et al., 2009] [Krassioukov, 2012].

If the assumption exists that an episode of autonomic dysreflexia occurs, rapid action is absolutely required. To reduce blood pressure elevation by using the orthostatic reflex, the patients head must be kept elevated and when possible the legs lowered. Tight clothing or equipment must be loosened or removed as quickly as possible. As the next step, the blood pressure is taken at least every five minutes. If the situation is not improving, potential trigger factors must be sought and if necessary eliminated. Since a full urinary bladder and bowel impaction are the most common causes, emphasis should be put on that first. If, despite exhausting of all initial steps, systolic blood pressure remains elevated (150mmHg or greater), a therapy with anti-hypertensive drugs should be initiated. The drugs most commonly used are short-acting drugs, like nifedipine or

nitrates [Hagen et al., 2012a] [Krassioukov et al., 2009] [Krassioukov, 2012] [Grigorean et al., 2009]. Table 16 summarizes the treatment steps that should be taken in case of suspected autonomic dysreflexia [Blackmer, 2003].

Since not all clinicians are familiar with AD, a SCI individual should carry a "Medical Emergency Card for Autonomic Dysreflexia" in the pocket, which should contribute to appropriate and timely recognition and intervention. An emergency card covers very brief and to the point, crucial information concerning autonomic dysreflexia and its urgently needed treatment as well as basic information about the injured individual [Krassioukov et al., 2009] [Apparelyzed, 2013].

4.4 Spinal Cord Injury and Exercise

As already stated, a stable and adaptable cardiovascular system is essential for our overall health and physical fitness. An imbalance in the coordination of the autonomic nervous system (sympathetic and parasympathetic nervous system) means for spinal cord injured individuals already numerous, sometimes life-threatening cardiovascular-related complications and sequelae, see section 4.1, 4.2 and 4.3.

The cardiovascular system ensures adequate blood redistribution to the muscles [Krassioukov, 2012] and transportation of oxygen, nutrients and metabolic products [Klabunde, 2011, pp.1-2]. The precondition for this to happen is a proper sympathetic regulation of cardiac and regional blood vessels and, in addition, active skeletal muscle pump. The ability of the organism to respond to the increased demands of the body during exercise, primarily blood pressure and heart rate regulation, is a fundamental key factor in exercise performance. Unfortunately, all this is affected in spinal cord injured athletes [Krassioukov, 2012].

In addition to the effects on the cardiovascular system following SCI, impact concerning voluntary muscle function, deep and superficial sensitivity, respiratory function and temperature and sweat regulation are clearly negatives for athletes with SCI, also in respect of cardiovascular adaptation to exercise [Theisen, 2012] [Krassioukov, 2012]. We must always be aware that, however, the extent of the dysfunction is determined by the level and completeness of the spinal lesion [Theisen, 2012] [Krassioukov, 2012] [Hagen et al., 2012a].

First of all, I would like to note the importance of physical activity in spinal cord injured individuals. In this context, the Paralympic Games will be mentioned briefly. In the following course, I will take a closer look at cardiovascular determinants of exercise

capacity in spinal cord injured individuals. The focus will set especially on arm exercise, both static and dynamic exercise. Subsequently, exercise-induced hypotension and, finally, boosting in SCI athletes will be outlined.

4.4.1 Importance of physical activity in SCI individuals

A spinal cord injury entails not only physical health problems, such as heart disease, obesity, lipid disorders or diabetes, but also psychological and social ones (relationships, education and profession, just to name a few examples). All these factors in turn interact with each other.
It is well known that regular physical activity reduces risk for physical health problems, as well as influences the psychological state. Physical activity encourages the motivation, self-confidence and interpersonal relationships.
Kawanishi and Greguol carried out a systematic review of literature and proofed that physical activity impacts positively on the quality of life (e.g. functional independence, greater perception of life satisfaction) in adults with spinal cord injury [Kawanishi and Greguol, 2013].

Disabled sports has become more and more attention of the public in recent years. The Paralympic Games takes place every four years, as in their recent summer games in London in 2012. Over 4000 athletes, representing 164 countries, competed in 20 different disciplines in front of about 2.7 million spectators. SCII are presented in almost all Paralympic disciplines, as the table 17 below shows [Paralympic, 2013].

Competitive athletes, such as Paralympians, serve as a role model for other spinal cord injured individuals as regards sport performance, as well as a person in all its aspects. The dark side of those kinds of events is that athletes themselves resort to illegal methods purposing elevation one's performance, even though they move themselves in a life threatening situation.

4.4.2 Arm exercise compared with leg exercise in SCI individuals

Due to the fact that SCI athletes rely on their upper body muscles during exercise, distinction must be made between upper body and lower body exercise in regard to exercise capacity. Arm exercise is characterized by lower peak oxygen consumption ($\dot{V}O_2peak$) and lower maximal power output in comparison with leg exercise. Theisen took up this subject in his 2012 published article in the Journal of physiology of where his findings are outlined in table 18.
Finally it should be noted that these findings indicate that upper body exercise, as it has also always been a matter by manual wheelchair propulsion, cause greater physiological

Table 17: Paralympic disciplines. Adapted from [Paralympic, 2013].

Summer Games		Winter Games
Archery	Rowing	Alpine skiing
Athletics	Sailing	Biathlon
Boccia	Shooting	Cross-country skiing
Canoe (included as of 2016)	Sitting volleyball	Ice sledge hockey
Cycling	Swimming	Wheelchair curling
Equestrian	Table tennis	
Football 5-a-side	Triathlon (included as of 2016)	
Football 7-a-side	Wheelchair basketball	
Goalball	Wheelchair fencing	
Judo	Wheelchair rugby	
Powerlifting	Wheelchair tennis	

load at a similar PO level compared to lower body exercise. Thus, exercise capacity is limited and untimely muscle fatigue results, which both have an adverse effect on their athletic performance. SCI athletes performing with their upper body are at a important disadvantage compared with lower body athletes [Theisen, 2012].

4.4.3 Arm static exercise and cardiovascular responses in SCI individuals

Previous studies reported that static exercise (isometric muscle contraction) causes cardiovascular responses, particularly an increase of cardiac output (CO) and total peripheral resistance (TPR). Consequently mean blood pressure (MBP) increases (as shown in equation 3), whereas the increase of MBP in cervical injured individuals was lower than the increase in able-bodied controls (7-12 and 16-18mmHg, respectively) [Sakamoto et al., 2012] [Takahashi et al., 2004].

The physiological principles of the autonomic regulation and innervation of the heart and vessels has already been presented in section 1.1.3. Especially the segmental distribution of the sympathetic nerve fibers as well as the dual innervation (parasympathetic and sympathetic) of the heart are of prime importance in terms of the cardiovascular control in spinal cord injured individuals (as shown in figure 6).
The impairment in cardiovascular control following SCI relates to the level of injury, as summarized in table 5.

Sakamoto et al. published in 2012 a study in which they compared 7 men with complete thoracic spinal cord lesion from T7 to T11 (TSCI) with 7 healthy, able-bodied men (AB) during static arm exercise. The static exercise was carried out at 35% of maximal voluntary arm flexor contraction [Sakamoto et al., 2012].
Takahashi et al. published in 2004 a study in which they compared 6 men with complete

Table 18: Upper body exercise compared with lower body exercise in individuals with SCI. Adapted from: [Theisen, 2012]

Determinants	Arm cranking vs. leg cycling
Maximal power output	Lower during arm cranking. Between 55 and 60% compared to leg cycling.
Peak oxygen consumption	Lower during arm cranking. Between 70 and 80% compared to leg cycling.
Active muscle mass	Smaller during upper body exercise, resulting in limited oxidative capacity.
Oxidative capacity	Limited in arm cranking, as a result of the smaller active muscle mass. Hence, muscle fatigue sets in at a much earlier stage in arm cranking than in leg cycling.
Oxygen uptake	At any given absolute PO, oxygen uptake is higher in arm cranking, due to the lower mechanical efficiency in upper body exercise compared to lower body exercise.
Cardiac output	For a given level of oxygen uptake, CO is more or less similar in both, arm cranking and leg cycling.
Heart rate	Upward trend observed in arm cranking.
Total peripheral resistance	Tends to be increased in arm cranking.
Cardiac stroke volume	Lower responses observed in arm cranking. One possible explanation is the fact that during sheer upper body exercise the legs are inactive → lack of skeletal muscle venous pumpin as a consequence.

cervical spinal cord lesion from C6 to C7 (CSCI) with 7 healthy, able-bodied men (AB) during static arm exercise. The static exercise was carried out at 35% of maximal voluntary contraction of the right elbow flexor muscle [Takahashi et al., 2004].
Both studied the cardiovascular responses of heart rate (HR), cardiac output (CO), mean blood pressure (MBP) and total peripheral resistance (TPR) [Sakamoto et al., 2012] [Takahashi et al., 2004].
Moreover, Takahashi et al. identified the responses of stroke volume (SV) [Takahashi et al., 2004]. Determinants of blood redistribution, such as skin blood flow (SBF) and muscle blood flow (MBF) in leg muscles (non-exercising muscles), were also studied by Sakamoto et al.. Furthermore, plasma levels of epinephrine, atrial natriuretic peptide (ANP), renin activity (PRA) and anti-diuretic hormone (ADH) were measured in both groups, TSCI and AB, during and after exercise [Sakamoto et al., 2012].

Arm static exercise in thoracic SCI In thoracic SCI individuals (TSCI), static arm exercise caused an increase of all variables (HR, CO, MBP, TPR, SBF and MBF), see figure 20 **(a-f)**. The figure also shows that those variables change in both the exercise period and in the recovery period without significant difference in TSCI compared to AB individuals. Immediately after static exercise period all those variables returned

to basal values. However, a further increase of MBF could be detected in the recovery period in both groups, as indicated in figure 20 **(f)** [Sakamoto et al., 2012].

That no significant difference of HR, CO and MBP by comparison of TSCI and AB individuals could be established, can be attributed to the fact that a spinal cord injury from T7 through T11 is accompanied with preserved sympathetic and parasympathetic (vagal) control of the heart (see table 5).
From a physiological point of view it is supposed that loss of supraspinal sympathetic control is accompanied with maximal dilatation in the peripheral arteries. This results in a reduction of TPR. However, the majority of studies have proven that the vascular resistance is increased in SCI individuals. The responsible mechanisms have not been clarified yet. It seems possible that the reduction of circulating hormones (epinephrine and norepinephrine) due to reduced sympathetic activity in cervical and high-thoracic injured individuals leads to a compensatory hypersensitivity of vasoconstrictor substances [West et al., 2013].
Other possible assumptions about the similar increases of TPR in both groups during arm static exercise are listed below [Sakamoto et al., 2012]:

- TPR response is not impaired by the lack of sympathetic vascular control in the leg muscles
- Sympathetic vascular control in the leg muscles of AB individuals is not meant to be crucial in TPR response
- TPR response in both groups is attributable to increase in vascular resistance in the active arm muscles

SBF and MBF changed in both the exercise period and in the recovery period without significant difference between TSCI and AB individuals. The increase of these two variables during arm static exercise in both groups suggest, that the increase of CO and pressor reflex attach more importance than the lack of sympathetic vasoconstriction in the paralyzed legs regarding the SBF and MBF.
Attention will be drawn here especially to following. Several previous studies have suggested that different structural and functional vascular changes occur in SCI individuals due to the lower sympathetic activity [Sakamoto et al., 2012]. In it above all the duration of SCI as well as physical activity are meant to be determining factors regarding vascular changes following SCI [Sakamoto et al., 2012] [West et al., 2013].

It is already known that soon after SCI, in particular within 6 weeks of SCI [Sakamoto et al., 2012], modifications of peripheral arteries in paralyzed extremities occur. The common femoral artery show losses of diameter between 30 to 50% and reduction of

resting blood around 30 to 40% in the leg compared to AB individuals. Consequently, the shear rate in common femoral artery increases 50 to 100% compared to controls (AB individuals) [Sakamoto et al., 2012] [West et al., 2013]. The vascular adaptation due to the inactivity and paralysis seems mostly to happen within 6 weeks. After this there were no further changes were. From this period to 13 months, no further changes were observed [West et al., 2013].

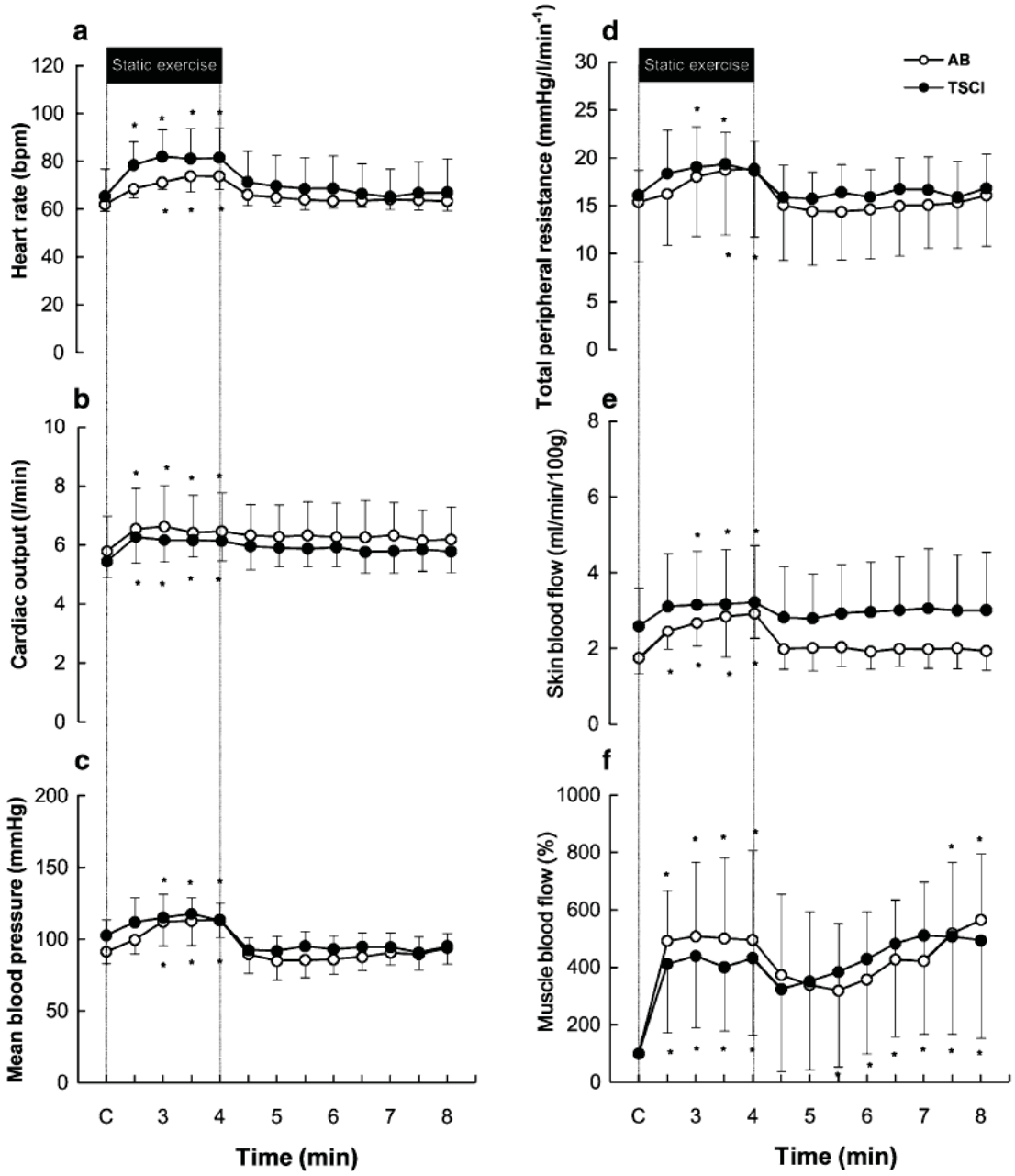


Figure 20: Comparison between thoracic SCI and able-bodied individuals during and after static arm exercise, in terms of **a)** heart rate (HR), **b)** cardiac output (CO), **c)** mean blood pressure (MBP), **d)** total peripheral resistance (TPR), **e)** skin blood flow (SBF) and **f)** muscle blood flow (MBF). 35% of maximal voluntary contraction. $*$ P<0,05 compared with the baseline. Taken from: [Sakamoto et al., 2012]

Boor et al. compared individuals with high-thoracic SCII, low-thoracic SCI individuals and AB controls against one another with the objective to evaluate the relation between inactivity and shear stress [Boot et al., 2002]. Table 5 reveals that the loss of supraspinal sympathetic control leads to different consequences depending on the level of injury:

- high-thoracic: Loss of supraspinal sympathetic control to the major splanchnic vascular bed
- low-thoracic: Loss of supraspinal sympathetic control of the blood vessels below the level of SCI

Despite this considerably different loss of vasculature control, no significant differences could be found in shear rate in high- and low-thoracic SCII. This implies that the increase in shear rate is likely due to the inactivity, as to the loss of supraspinal control [Boot et al., 2002]. Furthermore, it was shown that the blood vessels of the upper, active extremity are relatively well preserved compared to the blood vessels of the lower, inactive extremity, so that the acceptance is formed that structural adaptions below the level of injury is attributable to the decreased metabolic demands of the lower extremity's vasculature [West et al., 2013].
Patients who lack sympathetic vascular innervation due to sympathectomy, but perform physical activity, show no structural and functional vascular changes of any kind typically observed in SCI individuals [Sakamoto et al., 2012]. This would also be a possible explanation for why SBF and MBF values were so similar in the TSCI and AB individuals. Those TSCI individuals participated in the study of Sakamoto et al. were well trained and had chronic traumatic SCI [Sakamoto et al., 2012].

However, these finding raises the question of why a renewed increase of only MBF could be detected in the recovery phase [Sakamoto et al., 2012].

Sakamoto et al. have also found that plasma epinephrine, atrial natriuretic peptide (ANP), plasma renin activity (PRA) and anti-diuretic hormone (ADH) shows similar basal levels within both groups (TSCI and AB). The measurements revealed that ANP, PRA and ADH values do not change during the exercise period, either in TSCI or AB individuals. However, this doesn't apply to plasma epinephrine, since a change in level was observed during exercise period, but only in AB controls [Sakamoto et al., 2012].
The importance of the renin-angiotensin-aldosterone system (RAAS) as well as the ANP in blood pressure regulation is already pointed out in section 1.1.4. Table 2 provides an overview of their effects related to blood pressure regualtion. Nevertheless, arm static exercise at 35% of maximal voluntary contraction has not led to any changes in the RAAS, ADH and ANP. The latter mentioned suggest that central blood volume did not change under those conditions, otherwise ANP would have increased. Apart

from that, this result indicates that RAAS, ADH and ANP during 35% of maximal voluntary contraction in arms static exercises are not be involved in cardiovascular response [Sakamoto et al., 2012].
That plasma epinephrine increased only in AB individuals can be attributed to the fact that sympathetic preganglionic neurons are found within the intermediolateral horn [Hagen et al., 2012a] in the thoracic (T1-T12) and upper lumbal (L1-L2) spinal cord [West et al., 2013], with the major part between T5 and T9 [Sakamoto et al., 2012].

Arm static exercise in cervical SCI As outlined in table 19(a), the baseline cardiovascular values MAP, HR, SV and CO were significantly lower in tetraplegic individuals compared to AB controls. No difference could be observed in the case of TPR between AB and tetraplegic individuals [Takahashi et al., 2004].

Figure 21 shows the cardiovascular responses in cervical SCI (tetrapelgics) and AB individuals during 35% of maximal voluntary static arm exercise over time.
In addition to the absolute peak cardiovascular responses at the end of static exercise periode between tetraplegics and AB individuals summarized in table 19, also a relative comparison of peak changes in tetraplegics and AB individuals are compiled in figure 22.

Although HR didn't increase in tetraplegic individuals at the onset of static exercise periode as much as in the control group (at 20 sec. from exercise onset: 5 ± 2 bpm and 11 ± 2 bpm, respectively), peak absolute (18 ± 4 bpm and 17 ± 3 bpm, respectively) and relative changes (24 ± 4 and 28 ± 6%, respectively) at the end of exercise were in both groups without significant difference [Takahashi et al., 2004].

CO increase and change over the course of time were similar throughout the exercise periode in both groups (see figure 21). As shown in figure 22, peak increase, expressed in terms of relative percentage changes, was in the AB controls the same as in tetraplegic individuals (14 ± 3 % and 13 ± 7 %, respectively).
The increase in CO was accompanied by a small decrease in SV (see figure 21), whereas the peak decrease in SV at the end of exercise was similar between the two groups (8 ± 1 for AB controls and 12 ± 3 for tetraplegic individuals) [Takahashi et al., 2004].

As shown in figure 21, AB controls experienced a steady rise in MAP during static exercise period. Tetraplegic individuals experienced a small increase of MAP during the early exercise period and remained more or less at that level until the end of exercise. The comparison between AB controls and tetraplegic individuals showed an increase in absolute peak MAP approximately at a ratio of 3 to 1 (38 ± 4 mmHg and

Table 19: Baseline cardiovascular values and their responses at the end of static arm exercise in AB controls and tetraplegic individuals. Values are means ± SE. Abbreviations: MAP, mean arterial blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance. ∗ Significant difference from the baseline values ($P < 0.05$). † Significant difference between the 2 groups ($P < 0.05$). Adapted from: [Takahashi et al., 2004].

(a) Baseline cardiovascular values

	AB controls (n=6)	Tetraplegic individuals (n=6)
MAP, mmHg	78 ± 2	63 ± 2 †
HR, bpm	72 ± 2	62 ± 3 †
SV, ml	105 ± 2	85 ± 9 †
CO, l/min	7,5 ± 0,2	5,1 ± 0.05 †
TPR, MU	0,62 ± 0,01	0,73 ± 0,09

(b) Cardiovascular responses at the end of static exercise

	AB controls (n=6)	Tetraplegic individuals (n=6)
MAP, mmHg	116 ± 3 ∗	75 ± 5 ∗ †
HR, bpm	90 ± 5 ∗	80 ± 6 ∗
SV, ml	96 ± 2 ∗	75 ± 9 ∗
CO, l/min	8,6 ± 0,9 ∗	5,8 ± 0.5 †
TPR, MU	0,83 ± 0,04 ∗	0,80 ± 0,12

(c) Absolute changes

	AB controls (n=6)	Tetraplegic individuals (n=6)
MAP, mmHg	38 ± 4	12 ± 5 †
HR, bpm	17 ± 3	18 ± 4
SV, ml	- 8 ± 1	- 10 ± 2
CO, l/min	1.0 ± 0,2	0,6 ± 0,4
TPR, MU	0,20 ± 0,03	0,07 ± 0,04 †

12 ± 5 mmHg, respectively). As figure 22 reveals, relative peak changes at the end of exercise differed significantly in both groups (20 ± 8 % for tetraplegics and 50 ± 7 % for controls) [Takahashi et al., 2004].

TPR increased in AB individuals significantly during exercise period, primarily during the latter period (see table 19 and figure 21). In contrast, tetraplegic individuals showed no changes at all in TPR [Takahashi et al., 2004].

The fact that tetraplegic individuals experienced during static exercise period an increase in MAP, although TPR didn't rise at all, suggest that only the increase in CO determines the low pressure response in tetraplegic individuals (see also 3). This points to the fact that peripheral vasoconstriction doesn't contribute to blood pressure regulation during 35% of maximal voluntary arm static exercise.

Cervical SCI means loss of supraspinal sympathetic control of the heart and blood vessels, while parasympathetic (vagal) control of the heart remains intact. A further finding of this study was the decreased capacity to increase HR primarily at the

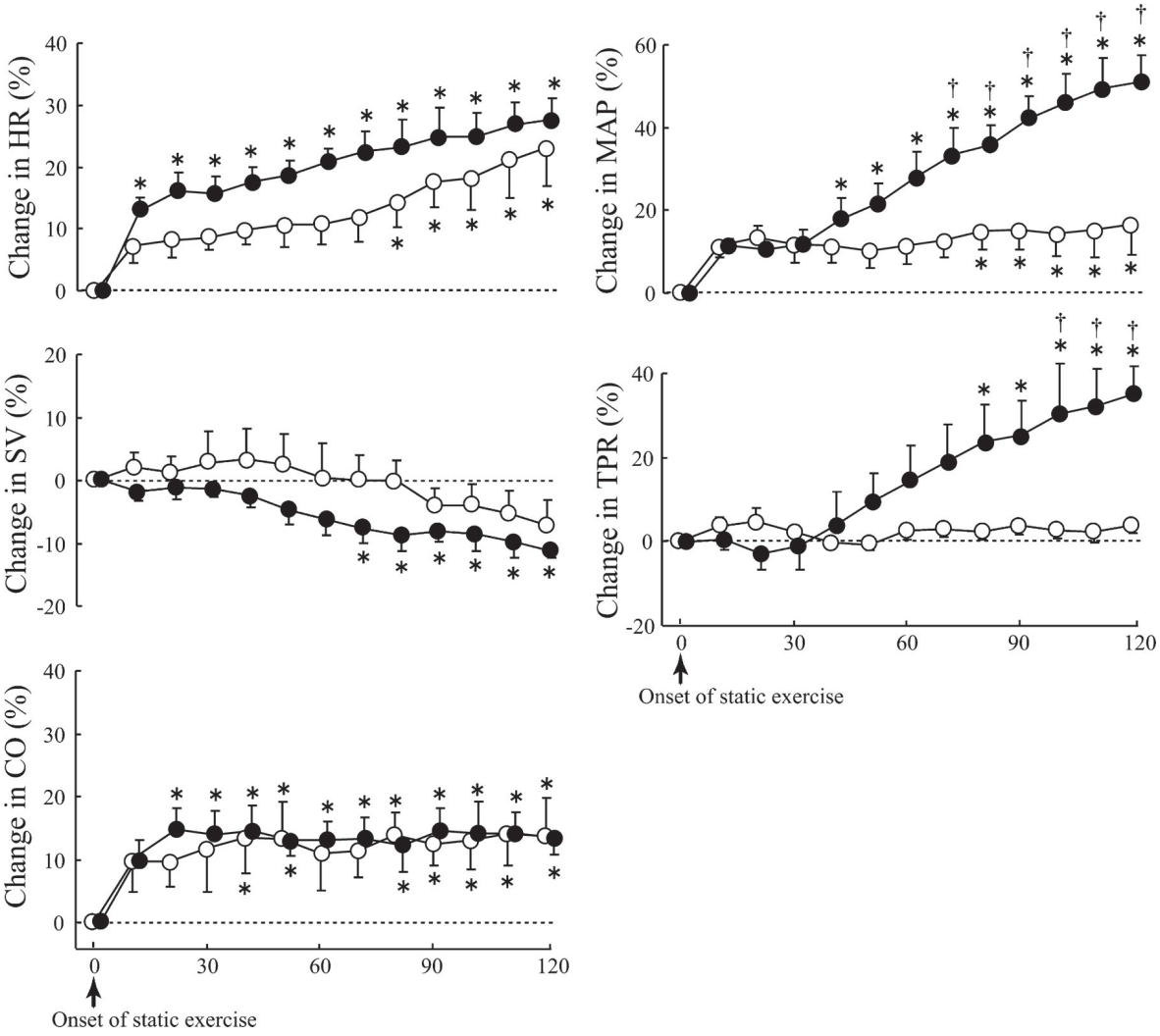


Figure 21: Comparison between cervical SCI (tetraplegics) and able-bodied individuals during and after static arm exercise, expressed in terms of the relative percent changes in heart rate (HR), stroke volume (SV), cardiac output (CO), mean blood pressure (MBP) and total peripheral resistance (TPR). Elbow flexors static exercise at 35% of maximal voluntary contraction (MVC) were performed by each individual as long as possible. Baseline cardiovascular values before exercise were defined as 0% control levels in each subject. Able-bodied individuals are emphasized by a dark filled circle, tetraplegics by an open circle. $*$ Significant difference from baseline control levels ($P < 0.05$). † Significant difference between the 2 groups at an individual time point ($P < 0.05$). Taken from: [Takahashi et al., 2004]

onset of exercise in tetraplegic individuals compared to AB controls. Thus indicates that sympathetic regulation especially in immediately acceleration of HR is of prime importance. Furthermore, the significantly increase of HR and CO, but not SV, during the later static arm exercise period in tetraplegic individuals stresses the major role of parasympathetic withdrawal in cardiac adaption to static exercise in cervical injured individuals. The obtained results of the study by Takahashi et al. suggest that loss of supraspinal sympathetic cardiovascular control cause lack of peripheral vasoconstriction and decreased capacity in HR control as well as that cardiac parasympathetic withdrawal is capable of CO adaption during static arm exercise [Takahashi et al., 2004].

Comparison of thoracic and cervical SCI during arm static exercise A comparison of both studies, [Sakamoto et al., 2012] [Takahashi et al., 2004], reveals that cardiovascular adaption to 35% of maximal voluntary arm static exercise is mainly determined by the level of injury. The study of Sakamoto et al. obtained similar findings concerning HR, CO, MBP and TPR in thoracic SCI (T7 to T11) compared to AB controls during exercise period, as shown in figure 20 [Sakamoto et al., 2012]. In contrast, Takahashi et al., who studied cervical SCI (C6 to C7) during arm static exercise, obtained different findings concerning HR, CO, MBR and TPR compared to AB controls., as figure 21 outlines [Takahashi et al., 2004].

Those findings emphazise that T6 and above injuries are regarded to be determining for the development of significant cardiovascular dysfunctions in individuals with SCI, as summarized in table 5. The cardiovascular regulation during arm static exercise in cervical SCI is only regulated by parasympathetic outflow, as those individuals have lost supraspinal sympathetic control of the heart and blood vessels [Krassioukov, 2012] [ASIA, 2013a] [Sakamoto et al., 2012]. Note that most peripheral blood vessels have no parasympathetic innervation, except the vessels that supply the pelvic organs [Hagen et al., 2012a]. However, level of injury from T6 through T12 means that sympathetic and parasympathetic (vagal) control of the heart is preserved (see figure 6) but also that supraspinal sympathetic control of the blood vessels below this level are impaired [Krassioukov, 2012] [ASIA, 2013a]. Thus, there is a lack of sympathetic vasoconstriction in paralyzed legs [Sakamoto et al., 2012]. The possible reasons why thoracic injured individuals still experienced similar TPR response to static exercise than AB controls are discussed below.

4.4.4 Arm cycling exercise and cardiovascular responses in SCI individuals

Claydon et al. studied the cardiovascular responses during, at the end of and after arm cycling (dynamic) exercise in chronic cervical (n=19) and thoracic (n=8) SCI individuals. All participants performed a graded arm cycling exercise on an arm ergometer until their

peak oxygen ($\dot{V}O_2peak$) consumption was reached. Thoracic individuals experienced a greater $\dot{V}O_2peak$ than cervical SCI individuals, as shown in table 20. Table 20 also provides and overview of baseline cardiovascular values and their responses at the end of arm cycling exercise [Claydon et al., 2006a].

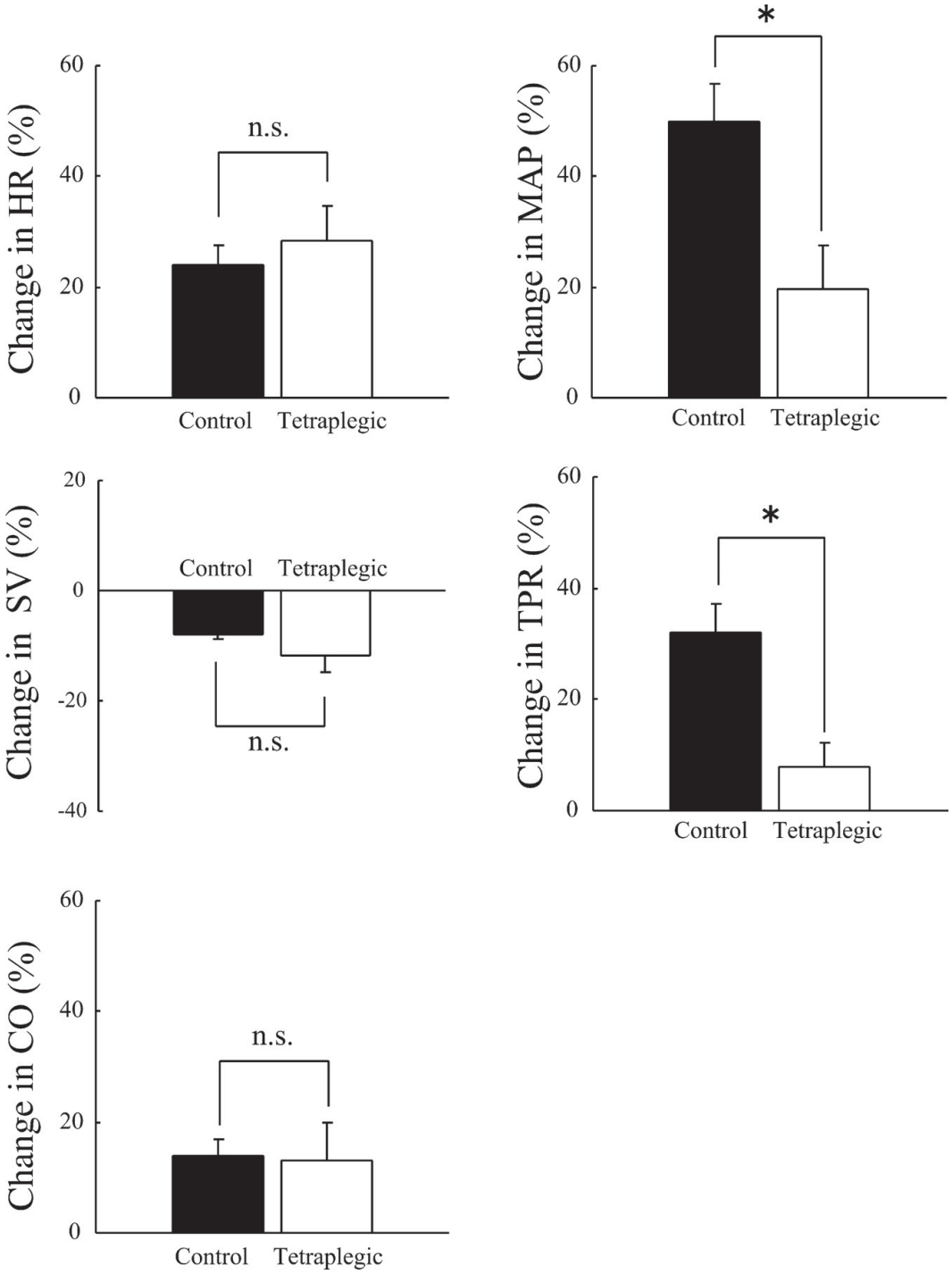


Figure 22: Peak relative changes in tetraplegics and AB individuals at the end of static exercise in terms of cardiovascular parameters: heart rate (HR), stroke voume (SV), cardiac output (CO), mean arterial blood pressure (MAP) and total peripheral resistance (TPR). $*$ Significant differences between the two groups (P$<$ 0,05). Not significant is named with n.s., (P$>$ 0,05). Taken from: [Takahashi et al., 2004]

Table 20: Baseline cardiovascular values and their responses at the end of dynamic arm exercise in cervical and thoracic SCI individuals. Abbreviations: $\dot{V}O_2peak$, peak oxygen consumption; MAP, mean arterial blood pressure; SAP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. $*$ Significant difference from the baseline values ($P < 0.05$). † Significant difference between the 2 groups ($P < 0.05$). Adapted from: [Claydon et al., 2006a].

(a) $\dot{V}O_2peak$ during graded arm cycling exercise

	Thoracic SCI (n=8)	Cervical SCI (n=19)
$\dot{V}O_2peak$, ml/(kg·min)	25,2 ± 2,6	14,9 ± 1,1 †

(b) Baseline cardiovascular values

	Thoracic SCI (n=8)	Cervical SCI (n=19)
MAP, mmHg	93,5 ± 3,3	76,6 ± 1,7 †
SAP, mmHg	115,3 ± 3,9	96,2 ± 2,4 †
DAP, mmHg	71, 8 ± 3,1	61,5 ± 2,0 †
HR, bpm	81,4 ± 6,5	68,3 ± 2,6 †

(c) Cardiovascular responses at the end of graded arm cycling exercise

	Thoracic SCI (n=8)	Cervical SCI (n=19)
MAP, mmHg	101,9 ± 3,4	62,2 ± 2,8 $*$ †
SAP, mmHg	133,5 ± 5,5 $*$	80,9 ± 3,5 $*$ †
DAP, mmHg	70,3 ± 1,9	53,6 ± 2,3 $*$ †
HR peak, bpm	158,6 ± 4,4 $*$	105,2 ± 4,4 $*$ †

MAP, SAP, DAP and HR values, both baseline and at the end of exercise, were significantly lower in cervical compared to thoracic SCI individuals.

Mean arterial pressure (MAP) was at any time of investigation (resting, during and after exercise) always greater in thoracic than in cervical individuals. Thoracic SCI individuals showed at the end of exercise an insignificant increase of 8,4 ± 5 mmHg, while cervical SCII experienced a significant decrease of 14,4 ± 2 mmHg. As shown in figure 23, thoracic SCII experienced a significantly increase of SAP, while SAP in cervical SCII significantly decreased. On the other hand, DAP didn't change relevant from baseline in thoracic SCII, while cervical SCII experienced a significantly decrease from baseline, see also table 20.

Table 20 reveals that thoracic SCII showed a significantly greater resting HR than cervical SCII. Figure 24 presents the HR response over time in cervical and thoracic

SCI individuals. As can be seen, HR response was directionally similar in both groups. However, thoracic SCII experienced greater HR responses at all times than cervical SCII. The increase of HR in thoracic SCII was significant greater compared to cervical SCII (increase of 80,3 ± 8,1 bpm and 36,9 ± 4,1 bpm, respectively). All variables MAP, SAP, DAP and HR gradually returned to baseline levels in the course of 5 minutes recovery period (in the case of SAP, DAP and HR see figures 23 and 24) [Claydon et al., 2006a].

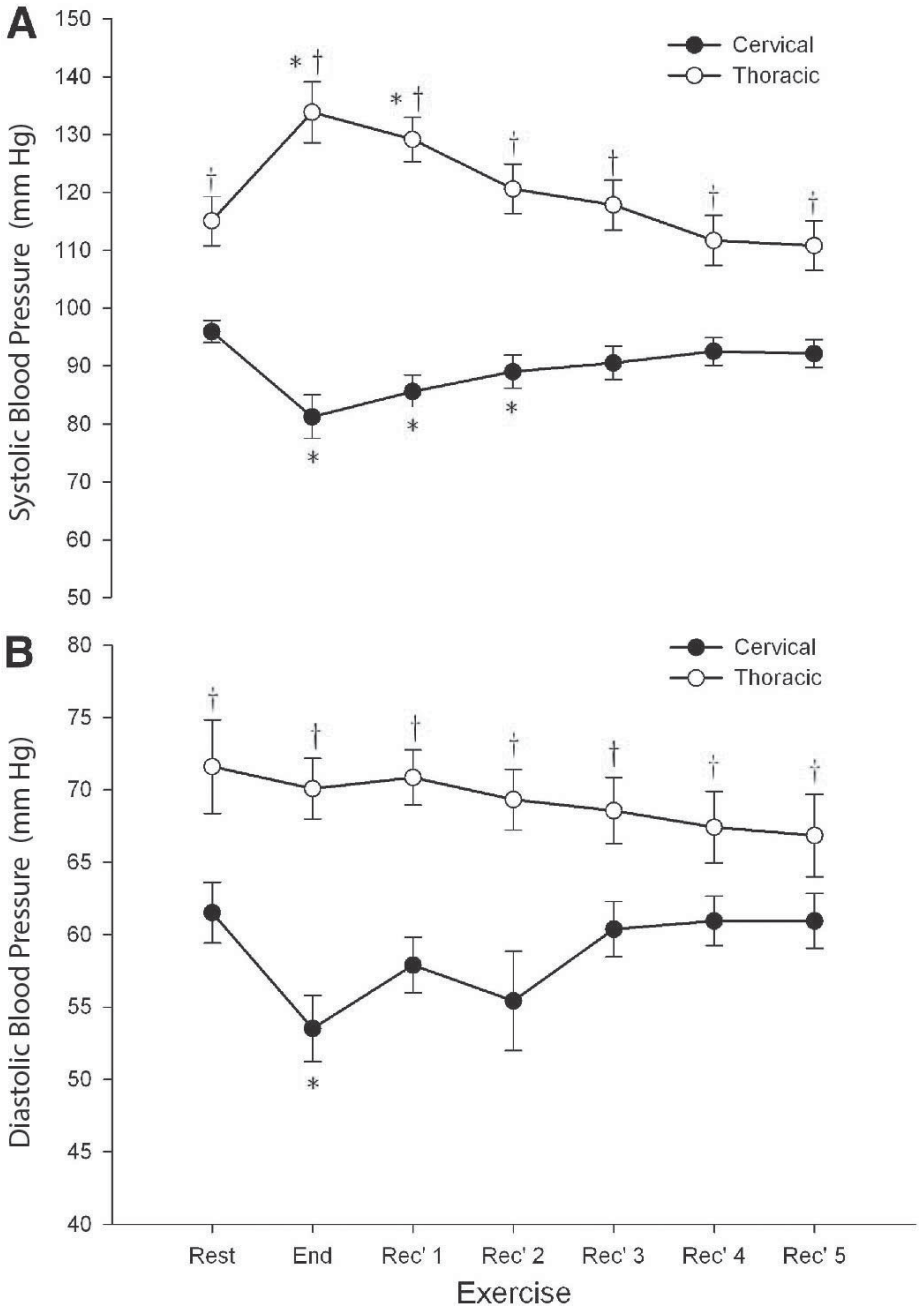


Figure 23: Comparison of systolic and diastolic blood pressure responses during arm cycling exercise and recovery period in chronic cervical and thoracic individuals. The recovery periode extended over 5 minutes. ∗ Significant difference from the baseline values ($P < 0.05$). † Significant difference between the 2 groups ($P < 0.05$). Adapted from: [Low et al., 2012]

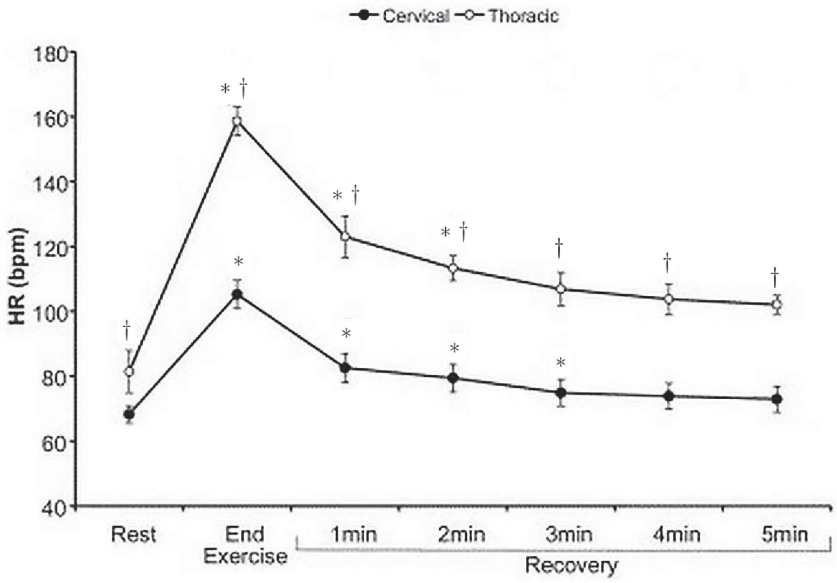


Figure 24: Comparison of HR responses during exercise and recovery period in chronic cervical and thoracic SCI individuals. Abbreviations: HR, heart rate; bpm, beats per minute. ∗ Significant difference from the baseline values ($P < 0.05$). † Significant difference between the 2 groups ($P < 0.05$). Adapted from: [Claydon et al., 2006a]

Comparison of resting cardiovascular parameters dependent on the level of injury in cervical, high-thoracic, low-thoracic lumbar and able-bodied (AB) individuals have been described in detail previously (section 4.2). Table 5 provides an overview of the level of injury related impairment in cardiovascular control following SCI.

The physiological increase of MAP in thoracic SCII following arm cycling exercise and recovery period is the result of a combination of following listed [Claydon et al., 2006a]:

a. Vagal activity to the heart

b. Increased sympathetic activity to the heart and vasculature

c. Pronounced vasoconstriction

Increase of CO causes an increase of SBP in thoracic SCII. The almost unaltered change in DBP (see figure 23] is due to the vasodilating exercising muscles, which buffer the increase in DBP. The damped heart rate in cervical SCII compared to thoracic SCII (see figure 24) are likely the result of the absence of descending sympathetic control of the heart. Anyway, the fact that cervical SCII experienced a peak HR of 105,2 ± 4,4 bpm is attributable to parasympathetic withdrawal. A former investigation has shown that peak heart rate of cervical SCII was similar to complete vagal blocked AB individuals during exercise [Claydon et al., 2006a].

4.4.5 Postexercise hypotension in SCI athletes

As known from section 4.3.2, OH occurs mainly in cervical and high-thoracic SCII caused by orthostatic maneuvers and can be exacerbated by various factors like time of day, food ingestion, state of hydration, hypertension, ambient temperature, recent recumbency, postural deconditioning, and medications. Light-headedness, blurred vision, , fatigue, dizziness, restlessness and dyspnea are caused by cerebral hypoperfusion occurring secondary to orthostatic drop in blood pressure [Con, 1996] [Popa et al., 2010] [Krassioukov, 2009] [Furlan and Fehlings, 2008] [Teasell et al., 2000]. The symptoms associated with OH complicate participation in work, rehabilitation as well as exercise [Sahota et al., 2012] [Popa et al., 2010] [Claydon and Krassioukov, 2006]. However, previous studies reported a transient hypotension and fainting as well as a prolonged fall in blood pressure for 1 hour up to 12 hours following exercise, also known as postexercise hypotension [Claydon et al., 2006a].

Claydon et al. examined the incidence of postexercise hypotension in cervical and thoracic SCII and observed that hypotension immediately after the end of arm cycling exercise period commonly occurred in cervical, but not in thoracic SCII. This is probably due to the fact that thoracic SCII, especially low-thoracic injured (T6 and below), are preserved of supraspinal sympathetic and parasympathetic control of the heart and the major splanchnic vascular bed [Krassioukov, 2012] [ASIA, 2013a] [Claydon et al., 2006a].

It is interestingly to note that postexercise hypotension in AB individuals depends strongly on their resting seated blood pressure and is unusual in AB individuals with resting seated BP below 130/85 mmHg. Higher resting seated BP is associated with larger and more prolonged postexercise hypotension in AB individuals. As table 20 provides, the thoracic SCII participating in the study of Claydon et al. showed a BP of approximately 115/72 mmHg. That is obviously below the treshold value of 130/85 mmHg. This furthermore explains the absence of postexercise hypotension in thoracic SCII.

While thoracic SCII experienced an insignificant increase of 8,4 ± 5 mmHg of MAP (baseline: 93,5 ± 3,3 mmHg; at the end of exercise: 101,9 ± 3,4 mmHg), MAP of cervical SCII decreased significantly by 14,4 ± 2 mmHg (baseline: 76,6 ± 1,7 mmHg; at the end of exercise: 62,2 ± 2,8 mmHg) (see also table 20 and figure 23). Although cervical SCII experienced distinct BP decrease, only 5 of 19 reported presyncope symptoms. This is due to the fact that those individuals are more tolerant to hypotension, which is probably attributable to alterations in cerebral blood flow autoregulation [Claydon et al., 2006a].

Although the mechanisms of exercise induced hypotension are not yet fully understood, it is assumed that postexercise hypotension can be attributed to a sustained drop in the TPR, which can't be adequately compensated by increase of CO. The sustained drop in TPR is caused by neural (distinct reduction in systemic vasoconstriction due to loss of supraspinal sympathetic control and reduced vascular responses to sympathetic vasoconstriction) and local (presence of local and circulating vasodilators) mechanisms. Supposingly, at the end of exercise CO quickly returns to baseline level, while TPR recovers more slowly. This mechanism is much more pronounced in cervical SCII [Claydon et al., 2006a], as it is well known that the degree of sympathetic dysfunction is greater the higher the level of injury [West et al., 2012] [Krassioukov, 2012].

Cardiovascular responses to exercise is not only related to the level, completeness and morphology of the injury [Claydon et al., 2006a], but also on the type of exercise (static and dynamic muscle contraction) [Theisen, 2012]. As can be seen in figure 23, cervical SCII experienced initial a significantly decrease of SAP and DAP after arm cycling exercise [Low et al., 2012]. On the other hand, cervical SCII experienced a small increase of MAP at the onset of static arm exercise and remained more or less at that level until the end of exercise (as shown in figure21) [Takahashi et al., 2004]. A comparison of these findings reveals that the severity of exercise-induced hypotension may be greater during dynamic compared to static arm exercise in cervical SCII [Low et al., 2012].

However, initial hypotension caused by arm cycling exercise in cervical SCII gradually returned to baseline levels in the course of 5 minutes recovery period (figure 23. As regards the fact that sympathetic nervous control of heart and vessels is disrupted in those individuals, the mechanisms underlying rapid recovery of BP are unknown. Claydon et al. assume that the rapid recovery of BP maybe can be attributed to following listed below [Claydon et al., 2006a]:

a. local reflexes that are independent of descending control

b. increased ADH release to hypotensive challenges

c. peripheral alpha-adrenoceptor hyperresponsiveness

4.4.6 Boosting: self-induced episodes of autonomic dysreflexia

Athletic performance is reversely related to the level of spinal lesion. Several studies have shown that the higher the injury the greater the limitations of endurance capacity. Cervical injured athletes have limited mechanical power output (PO) and maximal oxygen uptake ($\dot{V}O_2max$) in comparison to lower injured athletes and able-bodied

individuals during submaximal and maximal exercise [Theisen, 2012] [Krassioukov, 2012] [Bhambhani et al., 2010]. The amount of functional muscle mass is a key factor in this respect. Inevitably, respiratory function is affected because of limited function of expiratory and inspiratory muscles. Latter in the case of high-cervical injured individuals [Theisen, 2012].
Furthermore, due to lack of skeletal muscle pumping activity and lack of sympathetic vasoconstriction below the level of injury, the blood pools in the lower extremities [Krassioukov, 2012]. In addition to the fact that physical activity leads to vasodilation in working muscles, exercise-induced decrease in blood pressure occurs. Hence, critical drop in perfusion pressure in the working muscles cause early physical exhaustion [Hagen et al., 2012a].
Due to the lack of sympathetic innervation to the cardiovascular system, heart rate response rely on parasympathetic withdrawal and circulating catecholamines [Theisen, 2012]. Thus, maximal heart rate is limited. While those athletes with a spinal lesion below T6 will have normal HR responses (see table 5 and figure 6), athletes with lesion above T6 can barely rise their HR beyond 125 beats per minute [Bhambhani et al., 2010] [Hagen et al., 2012a] [Theisen, 2012] [Krassioukov, 2012], determined by sino-atrial activity [Bhambhani et al., 2010]. As a consequence, stroke volume (SV) is lower in those individuals [Bhambhani et al., 2010] [Krassioukov, 2012].
An overview of resting cardiovascular parameters (SDP, DBP and HR) dependent on the level of injury is given by table 6. It can be seen that cervical injured SCI have resting SBP's which are about 15 to 20mmHg lower than those in AB controls [West et al., 2012] [Krassioukov, 2012].
To all these just mentioned performance-limiting factors, there is also an exercise-induced hypotension occurring in some athletes (as indicated in section 4.4.5), which further affects their athletic performance [Krassioukov, 2012].

All in all, this physiological limitations create a disadvantage between SCI athletes who have normal blood pressure and heart rate responses to exercise and those who don't. However, the impairment of the autonomic cardiovascular control enables athletes with SCI at or above T6 to elevate one's performance during training or competition by intentional induction of autonomic dysreflexia (AD). This performing enhancing strategy is known as "boosting" and is performed by high-level SCI athletes to compensate their lower BP [Bhambhani et al., 2010] [Krassioukov, 2012].
AD refers to a condition characterized by a sudden, dangerous increase in blood pressure in response to a painful or non-painful stimulus below the level of injury. Further information, including the pathophysiology of AD, are presented in an earlier section 4.3.4.
Commonly used methods associated with boosting are to force bladder distension by

clamping of the urinary catheter, excessive tightening of leg straps or even twisting, strangulating or sitting on the testicles [Bhambhani et al., 2010].
Bhambhani et al. carried out a study of boosting among SCI athletes during the Paralympic Games in Beijing 2008. The study is based on a self-report questionnaire with a total of 99 Paralympians. The evaluation showed that slightly more than half (54,5%) have already heard of boosting while 39,4% were unaware. 16,7%, all males, had used boosting during training and/or competition, whereby all of them had experienced spontaneously triggered AD before [Bhambhani et al., 2010].
It's no wonder that the majority of athletes (about 80%) who admitted the use of boosting during competition were injured at spinal lesion level T6 or above. Those are the ones who experience the most severe cardiovascular dysfunction and, thus, the greatest loss of function for physical activities [Krassioukov, 2012].
The questionary revealed that only 5,3% classified boosting as not at all dangerous, while 48,9% classified it as somewhat dangerous. Anyhow, 21,3% and 25,5% agreed that boosting is dangerous or very dangerous to health, respectively. The participants reported that boosting causes most of all an increased circulation, less fatigue, increased endurance along with increased aggression as well as increased alertness [Bhambhani et al., 2010].

Studies investigating high-level injured athletes during boosted and non-boosted state while performing graded arm exercise and a 7.5 km wheelchair race, have reported that peak HR, peak BP, circulating norepinephrine levels, maximum $\dot{V}O_2$ and peak PO significantly increased during boosted state compared to the same athletes during non-boosted state. This was reflected by the fact that during boosted state a up to 9,7% improvement in race time was achieved (22.6 $\pm$ 6.6 min vs. 25.6 $\pm$ 9 min, during boosted and non-boosted, respectively). Significantly elevated blood pressure levels were recorded during the boosted state in these studies, some of them exceeded levels of 200 mmHg [Krassioukov, 2012].
Common symptoms and signs of AD are listed in table 15. High-level injured Paralympians of the Beijing Paralympic Games reported that high blood pressure (83.3%), excessive sweating (80.6%) and headache (70,9%) are the most frequently realized symptoms of boosting. Less frequently they experienced shivering (36.8%) and blurred vision (26%) and, in the case of some athletes, heightened anxiety and greater frustration during boosted state [Bhambhani et al., 2010].
Self-induced episodes of AD bears life-threatening health risks in athletes because of uncontrolled increase in blood pressure, as presented in section 4.3.4. For this reason, boosting was banned by the International Paralympic Committee (IPC) [Bhambhani et al., 2010] [Krassioukov, 2012] [Theisen, 2012] .

4.5 Anti-G suit and cardiovascular responses in SCI individuals

The impairment of the sympathetic nervous system (SNS) to induce vasoconstriction and the lack of skeletal muscle pumping activity due to paralysis below the level of injury in SCI individuals (SCII) have profound influences on their blood redistribution. Studies have shown that blood is redistributed from central circulation to the lower extremities and abdominal region (splanchnic vascular bed) during physical activity. A reduction of filling pressure and end-diastolic ventricular volume means that stroke volume doesn't increase in SCII as high as in AB individuals. Consequently, SCII are more intolerant concerning cardiovascular responses of physical activity, orthostatic maneuvers and during strenuous efforts in daily life [Houtman et al., 1999] [Pitetti et al., 1994] [Hopman et al., 1992].
Wide-ranging management strategies have been investigated to support the redistribution of blood during physical activity in SCII aiming an improvement of their maximal performance, reduction of postexercise hypotension and/or OH. The non-pharmacological intervention strategies to decrease venous pooling and improve venous return to the heart comprise the application of functional electrical stimulation (FES) of the paralysed lower limb muscles, various types of exercise, biofeedback as well as the application of different devices of compression and pressure to abdominal and leg regions. The latter includes, in addition to pneumatic leg splints, abdominal corset, gait harness and compressive stockings, wearing of an anti-gravity (anti-G) suit [Theisen, 2012] [Gillis et al., 2008].

The anti-G suit is a flight suit used by aviators and astronauts to prevent pooling of blood and to support maintaining the blood circulation during exposure of high gravity loads, since loss of consciousness would have devastating consequences.
In the following I would like to provide an overview of already obtained results, sorted by year of publication, of how an intervention such as an anti-G suit affect exercise performance in individuals with SCI.

In 1963, Vallbona et al. investigated the effect of an anti-G-suit on BP and HR parameters in SCII who were exposed to orthostatic challenge (60° head-up-tilting (HUT)). A total of 17 SCII, 12 tetraplegics and 5 paraplegics, were included in the study. As shown in table 21, they experienced a significant increase of systolic and diastolic BP (+24 mmHg and + 22mmHg increase, respectively) during inflated anti-G-suit compared to control conditions (60° HUT). It would be true to say that wearing an anti-G-suit diminished the fall in BP and the rise in HR (difference of 10 bpm, see table 21) during orthostatic challenge. Deflation of the anti-G-suit in turn induced an abrupt SBP and

Table 21: Effect on BP and HR in SCI individuals who wore an anti-G-suit during orthostatic challenge, 60° HUT. Abbreviations: HUT, head-up-tilting; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. † Significant difference compared to 60° HUT ($P < 0.005$). Adapted from: [Gillis et al., 2008].

Parameters	**60° HUT**	**60° HUT + anti-G-suit inflated**	**60° HUT + anti-G-suit deflated**
SBP, mmHg	81	105 †	86
DBP, mmHg	49	71 †	60
HR, bpm	92	82	compensatory rise

DBP drop (19 mmHg and 11 mmHg, respectively) accompanied by a compensatory rise in HR [Gillis et al., 2008].

In 1992, Hopman et al. suggested that during submaximal arm-cranking exercise venous blood pooling in paraplegics may be prevented by an inflated anti-G-suit. They compared fives paraplegic men with complete injury at levels between T6 and T12 with five male control individuals who were bounded to wheelchairs but with an intact sympathetic nervous system and an active leg muscle pump. All of them underwent submaximal arm-cranking exercise at 20%, 40% and 60% of their maximal power output (W_{max}), both with (G+) and without (G-) anti-G-suit. The inflated anti-G-suit applied a constant pressure of 52 mmHg on legs and abdomen. Table 22 compares the cardiovascular responses in SCII and control group with regard to exercise level and intervention of an anti-G-suit [Hopman et al., 1992].

Table 22: Cardiovascular responses to submaximal arm-cranking exercise with and without anti-G-suit in paraplegics and control group. Arm-cranking exercise was performed at 20%, 40% and 60% of W_{max}. Values are means ± SD. Abbreviations: W_{max}, $\dot{V}O_2$, oxygen consumption; maximal power output; G-, without anti-gravity suit; G+, with anti-gravity-suit; CO, cardiac output; SV, stroke volume; HR, heart rate. Adapted from: [Hopman et al., 1992].

	Paraplegics (W_{max})			**Control group (W_{max})**		
	20%	**40%**	**60%**	**20%**	**40%**	**60%**
CO, l/min						
G-	6,7 ± 1,4	8,8 ± 1,7	12,9 ± 3,5	8,0 ± 0,8	11,9 ± 1,0	16,5 ± 2,7
G+	5,8 ± 0,8	8,5 ± 1,6	12,2 ± 2,7	8,4 ± 1,8	11,8 ± 2,3	15,5 ± 1,0
SV, ml						
G-	78 ± 19	83 ± 18	99 ± 30	92 ± 15	117 ± 19	125 ± 14
G+	68 ± 17	87 ± 27	104 ± 25	96 ± 30	115 ± 36	129 ± 19
HR, bpm						
G-	88 ± 14	106 ± 13	132 ± 12	88 ± 11	103 ± 12	125 ± 14
G+	88 ± 15	100 ± 13	118 ± 13	86 ± 12	104 ± 10	121 ± 15

Table 23: Effect of an anti-G suit on SBP and DBP in paraplegics and control group before exercise. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; G-, without anti-gravity suit; G+, with anti-gravity-suit; Adapted from: [Hopman et al., 1992].

Parameters	Paraplegics	Control group
SBP, mmHg		
G-	117	123
G+	127	124
DBP, mmHg		
G-	78	84
G+	79	81

First of all I want to anticipate, not represented in the table, that wearing an anti-G suit didn't reveal any differences in oxygen uptake ($\dot{V}O_2$) for each participant (paraplegics and control group) at the same submaximal exercise level. However, $\dot{V}O_2$ was reduced, although not significant, at any submaximal exercise level in paraplegics compared to the control group.

As can be seen in the table 22, an anti-G suit seems not to influence CO at a given submaximal exercise level. Furthermore, no significant differences were obtained for both groups with or without an anti-G suit at 20% W_{max}. However, paraplegics experienced a significant decrease in HR during 40% and 60% W_{max} due to the inflated anti-G suit (reduction of 5,7% and 10,6%, respectively). Due to the fact that no differences in oxygen uptake using an anti-G suit were observed, this is a strongly indication that an anti-G suit support the circulation most likely as a result of diminished venous blood pooling. Furthermore, the anti-G suit offered no circulatory advantages in control individuals who have intact vasoconstriction and active muscle pump activity. In contrary, easier exercise performance by wearing an anti-G suit was subjectively reported by paraplegics. Anyway, an insignificant increase in SV was observed at 40% and 60% W_{max} (increase of 4,8% and 5,0%, respectively). Apart from the slight increase of SV at 60% W_{max} in the control group (increase of 3,2%), the anti-G suit didn't affect further changes.

Before starting the exercise, Hopman et al. measured SBP and DBP in both groups to determine the effect of an anti-G suit. The investigation showed that paraplegics experienced an increase of SBP with an inflated anti-G suit, while DBP remained unaltered. No changes could be observed in the control group. The values are provided in table 23. The increase of SBP in paraplegics immediately after inflating the anti-G suit suggest an increase of CO at that time, although no CO changes were observed during exercise. It should be noted that the paraplegic participants level of injury were between T6 and T12. Therefore (see figure 6), an intact sympathetic innervation of the heart and thus normal regulation of intrinsic cardiac function was to be expected [Hopman et al., 1992].

Table 24: Anti-G suit and its effects on performance during maximal arm-cranking exercise in paraplegics and control group. Abbreviations: W_{max}, maximal power output; $\dot{V}O_2peak$, maximal power output; HR_{max}, heart rate; G-, without anti-gravity suit; G+, with anti-gravity-suit. † Significant difference between the 2 groups ($P < 0.05$). ∗ Significant difference within the groups between G- and G+ ($P < 0.05$). Adapted from: [Hopman et al., 1993].

Parameters	Paraplegics	Control group
W_{max}, W		
G-	124,6 ± 18,6 †	148,5 ± 30,6
G+	123,3 ± 17,2 †	148,1 ± 28,1
$\dot{V}O_2peak$, l/min		
G-	1,9 ± 0,4 †	2,7 ± 0,5
G+	1,8 ± 0,2 †	2,6 ± 0,4
HR_{max}, bpm		
G-	184,0 ± 7,2 †	177,0 ± 9,3
G+	179,3 ± 10,4 † ∗	174,3 ± 8,4 ∗

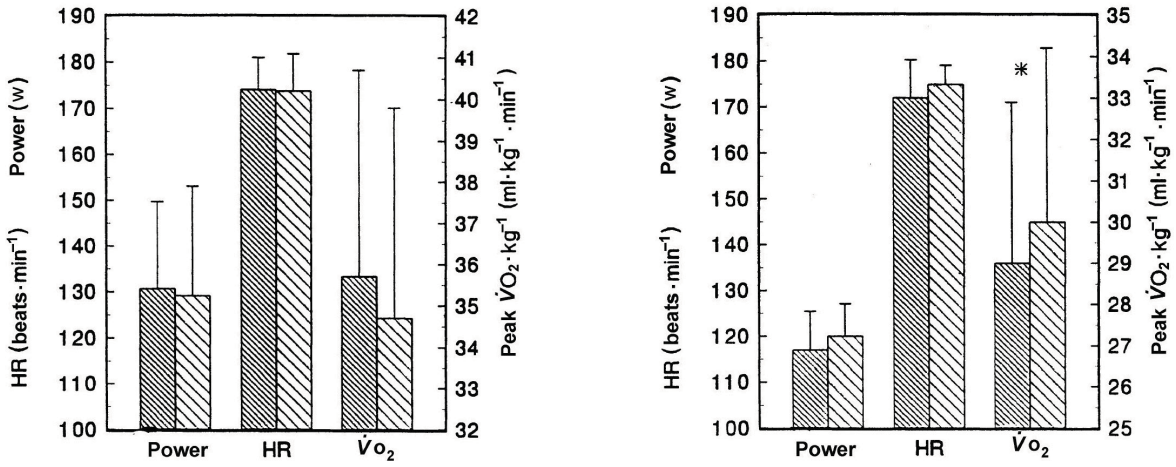
The following year, 1993, Hopman et al. studied whether lower body positive pressure by use of an anti-G suit could improve maximal performance in paraplegic individuals. Twelve mal paraplegics with a complete SCI between T6 and T12and 13 able-bodied (AB) men performed maximal arm-cranking exercise, both with (G+) and without (G-) an anti-G suit. The applied pressure on the lower body was 52 mmHg. Hopman et al. achieved unchanged peak power output (W_{max}) and oxygen uptake ($\dot{V}O_2peak$) in both groups by means of an anti-G suit during maximal exercise. However, paraplegics experienced significant lower W_{max} and $\dot{V}O_2peak$ than the individuals of the control group. In contrary, the peak HR was significantly higher in paraplegics compared to controls for both with and without an anti-G suit. However, maximal HR was significantly lower with an anti-G suit than without in both groups. Hence, these findings suggest that lower body positive pressure provides central hemodynamic benefits for both groups, even though no noticeable improvement on the maximal performance had been noted [Hopman et al., 1993].

On the other hand, however, in 1994, Pitetti et al. was able to demonstrate the effectiveness of an anti-G suit on peak power output (W_{max}) and oxygen uptake ($\dot{V}O_2peak$) in SCII (quadriplegics and paraplegics) during seated submaximal exercise. Departing from previous studies, Pitetti et al. used a slowly varying (every two minutes) alternating pressure between 50 mmHg and 75 mmHg. They recorded significant higher W_{max} and $\dot{V}O_2peak$ in the SCI group. In addition, they reported significantly higher CO and SV in SCII by means of an anti-G suit too [Pitetti et al., 1994]. These findings indicate that the function of muscle pump may be imitated more closely by means of a pulsating pressure rather than by means of a constant pressure application [Pitetti et al., 1994] [Houtman et al., 1999].

Due to the fact that Pitetti et al. have demonstrated the effectiveness of a pulsating anti-G suit in SCII performing submaximal exercise [Pitetti et al., 1994] and Phillips et al. have shown a decrease in venous blood pooling in SCII by means of a functional electrical stimulation (FES) over a duty cycle of 2,5 sec. "on" and 5 sec. "off" during arm exercise up to 80% $\dot{V}O_2peak$ [Phillips et al., 1995], Houtman et al. suggested that a higher pressure pulsation rate may correspond much better to the physiologically process of muscle pump activity than those one than that was used by Pitetti et al. (alternating pressure every two minutes) [Houtman et al., 1999].

1999, Houtman et al. included five SCI men with complete injury at levels between T6 and L1 and seven AB men in the study. All of them performed two arm-cranking tests, once by wearing an inflated (G+) and once by wearing a deflated (G-) anti-G suit. In contrast to the study conducted by Pitetti et al., the participants in the study of Houtman et al. were exposed to a rapidly pulsating anti-G suit (alternating every two seconds between 25 mmHg and 70 mmHg). The exercise was started with a power of 10 watts (W) and increased by 10 W every minute until exhaustion. Peak values of exercise intensity (power), HR and $\dot{V}O_2peak$ are given in figure 25.
Neither the comparison of both groups nor the differences between G+ and G- for any other parameters proved to be statistically significant. It is not surprisingly that there was no difference found between G+ and G- in AB individuals, as they have an intact sympathetic nervous system and muscle pump activity. Unexpectedly, it becomes evident that SCII experienced a significant lower $\dot{V}O_2peak$ during rapidly pulsating inflated anti-G suit compared to deflated state [Houtman et al., 1999], since Pitetti et al. demonstrated the effectiveness of an slowly pulsating anti-G suit on peak power output (W_{max}) and oxygen uptake ($\dot{V}O_2peak$) in SCII during submaximal exercise.
The explanation for this could be that the SCII participating in the study of Pitetti et al. had higher levels of injury (mostly between C5 and C7) [Pitetti et al., 1994] and therefore a pulsating anti-G suit could become more influential than in the SCII with a level of injury between T6 and L1 like in the study of Houtman et al. [Houtman et al., 1999].
Hopman et al. could not reveal a difference in $\dot{V}O_2peak$ by means of an inflated anti-G suit constantly pressurized at 52mmHg, either during submaximal [Hopman et al., 1992] or maximal arm-cranking [Hopman et al., 1993]. Beyond that, both studies revealed a significant lower HR in SCII with an inflated anti-G suit [Hopman et al., 1992] [Hopman et al., 1993], whereas an insignificant increase of SV could be found during submaximal exercise [Hopman et al., 1992]. The findings of Houtman et al. don't support that a rapidly pulsating anti-G suit enhance haemodynamic process, since no decrease in peak HR in SCII using a rapidly pulsating anti-G suit could be revealed. They concluded that a pulsating pressure does well imitate the function of the muscle pump in the

legs, but does not imitate the vasoconstriction in the abdomen, as the veins of the splanchnic bed have no valves. Assuming that the vessels of the splanchnic bed are more important for blood redistribution during exercise, it concludes that a constant pressure on the venous system of both legs and abdominal splanchnic bed will have greater hemodynamic benefits than an alternately pressurized anti-G suit [Houtman et al., 1999].



(a) AB individuals

(b) SCI individuals

Figure 25: Cardiovascular responses in SCI and AB individuals during arm exercise while wearing inflated and deflated anti-G suits with pulsating pressure. Left column shows inflated and right column shows deflated state of anti-G suit. The error bars indicate the standard deviation. $*$ Significant difference between inflated and deflated states ($P < 0.05$). Taken from: [Houtman et al., 1999]

V Acknowledgements

At first I like to thank my supervisors Sen.Scientist Dr.med. Nandu Goswami and Univ.-Prof. Dr.med.univ. Helmut Hinghofer-Szalkay for giving me the opportunity to write this thesis at the Institute of Physiology at the Medical University of Graz. I am very pleased that they have supported my interests.

My special gratitude goes to my parents, who gave me the possibility of an academic education and the freedom to create my living.

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VII Abbreviations

AB	able-bodied
ACE	angiotensin-converting enzyme
ACh	acetylcholin
AD	autonomic dysreflexia
ADH	antidiuretic hormone
AIS	ASIA Impairment scale
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
Anti-G	anti-gravity
APR	acute periode of rehabilitation
ASIA	American Spinal Injury Association
AV	atrioventricular
BP	blood pressure
BPM	beats per minute
C	cervical
CHD	coronary heart disease
CNS	central nervous system
CSCI	cervical spinal cord injury
CVD	cardiovascular disease
CVP	central venous pressure
DBP	diastolic blood pressure
DVP	descending vasomotor pathways
ECG	electrocardiography
FES	functional electrical stimulation
HF	high frequency
HRV	heart rate variability
HT	high thoracic
HUT	head-up-tilting
ISAFSCI	International standards on documentation of remaining autonomic function after SCI
ISCOS	International Spinal Cord Society
ISNCSCI	International standards for neurological classification of SCI
L	lumbal
LF	low frequency
LTL	low-thoracic lumbar
M	muscarinic

MBF	muscle blood flow
MI	myocardial infarction
MVC	maximal voluntary contraction
NE	norepinephrine
NTS	nucleus tractus solitarius
OH	orthostatic hypotension
PNS	parasympathetic nervous system
PO	power output
PRA	plasma renin activity
RAAS	renin-angiotensin-aldosterone system
S	sacral
SA	sinoatrial
SBF	skin blood flow
SBP	systolic blood pressure
SCI	spinal cord injury
SCII	spinal cord injured individuals
SCIWORA	spinal cord injury without radiologic abnormality
SNS	sympathetic nervous system
SPN	sympathetic preganglionic neuron
SSC	supraspinal sympathetic control
T	thoracic
TSCI	thoracic spinal cord injury
$\dot{\mathbf{V}}\mathbf{O}_2peak$	peak oxygen consumption
$\mathbf{W}_{max}$	maximal power output