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NEURAL CONTROL OF CARDIOVASCULAR FUNCTION FOLLOWING SPINAL CORD INJURY IN HUMANS

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ABSTRACT OF DISSERTATION

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School at the University of Kentucky

By
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Lexington, Kentucky

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Maintenance of stable arterial blood pressure during orthostatic challenges is a major problem after spinal cord injury (SCI). Since early participation in rehabilitation is critically important in reducing long term morbidity, recovering the ability to regulate blood pressure during therapy is essential for individuals with SCI. The objective of our study was to investigate short term cardiovascular function of able-bodied (AB), paraplegic (PARA) and tetraplegic (TETRA) subjects in response to head up tilt (HUT) as an early indicator of autonomic damage that might forewarn of future orthostatic regulatory problems. We acquired cardiovascular variables from able-bodied (AB; n=11), paraplegic (PARA; n=5) and tetraplegic (TETRA; n=5) subjects in response to HUT. The SCI patients in both groups were in their first two months post injury. Data were recorded at rest and during 7 min each at 20º, 40º, 60º and 80º HUT. Techniques used to estimate regulatory capability and reflex activity included: Mean values and spectral power of heart rate (HR) and arterial blood pressure (BP), baroreflex sequence measurements and cross correlation between HR and systolic blood pressure (SBP). An index of baroreflex sensitivity (BRS), baroreflex effectiveness index (BEI), and the percentage occurrence of systolic blood pressure (BP) ramps and baroreflex sequences were calculated from baroreflex sequence measurements. The spectral power of HR and BP, the cross correlation of systolic BP and heart rate (HR) were examined in low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz) ranges. The BRS index was significantly ($p < 0.05$) decreased from supine to 80^o HUT in AB and TETRA. This index in PARA was the lowest at each tilt position in the three groups, and decreased with tilt. The percentage of heart beats involved in systolic BP ramps and in baroreflex sequences significantly ($p<0.05$) rose from supine to 80^o HUT in AB, was relatively unchanged in PARA and declined in TETRA. Both of these indexes were significantly ($p<0.05$) lower

in the SCI than in the AB group at each tilt level. The BEI values were greatest in AB, and declined with tilt in all groups. Spinal cord injured patients had less power of BP and HR fluctuations than AB in both LF and HF regions. The LF spectral power of BP and HR increased with tilt in AB, remained unchanged in PARA and decreased in TETRA. The HF spectral power of HR decreased in all three groups. The peak HR / BP cross correlation in the LF region was greatest in AB, and significantly ($p<0.05$) increased during HUT in AB, remained fairly constant in PARA, and declined in TETRA. The peak cross correlation in the HF region significantly ($p<0.05$) decreased with tilt in all groups, and the SCI group had lower values than AB at each tilt level. We conclude that both PARA and TETRA had a smaller percentage of SBP ramps, BRS, and lower BEI than AB, likely indicating decreased stimulation of arterial baroreceptors, and less engagement of feedback control. The mixed sympathetic, parasympathetic innervations of paraplegics, or their elevated HR, may contribute to their significantly lower BRS. Our data indicate that the pathways utilized to evoke baroreflex regulation of HR are compromised by SCI and this loss may be a major contributor to the decrease in orthostatic tolerance following injury.

Key Words: orthostatic hypotension, baroreflex sensitivity, baroreflex effectiveness index, cross correlation, feed-back, open loop regulation

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April 20th, 2006

NEURAL CONTROL OF CARDIOVASCULAR FUNCTION FOLLOWING SPINAL CORD INJURY IN HUMAN

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I would like to dedicate this work to my dad, Kazim Coban, my mom, Sevim Coban, and my husband, Mustafa M. Aslan.

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Table of Contents

List of Figures

List of Tables

Chapter 1 : Introduction

Spinal cord injuries (SCI) occur approximately 12,000 times per year in North America; most SCI involve the cervical spine region. Patients who sustain cervical spine injuries have lasting, often devastating, neurological deficits and disabilities. Although the most visible effects of SCI are a loss of motor and sensory function below the lesion, acute SCI, especially those occurring in the cervical region, are often associated with hemodynamic instability. Cardiovascular problems known to arise from sympathetic nervous system dysfunction include low resting arterial blood pressure, orthostatic hypotension, autonomic dysreflexia, reflex bradycardia and cardiac arrest (2,7,11,47,77,78). These cardiovascular related conditions severely limit a patient's participation in rehabilitation, thus extending hospital stay, increasing the cost of rehabilitation, and possibly limiting the effectiveness of other treatment. Orthostatic hypotension is a common problem particularly in the acute phase of recovery (43,54,77) Traditional treatment consists of a series of cardiovascular challenges over several weeks using tilt or similar orthostatic stress, until the patient can reasonably tolerate an upright posture. However the physiological mechanisms leading to cardiovascular adjustments following SCI are not clearly understood. In addition, there are very limited assessments for clinicians to measure the patient's cardiovascular deficit and recovery following SCI. Consequently, cardiovascular recovery occurs with varying degrees of efficiency in individuals with SCI. Since most of the recovery following SCI occurs within the first six months of injury (17), and active rehabilitation within the first two weeks is critically important in reducing long term morbidity (43,59), recovering the ability to maintain stable arterial blood pressure (BP) during therapy and its accompanying orthostatic challenges is essential for individuals with SCI.

Short-term stability of arterial BP is achieved in large part by appropriate adjustments in sympathetic and parasympathetic outflow from the central nervous system to cardiovascular effector mechanisms (8,62,67,69) It is generally assumed that fluctuations in cardiovascular parameters originate from interactions between sympathetic and parasympathetic neural branches and other low frequency sources

(40,73,76). Spontaneous oscillations of heart rate (HR) and BP can be analyzed by extracting frequency-related information from their measurements. In particular, two rhythms are generally observed in short term heart rate recordings: a respiratory or high frequency (HF) rhythm (peak around 0.2 - 0.3 Hz in humans), is considered a marker of vagal activity, and a low frequency (LF) rhythm (peak around 0.1 Hz in human), a marker of sympathetic activity or combined vagal and sympathetic influence. During a sympathetic challenge, such as HUT, increases in the LF/HF ratio are expected in able-bodied persons due to shifts in autonomic modulation toward augmented sympathetic, and attenuated vagal, activity (61).

Both LF and HF components of HR are influenced by the gain of the baroreflex (23,56,75). The baroreflex provides powerful beat-to-beat negative feedback regulation that minimizes the short-term fluctuations in arterial pressure (51). Although there has been a long standing interest in assessing baroreflex characteristics, and the importance of determining baroreflex sensitivity (BRS) is widely recognized, there is no "gold standard" among techniques for spontaneous baroreflex assessment (67). One of the most frequently employed approaches is the sequence technique. Sequences of three or more consecutive heart beats in which monotonic increases (or decreases) of systolic blood pressure (SBP) are followed, usually after a delay of one beat, by monotonic lengthening (or shortening) of the RR interval, are accepted as baroreflex sequences (10). Recently, a baroreflex effectiveness index has been defined as the ratio between the total number of baroreflex sequences and the total number of systolic blood pressure ramps in a given time window (24). The BEI quantifies the number of times that the baroreflex is effective in driving the sinus node, and provides information on baroreflex function that is complementary to BRS (24). In normal subjects, the arterial baroreflex induces beat-by-beat RR interval changes in response to only 21% of all SBP ramps (24).

Besides BRS, there is an increasing interest in the occurrence of baroreflex sequences (12,14,24,36,38,53). To find an absolute value, the occurrence number can be normalized by time (24,53), by mean heart rate (14), by the number of validated sequences (36), and by the number of heart beats (12,36). Since the number of baroreflex sequences depends on the number of analyzed heartbeats, and the number of heartbeats varies among subjects and within a subject according to activity, normalization by time

would yield unreliable results. In addition, each baroreflex sequence can have various numbers of involved heartbeats, usually ranging from 3 to 6, but would still be counted as one-baroreflex sequence. Therefore using only the number of baroreflex sequences would lead to inaccuracy in the absolute value of the occurrence of baroreflex sequences. Consequently, normalization of the heart beats involved in baroreflex sequences by the total number of heart beats in a data segment yields more realistic information. Moreover, since occurrence of SBP ramps constitutes the input to the baroreceptors, the numbers of heartbeats involved in SBP ramps are reported in this paper as percentage of the total analyzed SBP.

Assessing vagal and sympathetic contributions to baroreflex actions includes decomposition of blood pressure and heart rate variabilities into LF and HF periodic components (6,18,72). Cross correlation of these LF and HF periodic components provides both magnitude and time lag (between the blood pressure and heart rate variability) information to quantitatively characterize vagal and sympathetic influences on autonomic regulation.

Cardiovascular function in spinal cord injured patients during their acute phase of recovery has not been addressed yet. In the literature, cardiovascular function following SCI had been focused on the patients' chronic phase of injury in which some degree of adaptation has taken. The effects of spinal cord injury on cardiovascular neural control might be more accurately identified during the acute phase rather than the chronic phase.

Objective

This study investigates short-term cardiac baroreflex regulation in able-bodied, paraplegic and tetraplegic subjects within the first two months following injury. The stimulus we employed was head up tilt (HUT). The objective was to examine cardiac indexes for their suitability as early indicators of autonomic damage. We compared results from able-bodied, paraplegic and tetraplegic subjects using four methods: a) mean values, b) spectral power estimation of blood pressure, heart rate, upper and lower body skin perfusions in low frequency (LF, 0.04-0.15Hz) and high frequency (HF, 0.15-0.4 Hz) regions, c) the baroreflex sequence technique and, d) the cross correlation between systolic blood pressure and heart rate examined in LF and HF regions for their potential to supply indexes to assess cardiovascular deficits following SCI. Our clinical aim is to find non-invasive indexes to be used in the clinical setting to assess damage and recovery of cardiovascular control in SCI patients

Chapter 2 : Physiological Background

Human Nervous System

The nervous system is a communications network that allows an organism to interact in appropriate ways with the environment. This system has *sensory components* that detect environmental events, *integrative components* that process sensory data and information that is stored in memory, and *motor components* that generate movements and other activity (9). The nervous system can be divided into the *central nervous system* (CNS), composed of the brain and spinal cord, and the *peripheral nervous system*, consists of sensory and motor components, which interface between the CNS and the environment. Nerve fibers in the peripheral nervous system transmit signals between the CNS and receptors and effectors in all other parts of the body. The peripheral nervous system consists of 43 pairs of nerves: 12 pairs of *cranial nerves* and 31 pairs that connect with the spinal cord as the *spinal nerves*. All the spinal nerves contain both afferent and efferent fibers, whereas some of the cranial nerves contain only afferent fibers. Afferent neurons convey information from peripheral sensory receptors to the CNS. Efferent neurons carry signals from the CNS to muscles, blood vessels and glands. The efferent division of the peripheral nervous system is divided into *somatic nervous system* and *autonomic nervous system* (79). The somatic portion of the efferent division of the peripheral nervous system is made up of all the nerve fibers going from the CNS to skeletal muscle fibers. The efferent innervation of all tissues other than skeletal muscle is by way of the autonomic nervous system (ANS). A special case occurs in the gastrointestinal tract, where autonomic neurons innervate a nerve network in the wall of the intestinal tract, which is called the *enteric nervous system*.

Anatomical and physiological differences within the ANS provide the basis for its further subdivision into *sympathetic* and *parasympathetic* nervous systems (79). The nerve fibers of the sympathetic and parasympathetic components leave the CNS at different levels – the sympathetic fibers from the thoracic and lumbar regions of the spinal cord, and the parasympathetic fibers from the brain and the sacral portion of the spinal cord. Both of these components consist of myelinated preganglionic fibers, which

make synaptic connections with unmyelinated postganglionic fibers, and it is the latter that innervate the effector organs. Most sympathetic preganglionic fibers are very short, synapsing with cell bodies of postganglionic neurons within ganglia that lie in a sympathetic ganglion chain located along either side of the spinal cord (74). Long postganglionic fibers originating in the ganglion terminate on the effector organ. Parasympathetic preganglionic fibers are long in comparison to sympathetic preganglionic fibers because they do not end until they reach terminal ganglia. Very short postganglionic fibers terminate on the cells of an organ itself (74). Most organs are innervated by fibers from both divisions of the ANS and the influence is usually opposing. In both sympathetic and parasympathetic nervous systems, acetylcholine is the major neurotransmitter released between pre- and post-ganglionic fibers in autonomic ganglia. In the parasympathetic system, acetylcholine is also the major neurotransmitter between the postganglionic fiber and the effector cell. In the sympathetic system, norepinephrine is usually the major transmitter between the postganglionic fiber and effector cell. Acetylcholine is also released by some sympathetic postganglionic endings; however, these play a relatively small role (9). As an exception, the sympathetic post-ganglionic neurons of the adrenal medulla never develop axons; instead they release their transmitters into blood steam upon activation by pre-ganglionic axons (79). The adrenal medulla, under sympathetic control, secretes a mixture of about 80% epinephrine and 20% norepinephrine (plus a small amount of other substances) into the blood. These hormones are transported in the blood stream to the effector cell.

The Anatomy and Physiology of the Spinal Cord

The spinal cord is a large collection of nerve tissue that extends from the base of the brain to the lower back. Messages between the brain and the nerve roots travel up and down the spinal cord, making it possible for brain and body to communicate. The spinal cord lies within the bony vertebral column. The central butterfly-shaped area of *gray matter* is composed of interneurons, the cell bodies and dendrites of efferent neurons, the entering fibers of afferent neurons, and glial cells (79). The gray matter is surrounded by *white matter*, which consists of groups of myelinated axons of interneurons. Groups of afferent fibers that enter the spinal cord from peripheral nerves enter the dorsal side of the cord via the *dorsal roots*. The axons of efferent neurons leave the spinal cord on the ventral side via the *ventral roots*. A short distance from the cord, the dorsal and the ventral roots from the same level combine to form a *spinal nerve*; one on each side of the spinal cord. The 31 pairs of spinal nerves are designated by the four vertebral levels: cervical, thoracic, lumbar, and sacral. In general, the eight cervical nerves (C) control the muscles and glands and receive sensory input from the neck, shoulder, arm, and hand. The 12 thoracic nerves (T) are associated with the chest and abdominal walls. The 5 lumbar nerves (L) are associated with the hip and leg, and 5 sacral nerves (S) are associated with the genitals and lower digestive tract (79,9).

The Physiology of Cardiovascular Regulation

Autonomic regulation of the cardiovascular system depends on a complex array of reflex circuits, interacting dynamically both at central and peripheral levels, and operating with negative and positive feedback (57). The central nervous system controls cardiovascular functions via the sympathetic and parasympathetic nervous systems. Changing arterial blood pressure is sensed by baroreceptors nerve endings located in carotid sinuses and the aortic arch. Baroreceptor activity is transmitted to the brainstem where signals are integrated and relayed through a network of central nervous that determine parasympathetic, and sympathetic nerve activity to effector organs including the heart, vasculature, and kidney. Changes in baroreceptor activity trigger reflex adjustments that buffer or oppose changes in blood pressure. A rise in blood pressure increases baroreflex activity leading to reflex inhibition of sympathetic nervous activity, activation of parasympathetic outflow, and subsequent decreases in vascular resistance and heart rate. Conversely, a fall in blood pressure decreases baroreceptor activity eliciting a reflex increase in sympathetic, inhibition of parasympathetic, and increases in vascular resistance and heart rate. In addition circulatory levels of norepinephrine, epinephrine, renin and vasopressin are modulated by the baroreflex (26). During a sustained increase in blood pressure, baroreceptor activity initially increases but declines (adapts) over time as the elevated pressure is maintained (23,19). Furthermore baroreflex activities are inhibited, the pressure threshold is increased, and the blood pressure activity function curve resets to higher levels of blood pressure after a period of acute hypertension (3).

Neural Control of Heart

While the heart inherently beats on its own, cardiac function can be influenced profoundly by neural inputs from the autonomic nervous system (ANS). The heart receives extrinsic nerve efferent (sympathetic and parasympathetic nervous systems) and afferent innervation, as well as own intrinsic (intracardiac) nerve supply (78). Intrinsic regulation is referred to as local or autoregulation and requires no external input from either the nervous or endocrine systems: Increasing the stretch of the myocardium by increasing end diastolic pressure causes a corresponding increase in ventricular pressure generated in the subsequent ventricular contraction (Frank-Starling mechanism). The extrinsic innervation, traveling in the cardiac branches of the parasympathetic and sympathetic trunks, enters the base of the heart to form a complex interconnecting network of mixed nerves called *the cardiac plexus* (78).

Efferent sympathetic nerve fibers, which are primarily noradrenergic, originate from the cell bodies of the paravertebral chain. These come from the superior, middle, and inferior cervical ganglia of the sympathetic trunk, together with the upper five ganglia of the thoracic segment trunk, chiefly the stellate ganglia and middle cervical ganglia (78,55). The number and location of sympathetic neurones in these extrinsic ganglia exhibit significant variations within mammalian species (4). Efferent PNS nerve fibers reach the cardiac plexus through the large vagal nerves, which carry preganglionic fibers from their cell bodies in the medulla oblongata. The mixed nerves of the cardiac plexus contain preganglionic and postganglionic parasympathetic and postganglionic sympathetic efferent fibers, as well as afferent fibers from cardiopulmonary receptors (9).

The sympathetic fibers richly innervate the ventricular muscles, the atria, and sinoatrial (SA) and atrioventricular (AV) nodes: The SA and AV nodes are controlled chiefly by fibers from the right paravertebral ganglia while the force of ventricular contraction is controlled chiefly by fibers from the left paravertebral ganglia (55). Unlike the sympathetic fibers, long preganglionic parasympathetic fibers synapse with the postganglionic parasympathetic neurons within the myocardium itself, mostly in the SA and AV nodes: Short postganglionic fibers innervate the nodes; there is only sparse parasympathetic innervation of the ventricles (46).

The sympathetic fibers release the neurotransmitter norepinephrine, which binds to β_1-adrenoceptors on the cardiac cell membrane. The heart also possesses α- and β_2 adrenoceptors, but β_1-receptors predominate (60). The hormone epinephrine secreted by the medulla of the adrenal gland controlled by sympathetic preganglionic fibers, acts similarly. Since the terminating action of norepinephrine requires diffusion into the blood stream and reuptake into the sympathetic nervous system, recovery from the sympathetic stimulation is slow. Firing of the parasympathetic postganglionic fibers releases the neurotransmitter acetylcholine from the nerve ending. Acetylcholine acts by binding to muscarinic receptors on the myocyte membrane, and is quickly removed by the enzyme cholinesterase, which is found throughout heart tissues. Consequently, once the parasympathetic stimulation ceases, the effects of the stimulation decay quickly (60).

The rhythm of the heart is normally determined by the firing of the SA node, located in the posterior wall of the right atrium near the superior vena cava. This intrinsic rhythm, 100 beats per minute in human, is strongly influenced by the ANS, with the parasympathetic being dominant over sympathetic influences at rest. Changes in heart rate usually involve a reciprocal action of the two branches of the ANS: Increase in heart rate is achieved by a waning of parasympathetic and concomitant increase in sympathetic nervous system. The sympathetic effects on the heart can be summarized as below:

- An increase in heart rate (positive chronotropic effects)
- A decrease in cardiac action potential duration
- An increase in rate of action potential conduction (positive dromotropic effect)
- An increase in cardiac contractility (positive inotropic effect)
- An increase in rate of cardiac relaxation

Parasympathetic effects are opposite. Parasympathetic effects on inotropy are weak in the ventricle, but relatively strong in the atria. Physiologically, whenever the body activates the sympathetic system, it down regulates parasympathetic activity, and visa versa, so that the activities of these two branches of the autonomic nervous system respond reciprocally.

Neural Control of Vasculature

The blood vessels are made up of high-pressure arterial and low-pressure venous networks. The arterial system is composed of a complex series of arteries, arterioles and capillaries, and the venous system is composed of venules and veins. The arterial network is responsibly for distributing nutrients and oxygen to the organs and the systems of the body. The venous side carries blood back to the heart. Because the arteries have large radii, and an elastic wall, they serve as low resistance tubes, and act as a pressure reservoir for maintaining blood flow through diastole. The small arteries and arterioles that regulate blood flow throughout the body are called the resistance vessels. Vascular smooth muscle, which constitutes a major fraction of the wall of the arterioles, controls total peripheral resistance, arterial and venous tone. Intrinsic and extrinsic mechanisms are responsible for regulating vascular tone. Intrinsic regulation is the regulation of tone by local factors sited entirely within an organ or tissue. Extrinsic regulation originates outside the organ. The CNS superimposes a control system over the entire peripheral vasculature by means of the ANS and endocrine secretions (55). Neural control of blood flow is accomplished mainly by the sympathetic nervous system. Sympathetic nerves to the blood vessels are tonically active; inhibition of the vasoconstrictor center in the medulla reduces peripheral vascular resistance. Stimulation of the sympathetic nervous system increases peripheral resistance (9,55,60). Descending excitatory and inhibitory fibers, *the bulbospinal fibers*, pass down the spinal cord and synapse with preganglionic neurons in the thoracicolumbar segments T1 to L3. Blood vessels do not receive innervation from the parasympathetic nervous system (55,60).

Spinal Cord Injury

Spinal cord injury (SCI) affects approximately 12,000 people in North America each year (38). It is a serious medical and socioeconomic problem associated with devastating functional and psychological effects 17. Of these, 53% are diagnosed with tetraplegia and 46% with paraplegia. The most frequent neurologic category is incomplete tetraplegia (30%), followed by complete paraplegia (26%), incomplete paraplegia (20%), and complete tetraplegia (23%) (38). Tetraplegia refers to damage or loss of motor and/or sensory function in the cervical segment of the spinal cord, and results in impairment of function in the arms, as well as in the trunk, legs and pelvic organs. Paraplegia refers to impairment or loss of motor and/or sensory function in thoracic, lumbar or sacral segments of the spinal cord. Depending on the level of injury, the trunk, legs and pelvic organs may be impaired. Complete injury is the term used when there is an absence of sensory and motor function in the lowest sacral segment, whereas incomplete injury is used when partial preservation of sensory and/or motor functions is found below the neurological level and includes the sacral segment. Most frequently SCI accidents occur in persons between 16 and 30 years of age (9). Frequent causes are automobile and motorcycle accidents and gunshot wounds. A lesion below the phrenic motor nucleus may result in paralysis of all four extremities, tetraplegia (quadriplegia), whereas a lesion of the thoracic spinal cord causes paraplegia, which is paralysis of the lower extremities. The average life time cost of treating an individual with SCI is in the range of $500,000 -2 million, dependant upon factors such as the extent and location of the injury (17).

Lesion of the Dorsal (Posterior) and Ventral (Anterior) Roots: Depending on the extent of injury to a dorsal root, various symptoms are present. Cutaneous afferents in the dorsal root are destined to innervate a specific strip of skin (dermatome). Therefore a lesion at this site produces symptoms that are localized in a dermatomal distribution rather than a peripheral nerve distribution. Because dermatomes overlap each other, sectioning one dorsal root produces different symptoms (i.e. hypesthesia or paresthesia) than sectioning many dorsal roots (i.e. anesthesia). Some injuries may not be as severe,

and lesion may cause pressure or irritation to the root. Pressure may produce paresthesia and hypesthesia in a dermatomal pattern whereas irritation and subsequent inflammation may result in radicular (root) pain located in a dermatomal area (82).

Two types of motor neurons are referred to clinically. One type is called lower motor neurons. The cell bodies of lower motor neurons reside in lamina IX of the cord's ventral horn. Their axons leave the cord in the ventral root, enter a spinal nerve, and continue in peripheral nerves to skeletal muscles. In general lower motor neurons can be defined as the only neurons that innervate skeletal muscle and are thus the final common pathway to the muscle. These neurons are found in spinal nerves originating from spinal cord and also in those cranial nerves emerging from the brain stem that innervate skeletal muscles located in the head region. Lesions of lower motor neurons produce various signs and symptoms based on the lower motor neurons being responsible for the contraction of muscle. Because of its developmental origin, a skeletal muscle becomes innervated by more than one cord segment, and one cord segment can innervate more than one muscle. If a lower motor neuron lesion involves the nerve fibers innervating the muscle being tested, the reflex response of that particular muscle nonexistent (areflexic) or diminished depending on how much of the muscle's innervation is affected. The other type of motor neuron is the upper motor neuron, which are clinically referred to as neurons that influence lower motor neurons. Since upper motor neurons are descending tract, unlike lower motor neurons, upper motor neurons located in the cerebral cortex, internal capsule, brain stem and white matter of the spinal cord. Lesion of the spinal cord probably interrupts a number of descending upper motor neurons and produce characteristic signs that are evident after the acute effects are gone. Lower motor neuron lesions may be restricted to individual motor muscle groups, whereas upper motor neuron lesion may affect the entire limb.

Alteration of Cardiovascular Control Following Spinal Cord Injury:

Besides loss of muscle control and sensation below the lesion, the injury also seriously compromises autonomic regulation of arterial blood pressure (e.g.16,15). The loss of autonomic control of cardiac and vascular regulatory mechanisms is dependent on the severity and level of injury to the spinal cord. Cardiovascular problems known to arise from SNS dysfunction include low resting blood pressure, orthostatic hypotension, autonomic dysreflexia, reflex bradycardia and cardiac arrest (e.g. 20,16,11,77). Treatment to achieve a mean arterial blood pressure of 85 mmHg for a minimum of seven days has been reported to result in better neurological outcomes (7). Rehabilitation is also critical to prevent long term immobilization. It has been reported that patients who spent less than 14 days in bed rest maintained systolic and diastolic blood pressure in response to head up tilt better than did those had more than 14 days bed rest (43). Therefore, cardiovascular related problems could be involved not only in life threatening complications, but also in delayed rehabilitation and poor quality of life (20,16,43).

Orthostatic hypotension

Orthostatic hypotension refers to a reduction in systolic blood pressure by at least 20 mmHg or diastolic blood pressure by 10 mmHg within 3 min of standing or being raised to greater than 60^{o} HUT. Symptoms of orthostatic hypotension include light-headedness, dizziness, unclear vision, ringing in the ears, nausea, fatigue, and cognitive impairment, palpitations, tremulousness, headache and neck ache (American Autonomic Society, 1996). Orthostatic hypotension is a common problem in both acute and chronic phases of injury, as the injury to the spinal cord interferes with normal transmission of sympathetic activity, a critical agent in short-term regulation of blood pressure (20,43). Conservative treatment includes the use of abdominal binders and support hose to prevent venous pooling and increased dietary salt and fluid intake to increase blood pressure. Patients are challenged with a series of head-up tilts, which become progressively greater with time; treatment continues until the patient can reasonably tolerate an upright posture, which may require weeks or months of intensive intervention.

Assessments of Cardiovascular Impairment Following Spinal Cord Injury:

Consistent and reproducible assessment scales are necessary to define acutely injured patient deficit(s) and to facilitate communication with caregivers regarding the patient's status (38). A variety of assessment systems is available for documenting neurological and functional status of patients after SCI. Among them, The American Spinal Injury Association (ASIA) scale for neurological status, and The Functional Independence Measure (FIM) for functional outcome, are the most common scales. The American Spinal Injury Association (ASIA) classification of SCI is assessed via sensitivity of the 28 dermatomes tested by pin prick and light touch, and of 10 myotomes graded by strength from 0 to 5. Dermatome refers to the area of the skin innervated by the sensory axons within each segmental nerve. Myotome refers to the collection of muscle fibers innervated by the motor axons within each segmental nerve. The final decision on the level of injury depends on the total number from each test. The Functional Independence Measure (FIM) measures independence of functioning such as self-care, sphincter control, mobility, locomotion, communication and social cognition.

Besides deficits of motor and sensory function following SCI, cardiovascular problems arising from sympathetic nervous system dysfunction are also common in acute SCI. Despite these problems, there is no assessment test available to identify patient's cardiovascular deficits following SCI. The importance of assessing autonomic deficits following SCI have been addressed in recent papers (e.g. 20,28,32). In this study, we attempt to discriminate an able-bodied group from SCI, and a paraplegic group from a tetraplegic group using cardiovascular variables in response to tilt.

Chapter 3 : Methods

Subjects

Eleven healthy, drug-free, able-bodied (AB) volunteers (age: 25±4, 8 men and 3 women) were recruited as a control group. Five paraplegic volunteers (PARA, age: 34±15, 4 men and 1 woman with lesions between T6-T11), and five tetraplegic volunteers (TETRA, age: 26±9, 5 men with lesions between C3-T5) were recruited from patients admitted to Cardinal Hill Rehabilitation Hospital (CHRH). Complete anthropomorphic data for all SCI subjects are given in Table 3.1. None of the participants had previous cardiovascular- related diseases and only a few of the able-bodied subjects took medication likely to affect the cardiovascular system. Some SCI patients were on blood pressure medication and some were on medication to treat muscle spasms. The list of medications is given in Appendix A. All SCI subjects wore abdominal binders and support hose during the study. Subjects were excluded based on the following conditions: any orthopaedic, neurological or dermatological disorder that would contraindicate a HUT, deep vein thrombosis or any psychological disorder. Most SCI subjects were in some degree of deconditioning secondary to extended bed rest and immobility, causing some degree of orthostatic intolerance during the rehabilitation phase.

Three able-bodied, one paraplegic and two tetraplegic subjects had pre-syncopal symptoms either at the end of 60^{o} HUT or at the beginning of 80^{o} HUT. They were returned to the supine position immediately. So data at 80^{o} HUT were not collected for these subjects.

Testing Schedules

All able-bodied subjects were studied once. All SCI subjects were scheduled to be studied eight times during their second, four, six, eight weeks, and six, eight, twelve months post injury. However, only one tetraplegic (C3 ASIA B) and one paraplegic (L1-T11 ASIA A) subjects were able to follow the planned schedule. One tetraplegic (C4 ASIA B) was studied four times, and one paraplegic (T11 ASIA A) was studied three times, and one paraplegic and tetraplegic (L1-L3 ASIA A, C5 ASIA B) were studied once, and the rest were studied twice according to the schedule given above.

For each SCI subject, initial studies (~ two, four, six and eight weeks post-injury) were conducted while the subject was a patient at Cardinal Hill Rehabilitation Hospital (CHRH). These sessions were performed at the Physical Therapy Clinic at CHRH. Subsequent studies (conducted three, six, eight and 12 months post-injury) were performed at the General Clinical Research Center (GCRC) at the University of Kentucky. Studies of able-bodied subjects were also performed at the GCRC at the University of Kentucky. For studies at the GCRC, the subjects (both able-bodied and SCI subjects) were admitted on the day prior to the data collection session in order to provide dietary and behavioral conditions similar to those at CHRH.

All studies were conducting in the morning, except two tetraplegic studies, which were performed at noon due to episodes of injury related problems in the morning. All participants were familiarized with the study and gave informed consent to a protocol approved by the University of Kentucky Institutional Review Board and Cardinal Hill Rehabilitation Hospital.

Tilt Protocol

All subjects were studied at least one hour post-prandial and refrained from alcohol and caffeine 24 hours before the study. All subjects consumed a fat free breakfast, so as to not interfere with the circulatory hormonal assay for pancreatic polypeptide. Spinal cord injured subjects wore abdominal binders and support hose. Thirty min before study, AB subjects emptied their bladder and SCI subjects had bladder catheterization. An IV cannula (Quick Cath, Baxter) was inserted into an antecubital vein to obtain blood for fluid volume and hormonal analyses. Non-invasive instrumentation, described below, was applied while the subject lay supine on the tilt table. These preparations took approximately 30 minutes. All subjects were fixed to the tilt table by straps at the chest and pelvis.

The study lasted about one hour, beginning with a 10 min period of supine control, followed by four levels of HUT (20^o, 40^o, 60^o, 80^o) each lasting 7 min. The recovery period consisted of one min at 20^o HUT followed by seven min. supine. During tilt, members of the research and clinical team continuously monitored the alertness of the subject as well as the quality of hemodynamic variables. If subjects developed syncopal symptoms (signs of fainting) during any part of the study, they were brought to supine and the recovery phase began. Blood samples for fluid volume and hormonal assays were taken at the end of supine control, 20^o, 40^o, 60^o, 80^o HUT and two minutes into recovery. A graphic illustration of the protocol is given in Figure 3.1.

Measurement Variables

Non-invasive instrumentation was used to measure the following hemodynamic variables.

Arterial Blood Pressure (AP): Beat-to-beat continuous blood pressure was acquired through a Portapres Model-2 (Finapres Medical Systems, The Netherlands) with a sphygmomanometer finger cuff placed around the left middle or index finger. Manual arterial blood pressure measurements were taken at the beginning of supine control and at the end of the recovery period with a digital blood pressure measurement device.

Thoracic Electrical Bioimpedance Cardiac Output (TEBCO): Eight thoracic impedance leads were placed on the neck and thorax to obtain analog ECG, ΔZ, dZ/dt, dZ/dt respiration, stroke volume, and heart rate through an EXT-TEBCO Module (Hemo Sapiens, Sedona, AZ).

Skin Perfusion and Concentration of Moving Cells (SP1, SP2, CMBC1, CMBC2): Cutaneous skin perfusion (also referred to as skin blood flow) and concentration of moving cells at locations on the forearm (upper body) and shin (lower body) were acquired through a Perimed (Perimed, Sweden) laser doppler flowmeter .

Calf Circumference (CC): Calf circumference was acquired with a Hokanson EC-4 Plethysmograph (Hokanson, Bellvue, Washington) via a mercury-in-rubber strain gauge placed around the largest part of the left calf.

Tilt Angle: Tilt angle was acquired from an accelerometer mounted on the tilt table.

Blood Sample: Eleven mL of venous blood were drawn from an antecubital vein at six intervals during the protocol. Each sample was analyzed to determine levels of epinephrine, norepinephrine, hematocrit (HCT), total proteins (TP), plasma renin activity (PRA) and pancreatic polypeptide (PPP). Laboratory analysis of blood samples was performed at laboratories with expertise in each analysis: catecholamines (one mL) by Michael Ziegler, Clinical Research Center, UCSD, San Diego, CA; PPP (three mL); PRA (five mL); HCT and TP (two mL) at the University of Kentucky clinical laboratory.

Data Acquisition:

All data were acquired at 250 Hz and saved as a LABVIEW file to a Dell Inspiron 4100. The list of all acquired variables and their calibration units are given in Table 3.3. Prior to analyses; all data were eye-scanned and abnormalities were removed with ViiSoftware Browser, C++ program written by Dr. David Brown (University of Kentucky, Biomedical Engineering). Detailed information for this program is given in Appendix B.

Data pre-processing for Mean Values, Spectral Power and Cross Correlation Analysis: In ViiSoftware Browser, heart rate (HR) and RR interval were calculated from ECG; systolic, diastolic blood pressure (SBP and DBP respectively) were calculated from arterial blood pressure. Detailed of these calculations were given in Appendix B. The time delay between HR calculated, from ECG and HR acquired from EXT-TEBCO was determined, and EXT-TEBCO variables were aligned with respect to their actual acquired time. Next, data were down sampled to 5Hz in Browser and converted to binary files for export into *Matlab (The Mathworks).* Finally, data were imported into Matlab using *fread* and *fopen* functions as a matrix consisting of 16 columns. Each column represented one variable.

Data pre-processing for baroreflex sequence technique: ECG, arterial blood pressure and tilt angle, sampled at 250 Hz, were converted to binary files and exported into Matlab. A Matlab program was written to identify the location of the R wave in the ECG, and to construct beat-to-beat sampled RR interval files. The maximum value of arterial blood pressure between the two R-R intervals (in msec) was computed and used to construct a beat-by-beat sampled systolic blood pressure (SBP) file.

Data Analysis:

Mean Value Analysis

The last 5 minutes (1500 data points) of data at each level of the protocol (supine control, 20^o, 40^o, 60^o, 80^o HUT and recovery) were used to calculate mean values of each variable. Cardiac output was found by multiplying heart rate and stroke volume. Data were averaged by group (i.e. able-bodied, paraplegic or tetraplegic group) and tilt position (i.e. supine control, 20^o, 40^o, 60^o, 80^o HUT and recovery). Standard error of the mean (SEM) was also calculated for each group and tilt position.

Spectral Power Analysis

A Matlab program was written to calculate spectral power, based on Welch's averaged periodogram method program. The last 10 minutes of data at supine control and the last 5 minute of data at each level of the tilt (20^o, 40^o, 60^o, 80^o HUT and recovery) were used for calculation. Data were divided into 500 points with 50% overlapping segments. The processes listed below were repeated for each segment: The Matlab *detrend* function was used to remove the mean value in order to remove any linear trend over the segment. The Matlab *Hanning* function with 500 data-points was used to decrease leakage of the power spectrum. The Matlab *fft* function with 1024 data-points was used to calculate discrete Fast Fourier coefficients.

A variable x(n) defines N-point data where n=0,1,2,3,…N-1, N=500, which x defines heart rate, blood pressure, upper or lower skin perfusions. Another variable h(n) defines N-point symmetric Hamming window, $h(n) = 0.5(1 - \cos(2\pi \frac{n}{N}))$, where n=0,1,2,..N-1, N=500. First y(n) was calculated by multiplying x(n) by h(n), which is $y(n) = x(n)h(n)$. Discrete Fourier coefficients of y(n) were calculated from following equation:

$$Y(k) = \sum_{j=0}^{N-1} y(j) e^{-2\pi ijk/N} \text{ , where k=0,1,2,…N-1……..…(1)}$$

The absolute value of Y(k) was used as the spectral power estimation of x(n), which is shown as S(k).

$$S(k) = |Y(k)|^2 \quad \text{.....(2)}$$

In discrete Fourier Transform the observed data sequence was considered as a multiplication of its periodic extension with a rectangular window. In the frequency domain, this corresponds to the convolution of the transform of the periodic extension and the transform of the window.

Total spectral power was calculated for two frequency regions: The low frequency region (LF, 0.04-0.15 Hz), sympathetic domination of regulation, and the high frequency region (HF, 0.15-0.4 Hz), parasympathetic domination of regulation (42).

$$LF\_S = \sum_{k=10}^{31} S(k) \quad \text{.....(3)}$$

$$HF\_S = \sum_{k=32}^{104} S(k) \quad \text{.....(4)}$$

Autonomic balance of heart rate was estimated based on the following indices:

$$SNS = \sum_{k=10}^{31} SHR(k) / \sum_{k=32}^{104} SHR(k) \quad \text{.....(5)}$$

$$PNS = \sum_{k=32}^{104} SHR(k) / (\sum_{k=10}^{104} SHR(k) \quad \text{.....(6)}$$

Where,

- SNS : Sympathetic nervous system index of heart
- PNS Parasympathetic nervous system index of heart
- SHR(k): Spectral power of heart rate

Cross Correlation Analysis

The last five minutes of the heart rate and systolic blood pressure time series from each tilt interval were filtered using fourth-order Butterworth band pass filters to separate oscillations in low frequency (LF: 0.04-0.15) and high frequency (HF: 0.15-0.45 Hz) regions. After filtering in the forward direction, the filtered sequence was then reversed and run back through the filter. The resultant series has precisely zero phase distortion. Each signal was divided into 30 sec segments (150 data points) for LF and HF analysis. Data segments overlapped by 50%, and were linearly detrended. Finally, cross correlation coefficients were calculated where the SBP segment was the reference signal and the heart rate segment was delayed with respect to the reference signal to create the time lag axis. All coefficient values were normalized by the product of the root mean square values of heart rate and systolic blood pressure. Matlab functions given below were used in the data analysis program; the *butter* function for finding the coefficients of the fourth-order Butterworth filter, the *filtfilt* function for filtering the data to obtain high and low frequency components, the *detrend* function for detrending the mean, and the *xcorr* function for calculation of correlation coefficients.

If s(n) and h(n), n=0,1,2,3,…N-1, N-point systolic blood pressure and heart rate, where N=150, then cross correlation coefficients can be calculated from the following equations:

$$CC_{sh}(m) = \frac{1}{N}\left(\sum_{i=0}^{N-|m|-1} s(i)h(i+|m|) \right) \quad \text{.....(7)}$$

$$CC_{sh}(m) = s(m) * h(-m) = \sum_{k=-\infty}^{\infty} s(k)h(m-k) \quad \text{.....(8)}$$

where * represents the convolution of two signals

The cross coefficients were normalized as below:

$$CCN_{sh}(m) = \frac{CC_{sh}(m)}{\sqrt{\frac{\sum_{j=1}^{N} s^2(j) \sum_{j=1}^{N} h^2(j)}{N^2}}} \quad \text{.....(9}$$

)

Baroreflex Sequences

A computer program similar to those of Blaber et al. (12) and Di Rienzo et al. (24,25) was written to scan the beat-to-beat time series of SBP and RR intervals with minimum 1 mmHg SBP, and 4 ms RR interval thresholds. The last five minutes of data acquired from each tilt position were used for further analysis. Three or more consecutive beats that independently contained increasing and decreasing pressure (SBP+, SBP-) and RR interval (RR+, RR-) were identified. If any SBP beats fell within the segment of a Portapress servo adjustment, that beat was excluded. The total number of excluded beats was less than 1% of the total number of analyzed beats. If an identified SBP sequence was followed by an identified RR interval sequence with delay of zero, one or two beats, these SBP and RR interval sequences were assigned as coupled. A regression Coefficient was calculated for each coupled SBP and RR interval sequences. Only coupled sequences with regression coefficients r>0.90 were accepted as baroreflex sequences. (BRsq): A positive BRsq included coupled SBP+ and RR+, and a negative BRsq included coupled SBP- and RR- sequences. The mean slope of all BRsq was calculated and taken as an estimation of baroreflex sensitivity (BRS, ms/mmHg). The numbers of beats involved in SBP ramps and BRsq were determined at each tilt position. Since the mean RR interval varied among subjects and from supine to head up tilt positions within the same subject, the number of beats involved in SBP ramps and BRsq are reported as percentage of the overall number of analyzed heart beats in the defined segment. The program gave acceptable BRS estimation results when tested on the EuroBavar data set (51). The EuroBavar data set provides a set of data from non-

homogenous subjects with a large BRS range. The aim of this web site is to provide an identical set of data to compare the results of different techniques.

The baroreflex effectiveness index (BEI) was evaluated as the ratio between the total number of BRsq and the total number of SBP ramps (24). Positive BEI, ratio between positive BRsq and SBP+, and negative BEI, the ratio between negative BRsq and SBP-, indexes were also analyzed to determine the "selective" responsiveness of the baroreflex to SBP+ and SBP- (24).

Statistical Analysis:

The mean values of each variable from the two studies on the SCI subjects were used for statistical analysis. Differences within and between the three groups (AB, PARA and TETRA) during supine control, the four levels of HUT and recovery were tested for significance using a two factor Analysis of Variance (ANOVA). The group factor was used to indicate differences among the three groups. The tilt factor was used to indicate tilt effects for all groups. The group by tilt factor was used to determine significantly different tilt effects among groups. A p value ≤ 0.05 was accepted as indicating statistical significance. Results are presented as mean and standard error of mean (SEM).

Table 3.1 Demographic information from the SCI patients. The American Spinal Injury Association (ASIA) classifies SCI into five categories, ranging from A to E: sensitiveness of 28 dermatomes are tested by pin prick and light touch, and 10 mytomes are tested and graded from 0 to 5 depend upon their strength. A: Complete: No motor or sensory function is preserved in the sacral segments S4-S5. B: Sensory incomplete: Sensory but not motor function is preserved below the level of injury and includes the S4-S5 sacral segment of the spinal cord. C: Motor incomplete: Motor function remains in more than half of key muscles below the level of injury, with muscle strength grade of less than 3. Sensory function is present below the neurological level and includes sacral segments S4-S5. D: Motor Incomplete: Motor function remains in more than half of key muscles below the level of injury, with muscle strength grade of 3 or greater. Sensory function is present below the neurological level and includes sacral segments S4-S5. E: Normal: Motor and sensory function are normal. Tetraplegia refers to an injury to the cervical section of the spinal cord. Paraplegia refers to an injury in the thoracic, lunbar or sacral section of the spinal cord.

					Post Injury time	
	Subject No	Age, yr	Sex	Level of Injury	First Session	Second Session
Paraplegics	1	31	M	T-11 ASIA A	1w, 2d	2w, 5d
	2	20	M	L1-L3 ASIA A	9w, 4d	-
	3	60	M	T-10 ASIA A	4w, 1d	7w, 2d
	4	23	F	T5-T10 ASIA A	2w,3d	3w, 2d
	5	38	M	T10 ASIA A	1w,2d	2w, 5d
Tetraplegics	6	19	M	C3 ASIA B	1w,5d	3w, 5d
	7	30	M	T5 ASIA A	8w,3d	-
	8	41	M	C3 ASIA A	1w, 5d	3w, 5d
	9	24	M	C4 ASIA B	3w, 6d	5w, 4d
	10	19	M	C5 ASIA B	2w,3d	-

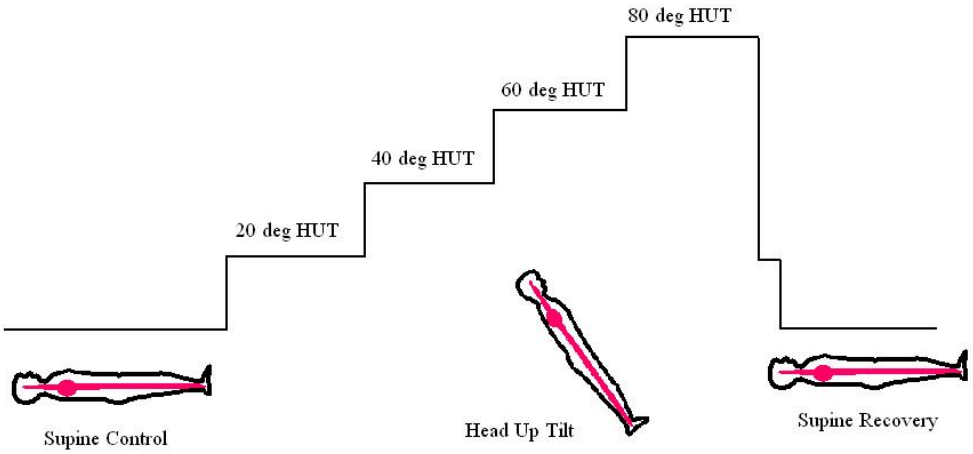


Figure 3.1 The standard tilt protocol included 10 minute supine control, 7-10 minute 20, 40 60 and 80 deg head up tilt, return to 1 minute 20 deg HUT and supine recovery positions. Blood samples were taken from an antecubital vein at the end of supine control, 20°, 40°, 60 °, 80 ° HUT and two minutes into recovery.

Table 3.2: The list of acquired variables with calibration values in voltage and in engineering units.

Channel	Signal	Voltage (V)	Engineering Units	
			Value	Units
0	AP	[0.00 2.00]	[0 200]	mmHg
1	ECG (analog)	no calibration	no calibration	
2	ΔZ	[0 0.98 1.95 4.88]	[0 50 100 250]	unitless
3	dZ/dt	[0 0.98 1.95 4.88]	[0 50 100 250]	unitless
4	SV	[0 0.83 1.67 2.5]	[0 50 100 150]	mL
5	HR (TEBCO)	[0 0.83 1.67 3.33]	[0 50 100 200]	beats/min
6	TFC	[0 4.03]	[0 0.033 0 0.033]	unitless
7	$\Delta Z/\Delta T_{resp}$	[0 0.98 1.95 4.88]	[0 50 100 250]	unitless
8	RespRate	[0 0.5 1.0 1.5]	[0 10 20 30]	breaths/min
9	RF	±0.35V	±10, 0	cm/sec
10	CC	[0 0.025], [0 0.25]	[0 0.1], [0 1]	%
11	Tilt Angle	[0.62 3.20]	[0 90]	degrees
12	SP1	[0 1]	[0 100]	perf. Units
13	CMBC1	[0 1]	[0 100]	perf. Units
14	SP2	[0 1]	[0 100]	perf. Units
15	CMBC2	[0 1]	[0 100]	perf. Units

Chapter 4 : Results

At their first study, three able bodied, one paraplegic and three tetraplegic subjects demonstrated symptoms of presyncope at the end of 60^{o} head up tilt (HUT), and were returned to the supine position immediately. The paraplegic and one of the tetraplegic subjects were able to finish the whole protocol at their second study. The four remaining paraplegic and two tetraplegic subjects finished the protocol at both their first and second studies.

Typical hemodynamic responses to HUT for one able-bodied (left) and for one tetraplegic (right, C4 ASIA B) are illustrated in Figure 4.1. In this figure, heart rate (HR, bpm), arterial blood pressure (AP, mmHg), stroke volume (SV, mL), calf circumference (CC, % change), and the tilt protocol (time, minute) are plotted on the first, second, third, fourth and last rows respectively. After supine control, the able-bodied subject was head-up-tilted to 20^{o}, 40^{o}, 60^{o} and 80^{o} and then returned to the supine position. Each tilt level lasted 7 to 10 min. The spinal cord injured subject (right) was returned to the supine position immediately when he demonstrated symptoms of presyncope (at the beginning of 80^{o} HUT). The able-bodied subject regulated blood pressure primarily by using increases in heart rate and peripheral resistance while the spinal cord injured subject was much less successful in minimizing blood pressure changes during tilt and was generally ineffectual in modulating heart rate to compensate for orthostatic challenges. At the onset of tilt, calf circumference, an estimation of blood pooling to the lower extremities, started to rise, and was not different between subjects eve though the SCI subject wore support hose.

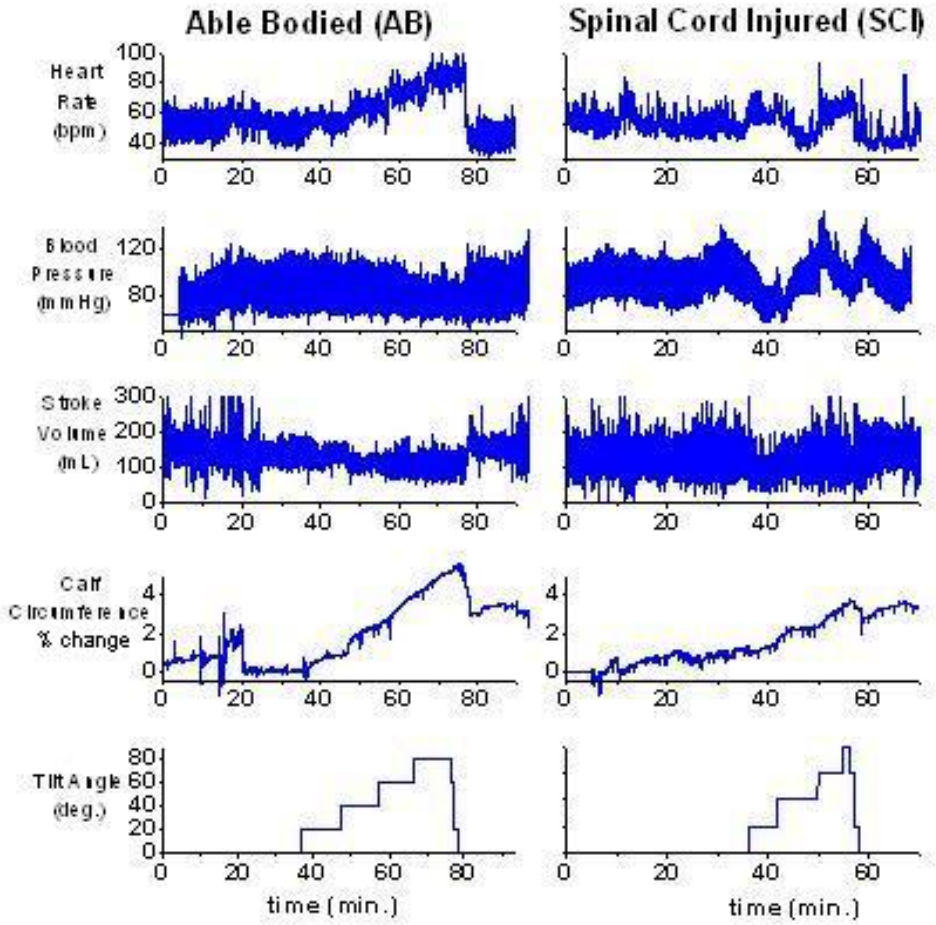


Figure 4.1: Time series plots of cardiovascular variables for an able-bodied (left) and a spinal cord injured subject (right, C4 ASIA B) undergoing increasing levels of head-up tilt.

Mean Values

Arterial Blood Pressure: Averaged (±SEM) arterial blood pressures for able-bodied, paraplegic and tetraplegic subjects in response to head-up-tilt are given in Figure 4.2. Able bodied and paraplegic subjects maintained their blood pressure, while tetraplegics exhibited a significant reduction in blood pressure ($p < 0.05$) under increasing orthostatic stress. The standard error around the mean value was also higher in the tetraplegic group indicating more variability in that group.

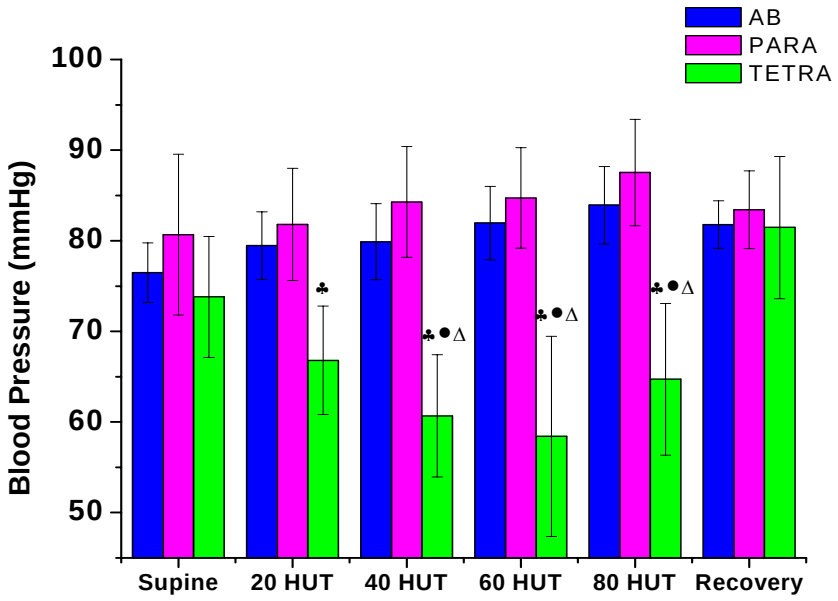


Figure 4.2: Average (±SEM) arterial blood pressure for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. Group, tilt and group/tilt interaction, p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from supine condition (same group).

Heart Rate: Averaged (±SEM) heart rates for able-bodied, paraplegic and tetraplegic subjects in response to head-up-tilt are illustrated in Figure 4.3. The able-bodied subjects increased their heart rate in order to compensate for the reduction in blood pressure induced by head-up-tilt. Tetraplegics were significantly ($p < 0.05$) less effective in increasing heart rate to accompany the tilt-induced decrease in blood pressure. The paraplegic group had the highest mean heart rate among three groups.

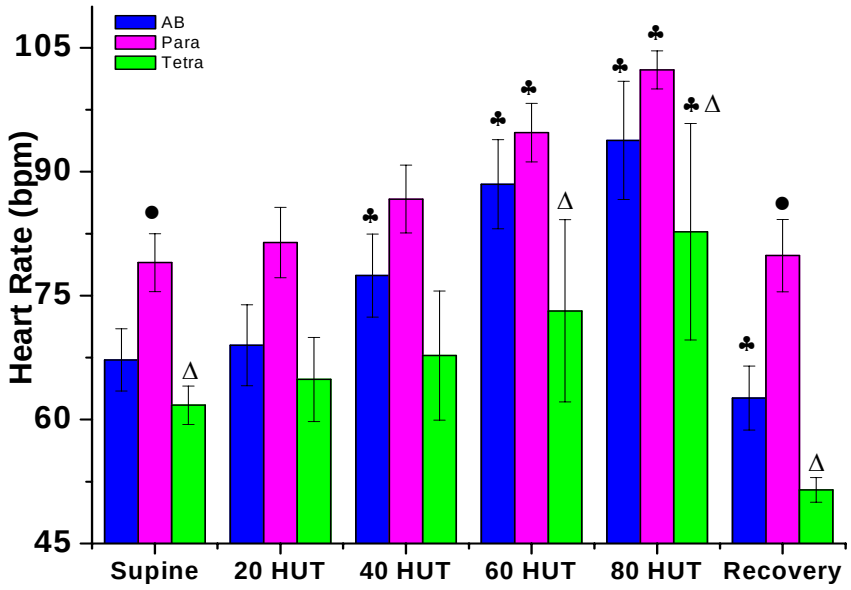


Figure 4.3: Average (±SEM) heart rate for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. Group/tilt interaction, p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from supine condition (same group).

Stroke Volume: Averaged (±SEM) stroke volumes for able-bodied, paraplegic and tetraplegic subjects are shown in Figure 4.4. As expected, stroke volume significantly ($p < 0.05$) decreased in the able-bodied group in response to HUT. Mean stroke volume also decreased with increasing HUT in both SCI groups; however, only paraplegics decreased their stroke volume significantly from supine to 80 deg HUT. There was no significant reduction at any tilt level in the tetraplegic group. The difference between the paraplegic and control groups was greatest at supine and 20 deg HUT, and dimished at higher tilt levels. The tetraplegic group exhibited high variances around the mean values at each tilt level.

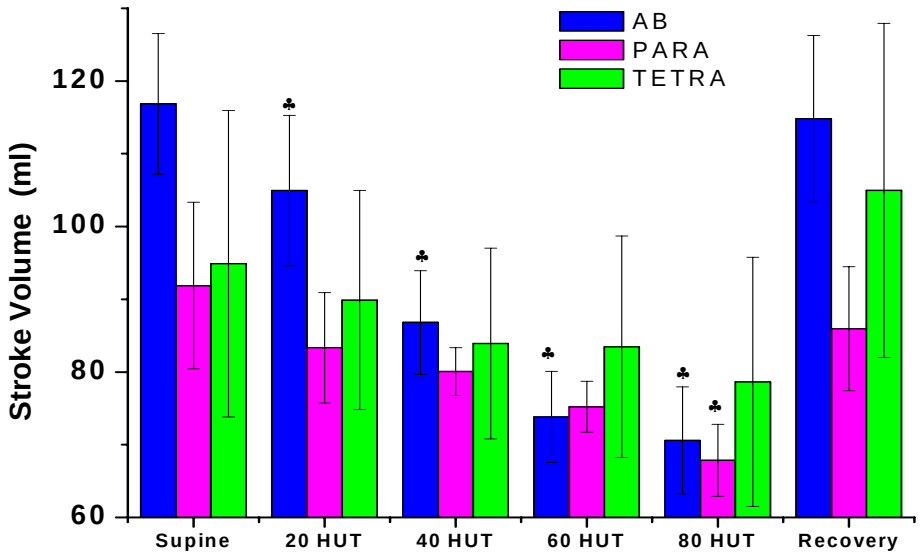


Figure 4.4: Average (±SEM) stroke volume for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. ♣ significantly different from supine condition (same group).

Upper Body Skin Perfusion: Averaged (±SEM) upper body skin perfusion was maintained in able-bodied and in paraplegic groups but paraplegics had lower values than able-bodied at rest and in response to ead up tilt, Figure 4.5. The tetraplegic response was similar to able-bodied at rest, but significantly decreased from supine to 80 deg HUT, Figure 4.5. The paraplegic group had the lowest values among the three groups.

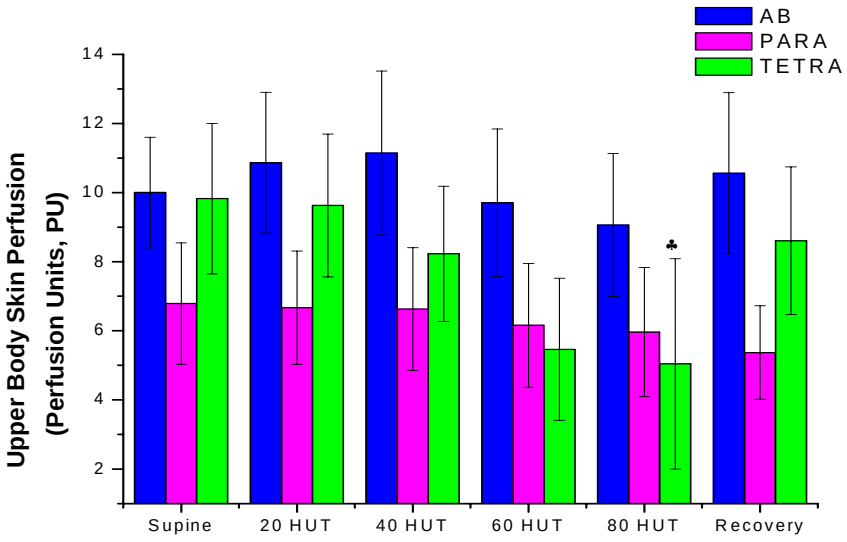


Figure 4.5: Average (±SEM) upper body skin perfusion for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. Tilt effect, p value ≤ 0.05; ♣ significantly different from supine condition (same group).

Lower Body Skin Perfusion: Averaged (±SEM) lower body skin perfusion for able-bodied, paraplegic and tetraplegic subjects are shown in Figure 4.6. Mean values of lower body skin perfusion decreased significantly in response to increasing tilt levels in all three groups, and returned to control values in supine recovery. The tetraplegic group had the lowest values among the three groups.

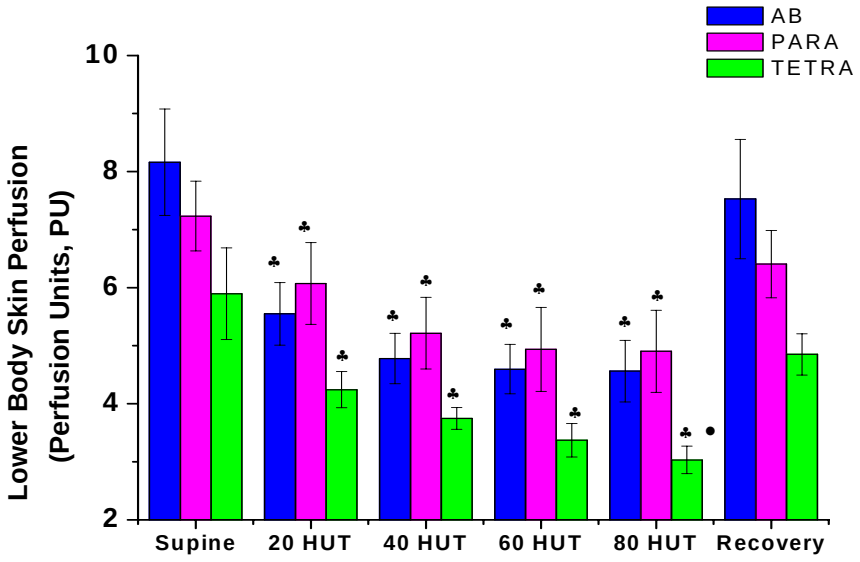


Figure 4.6: Average (±SEM) lower body skin perfusion for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. Tilt effect, p value ≤ 0.05; ● significantly different from AB (same stress level), ♣ significantly different from supine condition (same group).

Calf Circumference: Due to the time-dependant nature of calf circumference during orthostatic stress, the rate of vascular fluid shift to the leg was evaluated as the ratio between the difference of calf circumference at end of the 80 deg HUT and supine control divided by the intervening time in Figure 4.7.

Rate of vascular fluid shift = $(CC_B - CC_A)/(time_B - time_A)$,

where CC_A and CC_B are the calf circumference values at $time_A$ and $time_B$ which correspond to the end of the supine (A) and the end of 80 deg HUT (B), Figure 4.7.

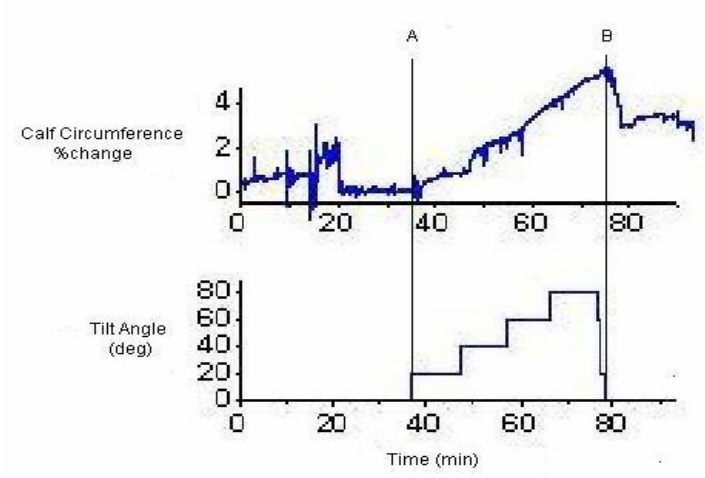


Figure 4.7: Calf Circumference and tilt protocol for one able-bodied subject illustrating the calculation of the rate of vascular fluid shift.

The average tilt-induced rate of vascular fluid shift to the lower extremities was lower in SCI subjects but not significantly different among the three groups, Figure 4.8.

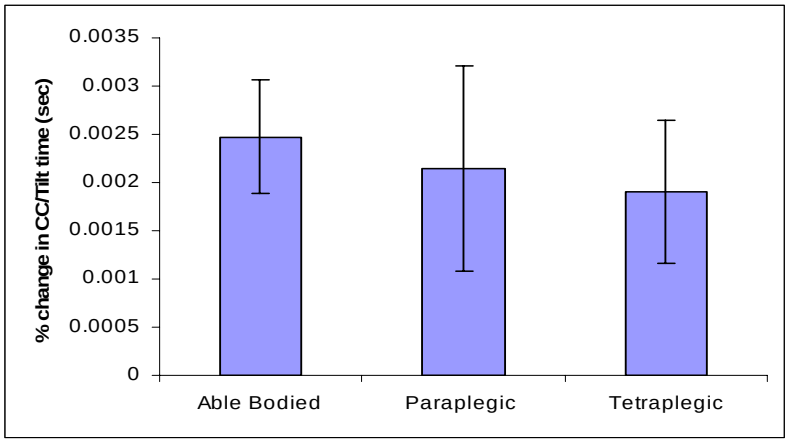


Figure 4.8: Average (±SEM) the rate of vascular fluid shifts to the leg for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects. There was no significant difference among the three groups.

Spectral Power Analysis

Variability of blood pressure and heart rate during head-up-tilt can be quantified using power spectral analysis. This approach yields an objective indication of blood pressure regulatory capability in each subject and indicates involvement of heart rate control in blood pressure regulation. The sympathetic and parasympathetic branches of the nervous system are main sources for oscillations in heart rate in response to HUT, respiration also plays a significant role in creating oscillations around the breathing frequency (0.2-0.25 Hz) in humans as well.

An example of spectral power of heart rate is shown in Figure 4.9 for an able bodied subject (left) and a spinal cord injured subject (right, C3 ASIA B). The vertical axis in these figures gives the power at frequencies between 0.4 Hz on the left to 0.01 Hz on the right (axis running approximately parallel to text lines). The spectral power peaks were analyzed in three frequency ranges: a very low frequency range (centered around 0.03 Hz, far right) and a low frequency range around 0.07 Hz, a high range center around 0.25 Hz. The time axis (running into the plane of the paper) shows progressively later times in the experiment; for example, the control period, before tilt actions begin, is nearest the front of the graph.

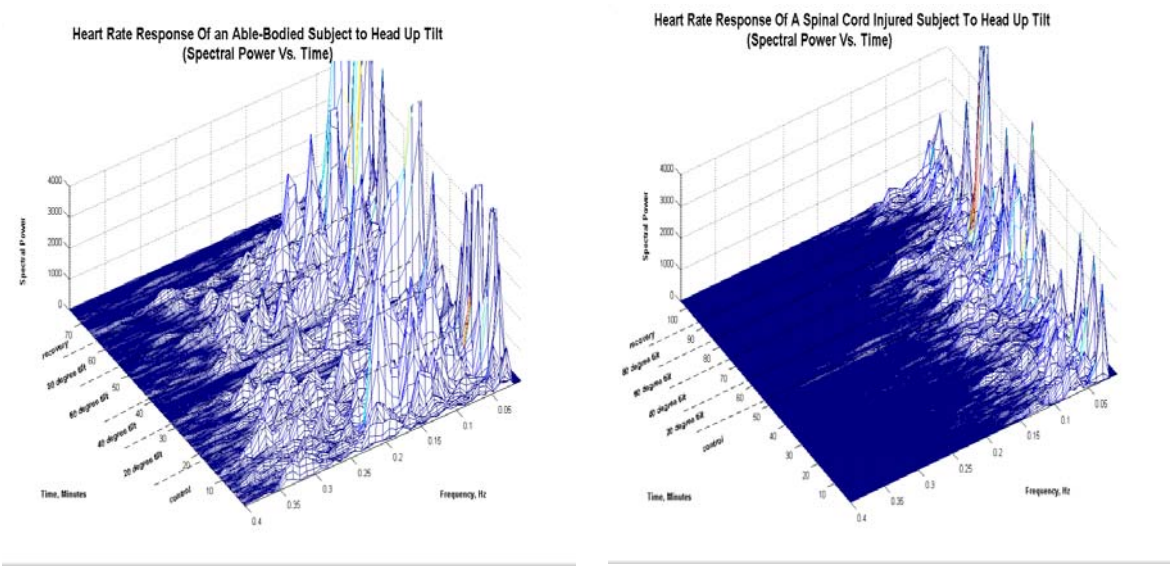


Figure 4.9: Heart rate spectral power of one able-bodied (on the left), and one SCI (on the right, C3 , ASIA B) subject, each undergoing increasing levels of head-up tilt. Note reduced power in SCI patient (right) as compared to able-bodied subject (left).

Mean values of the spectral power of blood pressure in the 0-0.3 Hz frequency range, of heart rate and Δz/dt respiration in the 0-0.4 Hz frequency range, of upper and lower body skin perfusion in the 0-0.2 Hz frequency range are illustrated below for able-bodied, paraplegic and tetraplegic groups. In order to provide clear visual presentation, standard errors around the mean values at each frequency are not included in these figures. The figures that include average (±SEM) spectral power of blood pressure, heart rate and Δz/dt respiration at each tilt level for all three groups are given in Appendix A.

Arterial Blood Pressure

Mean spectral power of arterial blood pressure in the 0-0.3 Hz frequency range at each tilt position is given in Figure 4.10 for the able-bodied group. The power at each tilt is plotted in a different color. Color codes of tilt positions are given in the upper right corner of the figure. As seen in the figure, the power in the very low frequency range (0.01-0.03Hz) decreased with tilt, and the power around 0.1 Hz increased with increasing orthostatic stress, which we interpret as an index of sympathetic outflow to the heart and vasculature (65). There were no major changes in frequencies above 0.3Hz.

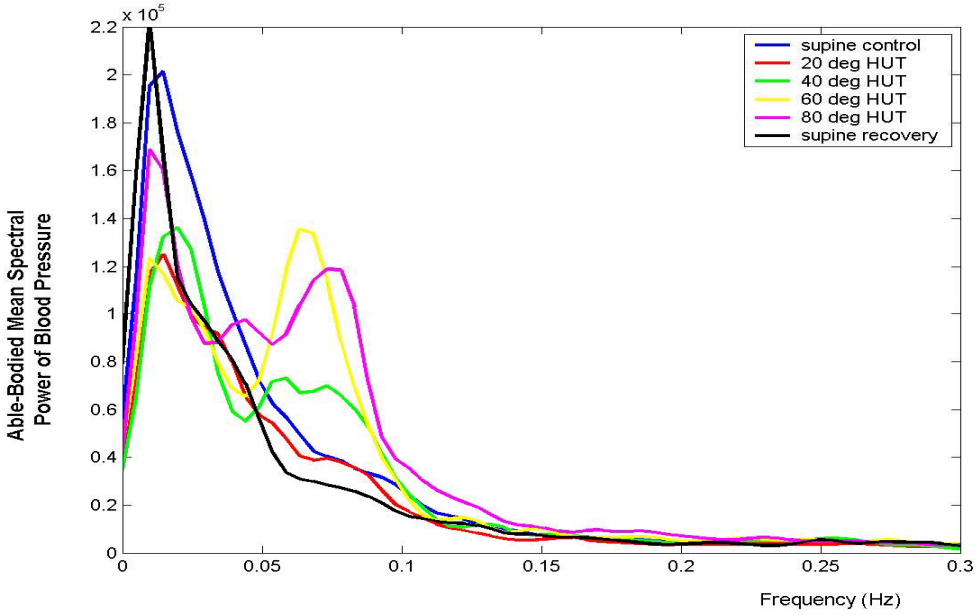


Figure 4.10: Mean spectral power of arterial blood pressure for the able-bodied group (11 studies from 11 individuals) at supine control, 20, 40, 60 deg head-up-tilt (HUT), and supine recovery. The power around 0.1 Hz increased with increasing orthostatic stress induced by tilt.

The paraplegic group-mean spectral power of arterial blood pressure in the 0-0.3 Hz frequency range is given in Figure 4.11 at each tilt position. The spectral power of blood pressure was lower than in able-bodied, and was almost unchanged in all frequencies during increasing orthostatic stress induced by increasing tilt. The power in the very low frequency range was the lowest of the three groups, and decreased with tilt as in the able-bodied group. There were no major increases in the power around 0.1 Hz.

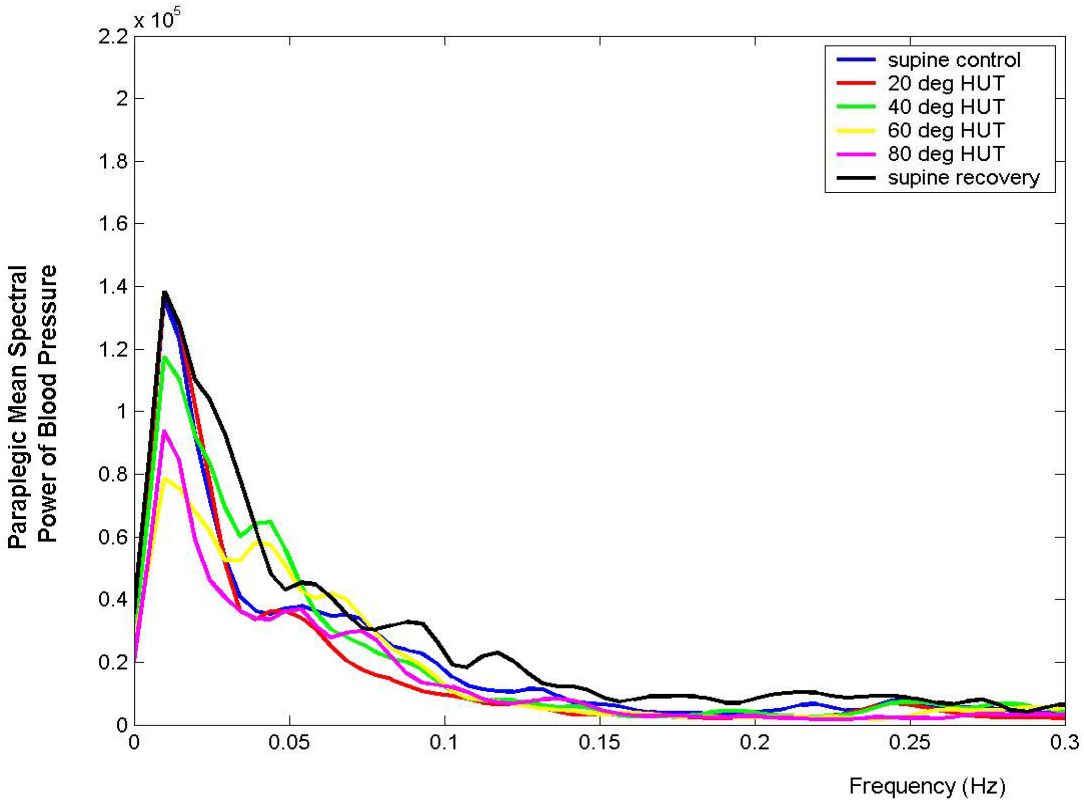


Figure 4.11: Mean spectral power of arterial blood pressure for the paraplegic group (10 studies, 5 individuals) undergoing five levels of head-up-tilt (HUT). The power around 0.1 Hz almost remained in that group through the study. The power in very low frequency range (0.01-0.04) was lowest in all three groups.

Mean spectral power of arterial blood pressure of the tetraplegic group in the 0-0.3 Hz frequency range at each tilt position is illustrated in Figure 4.12. The spectral power of blood pressure in the very low frequency range increased with tilt and reached a maximum at supine recovery. Power in this group clustered more sharply around the very low frequency peak than in able-bodied and paraplegic groups. The power around 0.1 Hz was the smallest of three groups, and diminished with increasing orthostatic stress induced by tilt.

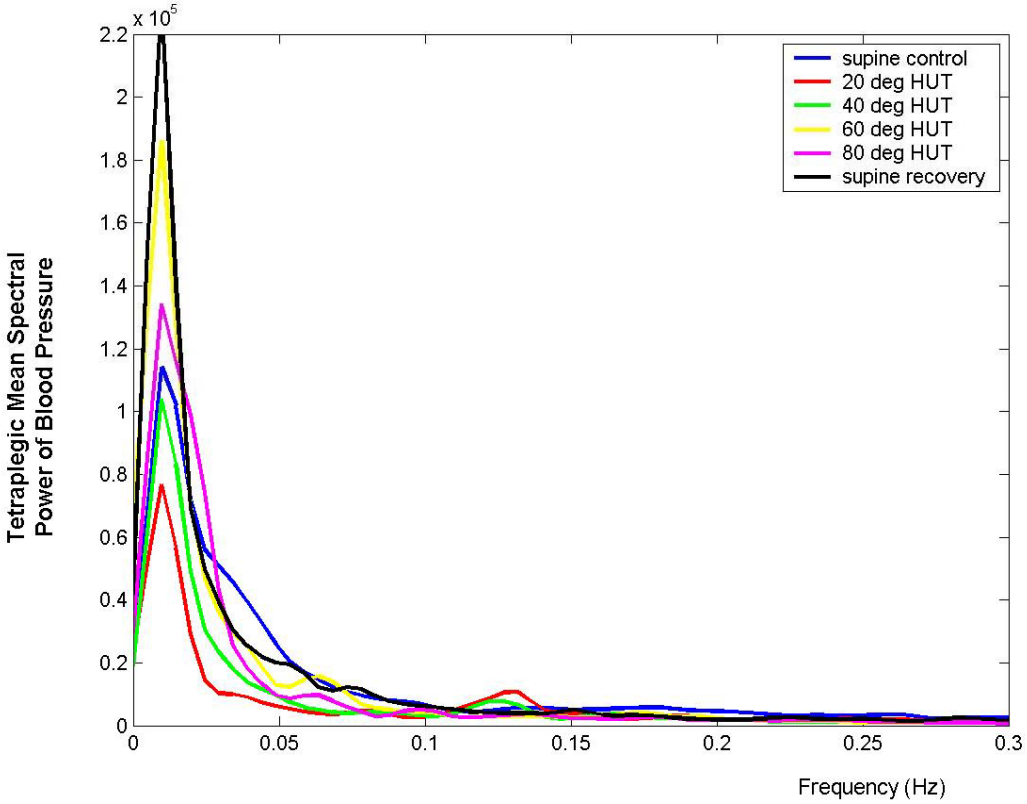


Figure 4.12: Mean spectral power of arterial blood pressure for the tetraplegic group (8 studies from 5 individuals at supine control, 20, 40, 60 deg HUT, supine recovery, 5 studies from 3 individuals at 80 deg HUT). In all groups, the spectral power was lowest around 0.1 Hz, and the peak at 0.01 Hz sharply decreased with increasing tilt.

Heart Rate

Mean spectral power of heart rate across the 0-0.4 Hz frequency range for the able-bodied group at each tilt position is demonstrated in the large graph of Figure 4.13. The mean spectral power of respiration in the 0.15-0.45 Hz frequency range is given in panel *b* of this figure. Breathing frequency occurred around 0.25 Hz (15 breath/min), the normal range for free breathing. The respiration spectral power was broad during supine

control and recovery positions, but gradually concentrated around 0.25Hz, and lost its magnitude with increasing tilt levels. The powers of breathing-induces oscillations in heart rate (respiratory sinus arrhythmia) are illustrated in panel *a* as a peak around 0.25 Hz in the heart rate spectral power. Breathing effects on heart rate were more pronounced at supine positions, and decreased with increasing tilt levels ostensibly due to parasympathetic withdrawal. The peak around 0.1 Hz increased with increasing orthostatic stress, a normal response due to increasing sympathetic activity to the heart.

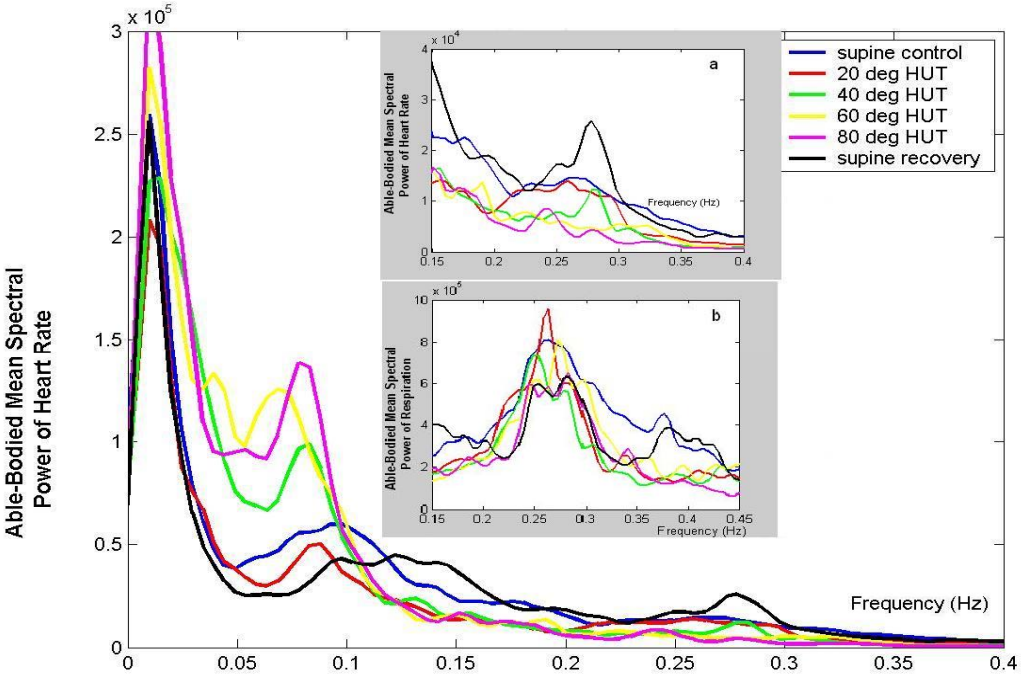


Figure 4.13: Main Figure: Mean spectral power of HR in the 0-0.4 Hz frequency range; Panel a: Mean spectral power of HR expanded to show detail in the 0.15-0.4 Hz frequency range; Panel b: Mean spectral power of respiration (panel b) for AB group (11 individuals, 11 studies) undergoing five levels of head-up-tilt (HUT).

Paraplegic mean spectral power of heart rate in the 0-0.4 Hz frequency range at each tilt position is given in Figure 4.14. The maximum scale of the vertical axis is 2/3 that of the able-bodied mean spectral power of heart rate, Figure 4.13. Mean spectral power of respiration in the 0.15-0.4 Hz frequency range at each tilt position for this group is illustrated in panel *b* in this figure. The mean breathing frequency occurred around 0.25 Hz (15 breath/min), close to that of able-bodied subjects, but with higher variance.

Breathing power was broad during supine control and recovery positions like the able-bodied group, but did not concentrate with increasing tilt levels. Smaller breathing effects on heart rate are observed than for able-bodied, which can be seen as less pronounced peak around 0.25 Hz in the heart rate spectral power, panel *a* (the vertical scale is half of the scale of Figure 4.13 panel *b*). Power around 0.25 Hz decreased, and power around 0.1 Hz increased in heart rate spectral power with increasing tilt levels similar to heart rate power of the able-bodied group, however, both peaks were less pronounced than in the able-bodied group.

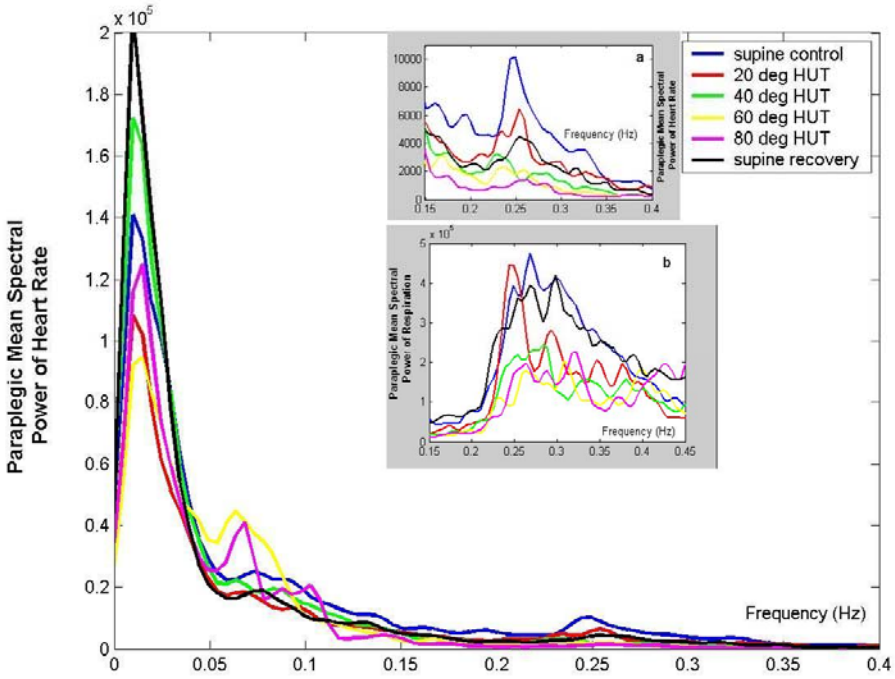


Figure 4.14; Main Figure: Mean spectral power of heart rate in the 0-0.4 Hz frequency range; Panel a: Mean spectral power of respiration for the paraplegic group (10 studies, 5 individuals) at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery.

Tetraplegic mean spectral power of heart rate in the 0-0.4 Hz frequency range at each tilt position is given in Figure 4.15. The maximum scale of the vertical axis is about 10 times smaller than the maximum scale of Figure 4.13, and Figure 4.14. Mean spectral power of respiration in the 0.05-0.45 Hz frequency range at each tilt position is illustrated in the small panel in this figure. Respiration is the main source for peaks around 0.15 Hz and 0.25 Hz at supine, 20 and 40 deg HUT as tetraplegics tended to have lower breathing frequencies than did able-bodied at these tilt positions. Since slow breathing has a greater

effect on heart rate spectral power than fast breathing (40) the peak around the breathing frequencies was stronger in tetraplegics at supine and 20 deg HUT than in able-bodied and paraplegic groups. Respiration effects on heart rate virtually disappeared at 60 and 80 deg HUT, again ostensibly due to withdrawal of parasympathetic influence. The heart rate spectral power around 0.1Hz and tilt-induced changes were not easily noticeable due to respiration effects in this frequency range.

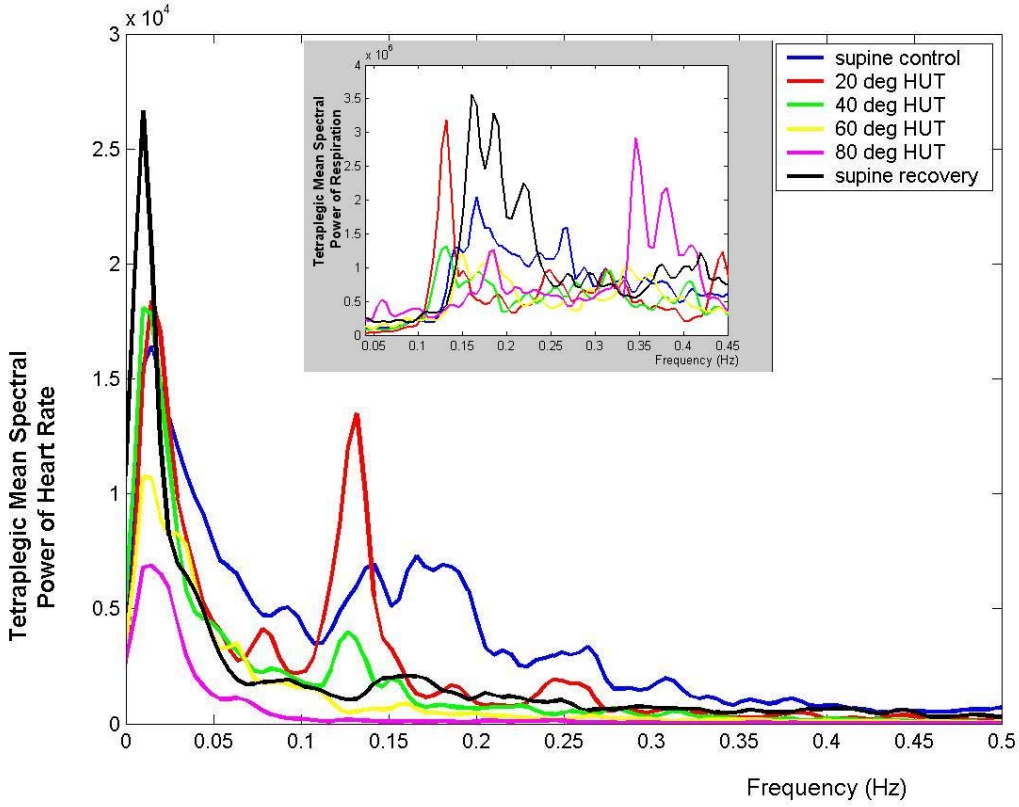


Figure 4.15: Mean spectral power of heart rate (main figure) and respiration (small window) for the tetraplegic group (8 studies from 5 individuals at supine control, 20, 40, 60^{o} head-up-tilt (HUT), supine recovery, 5 studies from 3 individuals at 80 deg HUT).

Upper Body Skin Perfusion

Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range at each tilt position is given in Figure 4.16 for the able-bodied group. The mean power around 0.03 Hz frequency decreased at 20^{o} HUT, and then increased with increasing orthostatic stress. The mean spectral power around 0.1 Hz decreased at 20^{o}

HUT and then increased with increasing tilt levels, and returned to the control value at recovery.

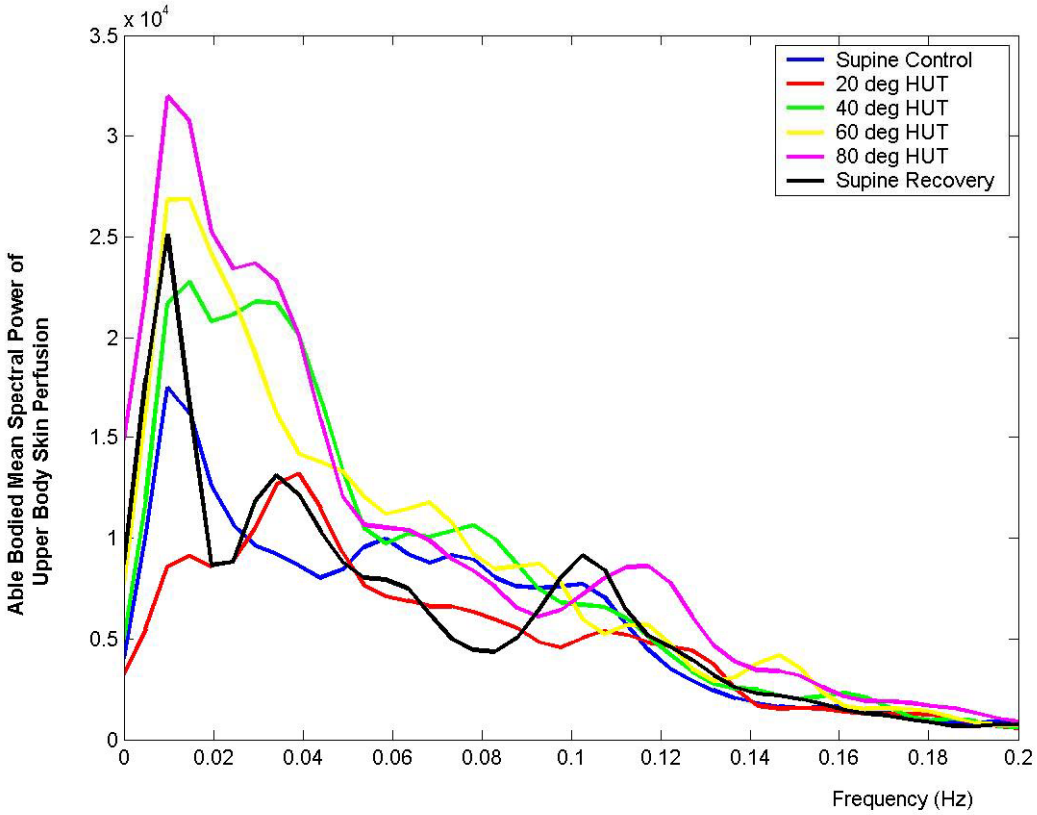


Figure 4.16: Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range for the AB group (11 studies from 11 individuals) at supine control, 20, 40, 60 deg head-up-tilt (HUT), and supine recovery. The power around 0.03 Hz and 0.1 Hz frequencies increased with increasing orthostatic stress induced by tilt.

Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range at each tilt position for the paraplegic group is given in Figure 4.17. The maximum scale on the vertical axis is around 1.5 times lower than the maximum scale in Figure 4.16. The power around 0.02 Hz frequency was higher at supine control. Unlike the able-bodied group, the power around 0.02 Hz in this group decreased with increasing tilt

levels, and did not return to the supine control value at recovery. The mean spectral power around 0.1 Hz decreased with tilt levels, also different than the able-bodied group.

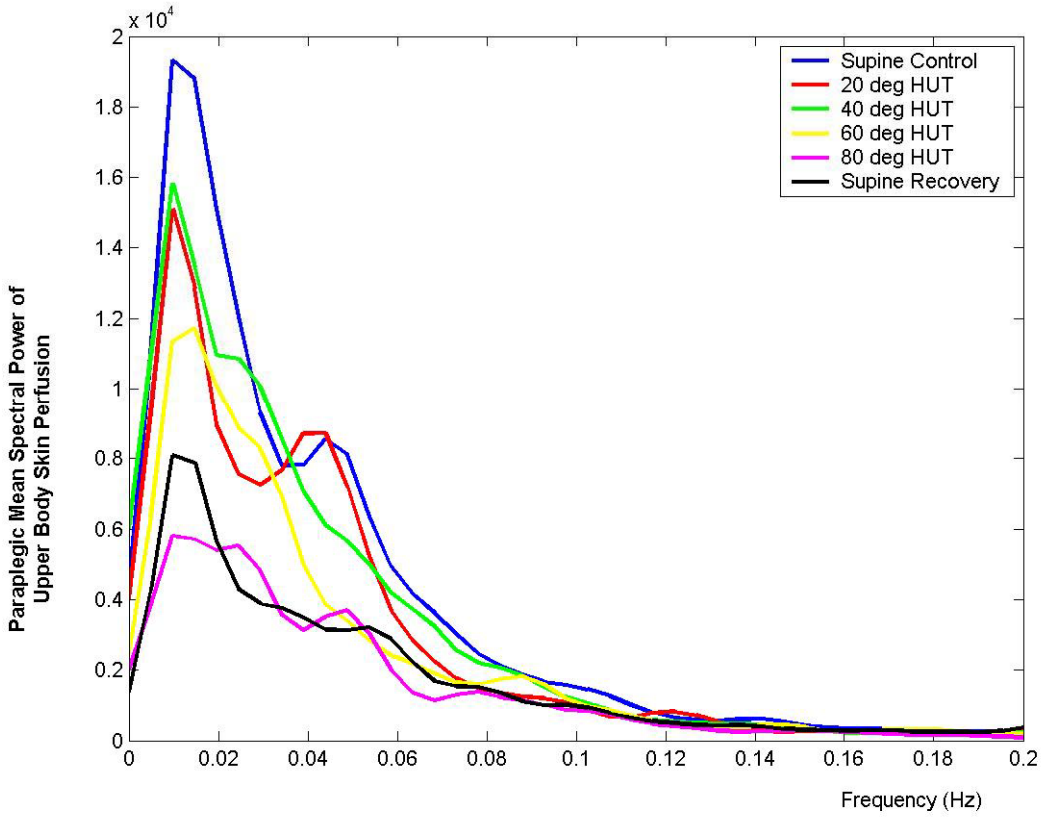


Figure 4.17: Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range for the paraplegic group (10 studies, 5 individuals) undergoing five levels of head-up-tilt (HUT). The power around 0.03 Hz and 0.1Hz decreased with increasing orthostatic stress induced by tilt.

Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range is illustrated in Figure 4.18 for the tetraplegic group at each tilt position. The scale on the vertical axis is the same as the scale in Figure 4.17, around 1.5 times lower than the scale in Figure 4.16. The mean spectral power at all frequencies was lowest in the three groups, and diminished with increasing orthostatic stress induced by tilt.

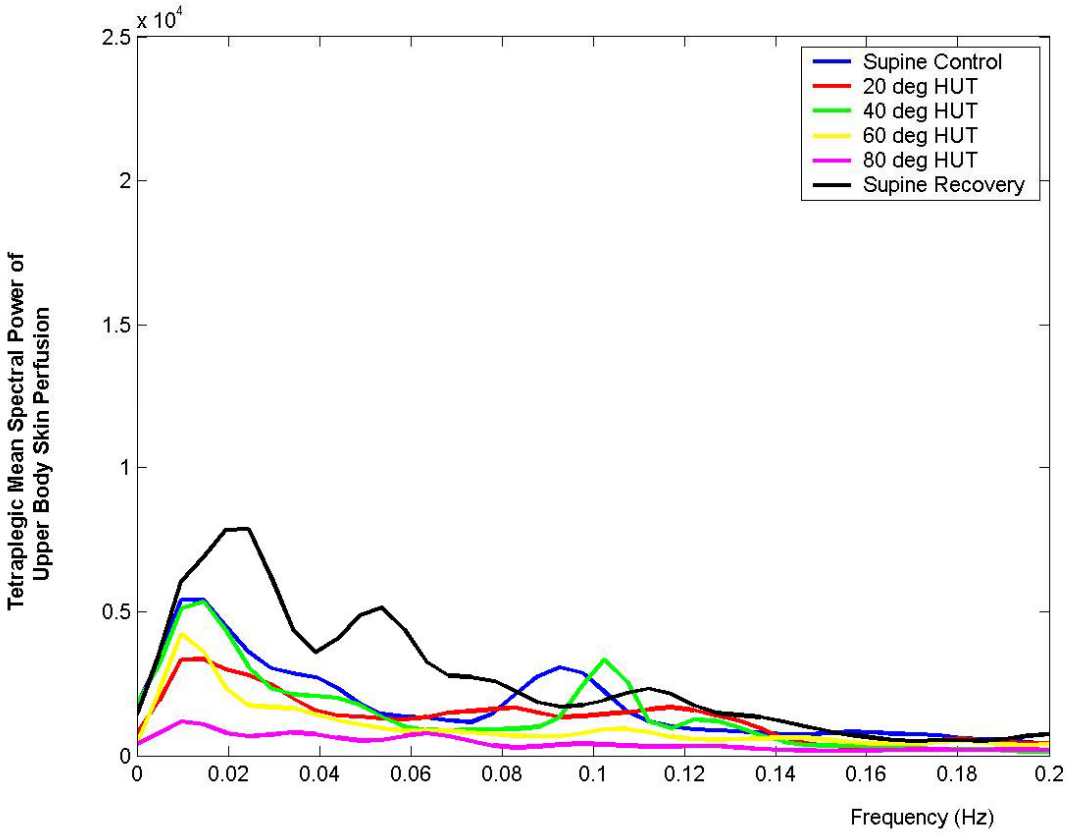


Figure 4.18: Mean spectral power of upper body skin perfusion in the 0-0.2 Hz frequency range for the tetraplegic group (8 studies from 5 individuals at supine control, 20, 40, 60 deg HUT, supine recovery, 5 studies from 3 individuals at 80 deg HUT). The mean spectral power was the lowest in all frequencies, and diminished with increasing orthostatic stress induced by tilt.

Lower Body Skin Perfusion

Mean spectral power of lower body skin perfusion in the 0-0.2 Hz frequency range at each tilt position is given in Figure 4.19 for the able-bodied group. After decreasing from supine control to 20 deg HUT, the mean power around 0.02 Hz

increased with increasing orthostatic stress, and had the highest value at the recovery position. The mean power around 0.1 Hz decreased with increasing tilt levels.

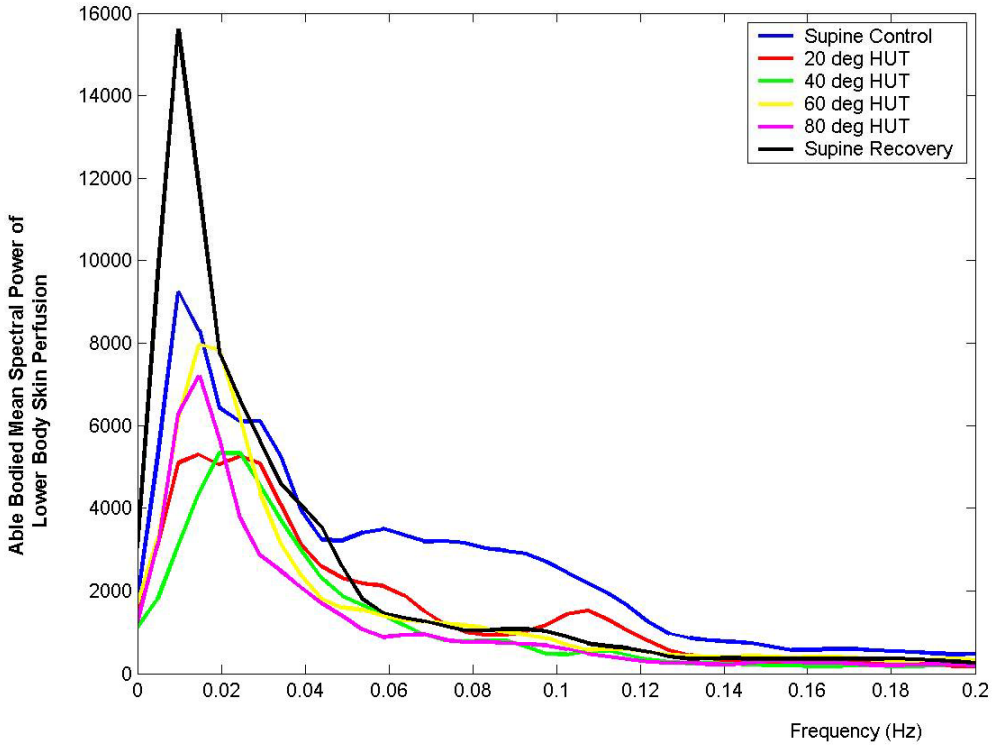


Figure 4.19: Mean spectral power of lower body skin perfusion in the 0-0.2 Hz frequency range for the AB group (10 studies from 10 individuals) at supine control, 20, 40, 60 deg head-up-tilt (HUT), and supine recovery.

Mean spectral power of lower body skin perfusion in the 0-0.2 Hz frequency range is given in the main Figure 4.20 for the paraplegic group at each tilt position. The scale on the vertical axis is half the scale on Figure 4.19. The power around 0.02 Hz frequency was higher at supine recovery positions like the able-bodied group, and decreased with increasing tilt levels. The mean power around 0.1 Hz, given in the small window, also decreased with increasing tilt levels (like the able-bodied group).

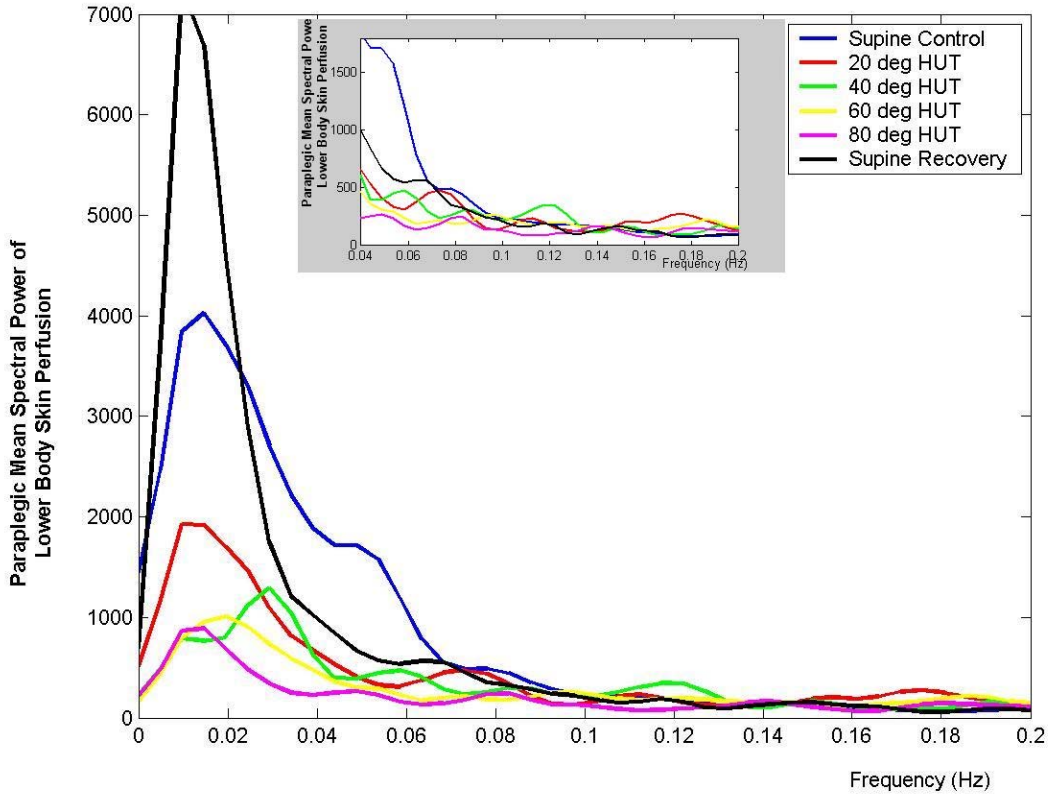


Figure 4.20: Mean spectral power of lower body skin perfusion in the 0-0.12 Hz frequency range for the paraplegic group (10 studies, 5 individuals) undergoing five levels of head-up-tilt (HUT). The vertical scale is half of the vertical scale of Figure 4.19. The power around 0.1 Hz illustrated in the small window. The power around 0.03 Hz and 0.1 Hz decreased with increasing orthostatic stress induced by tilt.

Tetraplegic group mean spectral power of upper body skin perfusion in the 0-0.12 Hz frequency range is given in Figure 4.21 at each tilt position. The maximum of the vertical axis is approximately half of the scale of Figure 4.20, and one third of the scale of Figure 4.19. The mean power at each frequency was the lowest among the three groups and decreased with increasing orthostatic stress. The mean power around 0.1 Hz decreased with increasing tilt levels.

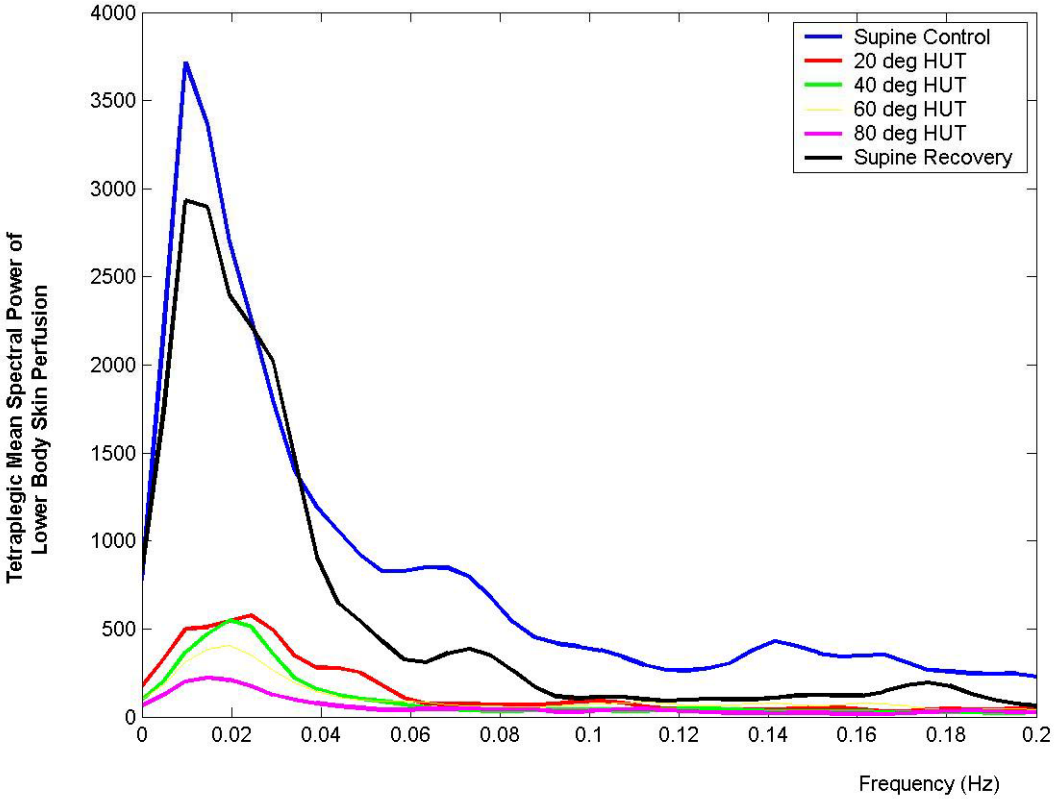


Figure 4.21: Mean spectral power of lower body skin perfusion in the 0-0.2 Hz frequency range for the tetraplegic group (8 studies from 5 individuals at supine control, 20, 40, 60 deg HUT, supine recovery, 5 studies from 3 individuals at 80 deg HUT). The mean power decreased with increasing tilt levels, and had the smallest values at all frequencies.

Indexes of Sympathetic Activity via Spectral Power Analysis

Low frequency (LF, 0.04-0.15 Hz) spectral power of blood pressure has been used as a noninvasive index of sympathetic control of vasomotion. Average (±SEM) spectral power of blood pressure in the LF region for able-bodied, paraplegic and tetraplegic subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery,

are given in Figure 4.22. The power in this region significantly increased with increasing orthostatic stress in able-bodied, but remained fairly constant in SCI subjects. Paraplegics had significantly ($p < 0.05$) lower values than able-bodied at each tilt level, and tetraplegics had significantly ($p < 0.05$) lower values than both able-bodied and paraplegics at each tilt level. This index is a good candidate for a non-invasive index to discriminate able-bodied from SCI, and paraplegic from tetraplegic.

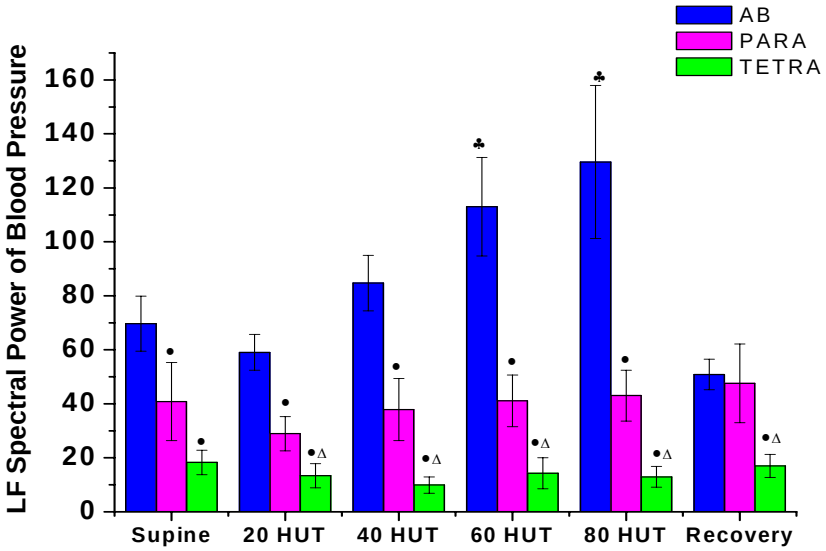


Figure 4.22: Average (±SEM) spectral power of blood pressure in the LF region for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT) and supine recovery. Group, tilt and group/tilt interaction, p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from supine condition (same group).

Low frequency spectral power of heart rate has been used as a noninvasive index of sympathetic outflow to the heart. Average (±SEM) spectral power of heart rate in the LF region for able-bodied, paraplegic and tetraplegic subjects at supine control, 20, 40, 60 deg HUT, supine recovery are given in Figure 4.23. The power in this region increased with increasing orthostatic stress in able-bodied, remained fairly constant in paraplegics, and decreased in tetraplegics with increasing tilt. The SCI individuals'

values were significantly lower than able-bodied subjects at 60 and 80 deg HUT and in supine recovery. This result indicates that SCI individuals had less dynamic activity in the LF frequency range compared to able-bodied subjects which was expected due to damage of sympathetic outflow to the heart.

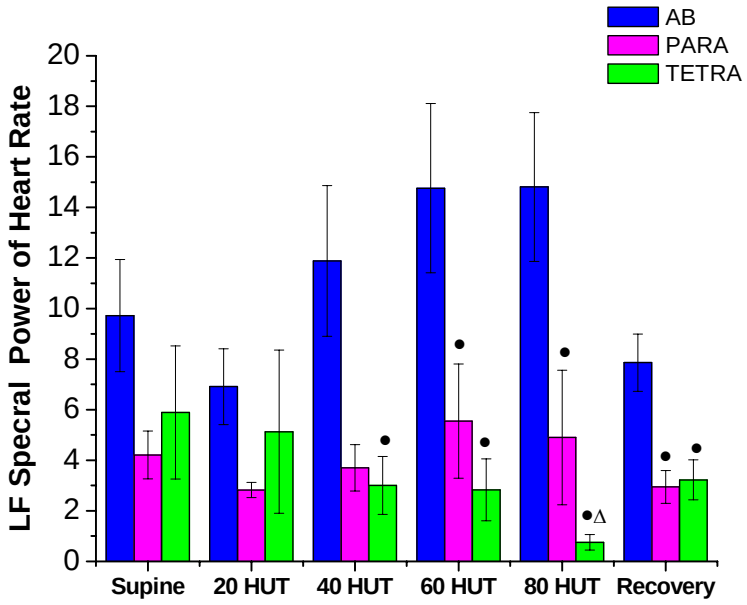


Figure 4.23: Average (±SEM) spectral power of heart rate in the LF region for able-bodied (n=11), paraplegic (n=5) and tetraplegic ((n=5, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery. subjects. Group, tilt and group/tilt interaction p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from supine condition (same group).

Low frequency spectral power of upper body skin perfusion can be used to indicate sympathetic activity to skin arterioles controlling blood flow in the forearm. Figure 4.24 illustrates average (±SEM) spectral power of upper body skin perfusion in LF region for able-bodied (n = 10, result of one able-bodied subject was not used due to high

noise), paraplegic (n = 5) and tetraplegic (n = 4, but n = 3 at 80^{o} HUT) subjects at supine control, 20^{o}, 40^{o}, 60^{o} HUT, and supine recovery. Power in this region tended to increase in able-bodied and significantly decreased in SCI subjects in response to HUT. The able-bodied group had significantly higher power than paraplegics and tetraplegics at each tilt level.

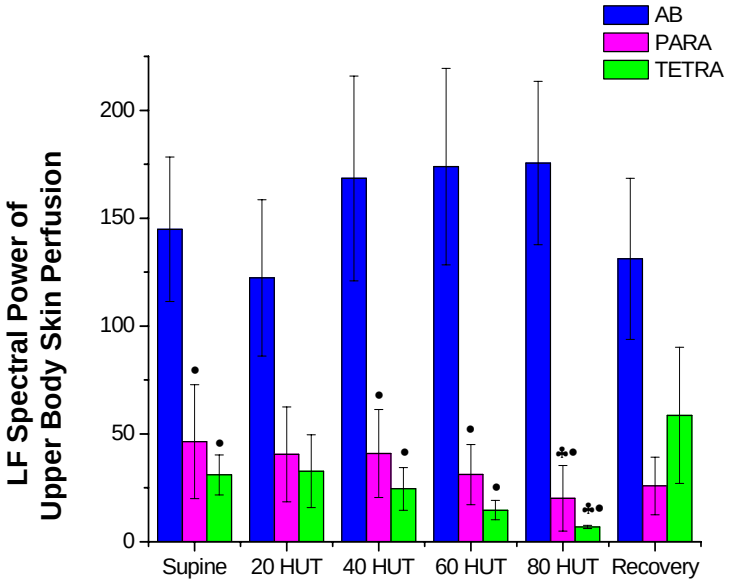


Figure 4.24: Average (±SEM) spectral power of upper body skin perfusion in the LF region for able-bodied (n=10), paraplegic (n=5) and tetraplegic (n=4, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery. Group, tilt and group/tilt interaction, p value ≤ 0.05; ● significantly different from AB (same stress level), ♣ significantly different from supine condition (same group).

Low frequency spectral power of lower body skin perfusion can be used as an indicator of sympathetic activity to skin arterioles controlling blood flow in the shin. Figure 4.25 illustrates average (±SEM) spectral power of lower body skin perfusion in the LF region for three groups in response to HUT. The able-bodied group significantly ($p < 0.05$) decreased power in that region to regulate blood pressure in response to increasing orthostatic stress. Both SCI groups also demonstrated significant reduction in

power from supine control to 80° HUT, but their power was significantly ($p<0.05$) lower than in the able-bodied group at all tilt positions.

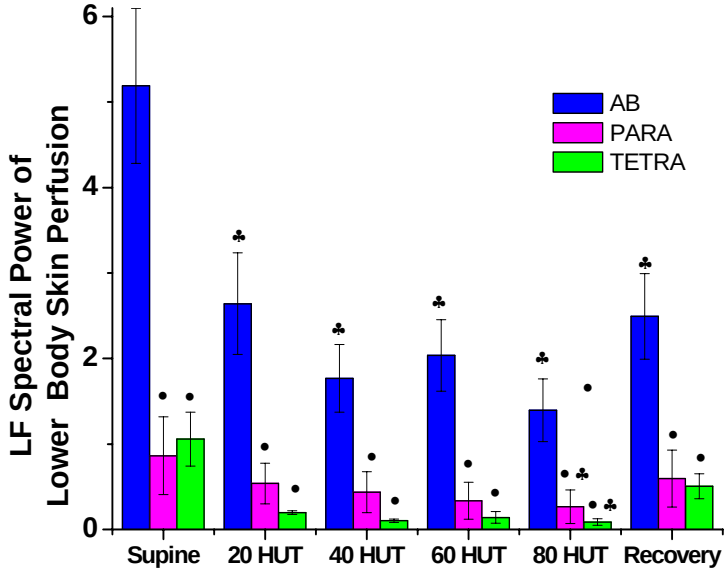


Figure 4.25: Average (±SEM) spectral power of lower body skin perfusion in the LF region for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=4, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery. Group, tilt and group/tilt interaction, p value ≤ 0.05; ● significantly different from AB (same stress level), ♣ significantly different from supine condition (same group).

Indexes of Parasympathetic Activity via Spectral Power Analysis

High frequency (HF, 0.15-0.4 Hz) spectral power of heart rate has been used as a noninvasive index of parasympathetic control of heart rate. Average (±SEM) spectral power of heart rate in the HF region for able-bodied, paraplegic and tetraplegic subjects at the supine control, 20°, 40°, 60° HUT, the supine recovery are given in Figure 4.26.

The power in this region decreased with increasing orthostatic stress in all groups. Paraplegics had significantly lower values than able-bodied at each tilt level except supine control. Tetraplegics also had significantly lower values at 40^o, 60^o, 80^o HUT and the supine recovery with respect to able-bodied, and with respect to paraplegics at 80^o HUT and the supine recovery.

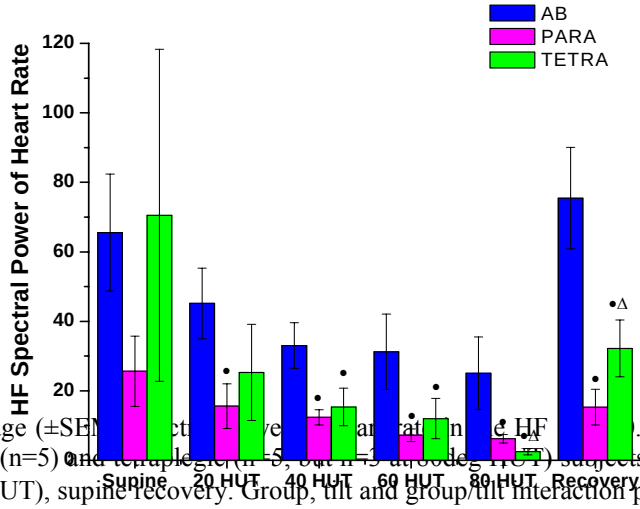


Figure 4.26: Average (±SEM) spectral power of ΔZ/dt respiration in the HF (0.15-0.4 Hz) region for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5, but n=4 at 60deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery. Group, tilt and group/tilt interaction p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from supine condition (same group).

Since the power of heart rate in this region is strongly coupled with respiration, average (±SEM) spectral power of ΔZ/dt respiration is illustrated in Figure 4.27. Respiratory power was relatively unchanged by tilt in able-bodied and paraplegics with small variances around the mean. Mean power and variance in tetraplegic subjects was highest among the three groups indicating increased respiratory variabilities in that group.

Similarities of respiration and high frequency spectral power of heart rate (Figures 4.26 and 4.27) at rest and in response to tilt indicate that tetraplegics had higher respiratory influences in their HF spectral power of heart rate than did able-bodied and paraplegics.

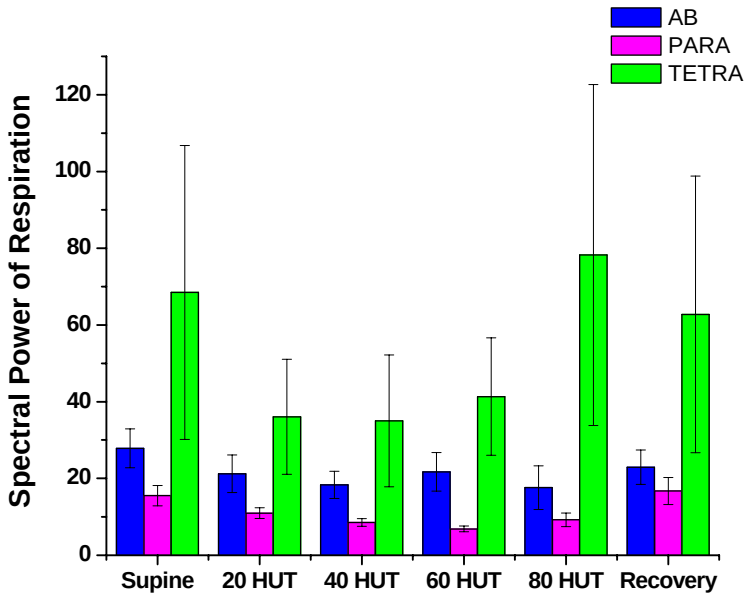


Figure 4.27: Average (±SEM) spectral power of ΔZ/dt respiration for able-bodied (n=11), paraplegic (n=5) and tetraplegic ((n=5, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt (HUT), supine recovery.

The Balance between Parasympathetic and Sympathetic Branches of Nervous System

The powers of the LF and HF oscillations characterizing heart rate variability appear to reflect, in their reciprocal relationship, changes in the state of sympathovagal balance occurring during numerous physiological and pathophysiological conditions. The

sympathetic autonomic nervous system (SNS) index was estimated as below (Equation 5):

SNS : LF power/HF power of heart rate

The parasympathetic autonomic nervous system (PNS) index was estimated as below (Equation 6):

PNS : HF power/(LF+HF) power of heart rate

During a sympathetic challenge, such as head-up tilt, increases in the SNS index are expected in able-bodied persons due to shifts in autonomic modulation toward augmented sympathetic, and attenuated vagal, activity (Montano N, 1994). Figure 4.28 illustrates the SNS index of heart rate for the three groups. As expected, the able-bodied group significantly increased their index from supine control to 40^{o}, 60^{o} and 80^{o} HUT. Paraplegic subjects also demonstrated a comparable pattern in which the index significantly increased from supine to 60^{o}, 80^{o} HUT. In the tetraplegic group, the index showed little change with increasing orthostatic stress but none of these increases was significant. The paraplegic index value was close to that of able-bodied, and tetraplegics had the lowest index value at each tilt level (significant at 60^{o} and 80^{o} HUT).

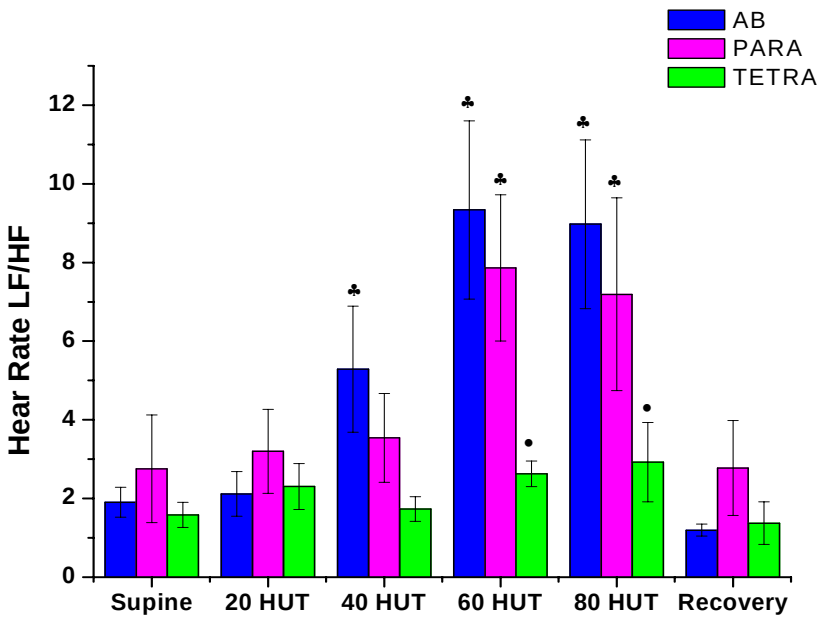


Figure 4.28: Average (±SEM) heart rate SNS index for able-bodied (n=11), paraplegic (n=5) and tetraplegic ((n=5, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt, supine recovery. Tilt effect, $p<0.05$; ● significantly different from AB (same stress level), ♣ significantly different from supine condition (same group).

The PNS index significantly ($p<0.05$) decreased in the able-bodied and the paraplegic groups in response to HUT, Figure 4.29. This lessening also occurred in the tetraplegic group, but there was no significant change at any tilt level.

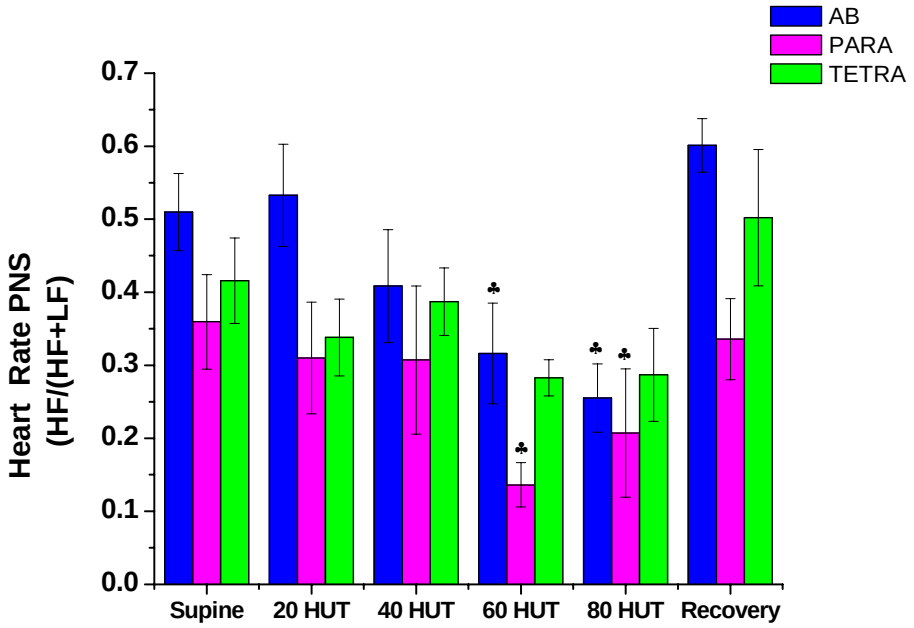


Figure 4.29: Average (±SEM) PNS index of heart rate for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5, but n=3 at 80deg HUT) subjects at supine control, 20, 40, 60 deg head-up-tilt, supine recovery. Tilt effect, $p<0.05$: ♣ significantly different from control (same group).

The Cross Correlation Technique

Cross correlation of blood pressure and heart rate can be used to evaluate both feed-forward and feed-back characteristics of the relationship between blood pressure and heart rate (6). Figure 4.30 illustrates 50 sec. of systolic blood pressure (SBP) (a), heart rate (HR) (b), and cross correlation (c) and 50 sec of the correlogram (d) between these two variables for one able-bodied subject at 80^{o} head-up tilt. The correlation graph in Figure 4.30c has two main features; the magnitude of the correlation on the vertical axis and the lead/lag time between systolic blood pressure and heart rate on the horizontal axis.

The negative magnitude represents the strength of the feed-back relationship, and the positive magnitude represents the strength of the feed-forward relationship between the two signals. A correlation magnitude value of 1 indicates perfect correlation between these two signals. Since SBP was used as a reference signal and HR was slid backward and forward, negative lags refer to SBP leading HR, and positive lags refer to SBP lagging HR. The negative peak at -0.86 occurring around -1.5sec in Figure 4.30c indicates that changes in SBP drive the opposite (feed-back) changes in HR with 1.5 sec time delay.

The positive peak value of 0.75 occurring around 4.5 sec in Figure 4.30c indicates that changes in HR drive same directional (feed-forward) changes in SBP with a 4.5 sec time delay. The correlogram illustrated in Figure 4.30d adds time to the correlation of SBP and HR. The vertical axis shows lead/lag time, and the horizontal axis shows the progression time of the data record. The magnitude of the correlation is indicated by the color density. The negative magnitude (feed-back) appears in blue, and the positive magnitude (feed-forward) appears in red.

The bar on the right shows the magnitude of the correlation, the darker the color, the stronger the correlation. Since SBP and HR are non-stationary signals and features of the correlation of these two signals changes over the data record, the correlogram gives information concerning dynamics of the system. As seen in Figure 4.30d, the positive magnitude lost strength between 30-38 sec of HUT but regained strength while the negative magnitude became wider after 30 sec with the same strength.

The value of the cross correlation (Figure 4.30c) lies in its ability to quantify the magnitude of the correlation between related phenomena separated by a time delay.

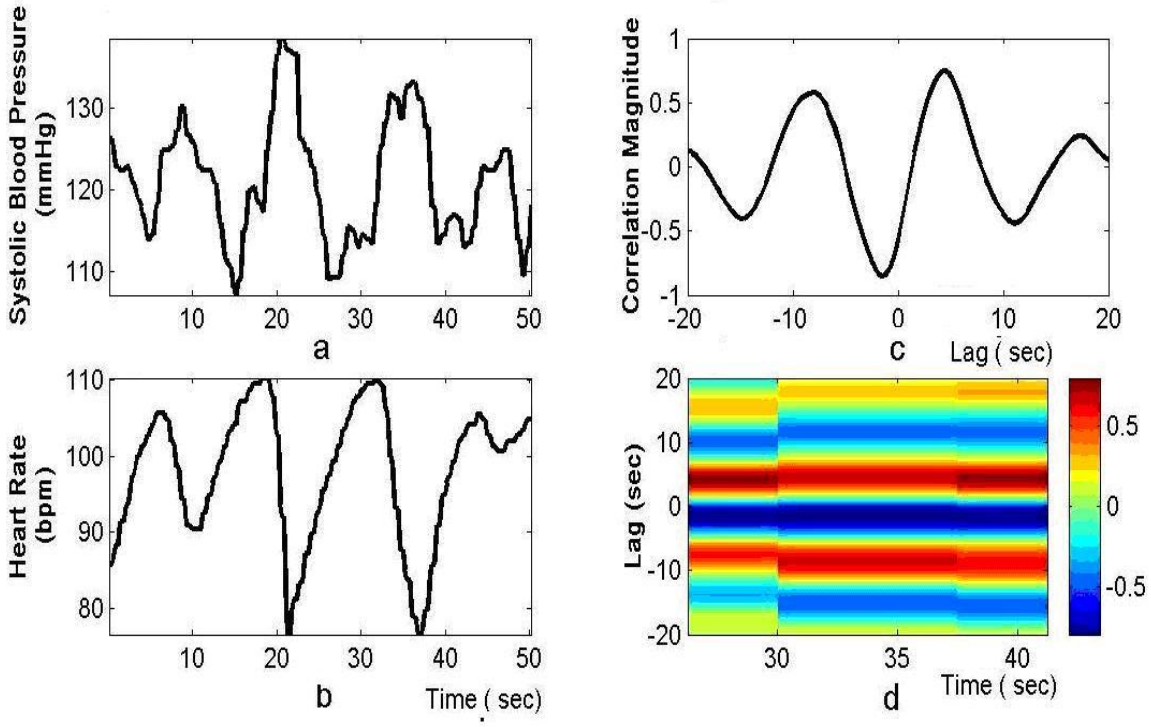


Figure 4.30: Fifty seconds of systolic blood pressure (a), and heart rate (b) of one able-bodied subject at 80^{o} head up tilt. The cross correlation between these two variables is shown in (c) and the correlogram between the two signals is shown in (d). Lead/lag time information is on the vertical, and the experiment progression time is on the horizontal axis. The magnitude of the correlation is indicated by the color density; blue represents negative, red represents positive correlation. The bar shows the magnitude of the correlation-; the darker the color, the stronger the correlation.

Figure 4.31 illustrated the systolic blood pressure and heart rate correlogram across a full range of tilt studies for an able-bodied (a) and a tetraplegic patient (b, C3 ASIA B) in the HF region where regulation by the parasympathetic nervous system is dominant. The tilt angle increments are superimposed over the graph to increase interpreting of correlation patterns relative to tilt events. Note the appreciably stronger correlation throughout the study in the able-bodied compared to the tetraplegic subject that became more pronounced at higher levels of tilt. The SCI subject was returned to supine position immediately after 1 min. of 80^{o} HUT because of development of presyncopal symptoms.

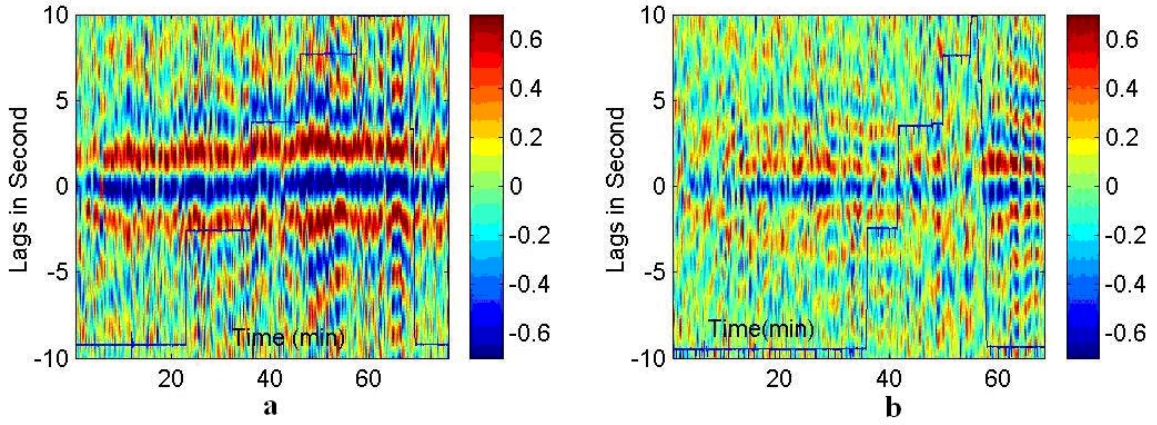


Figure 4.31: Correlogram between HR and SBP in the HF (0.15-0.45 Hz) region, with tilt angle superimposed, plotted as a function of time for an able-bodied (a) and a tetraplegic patient b, C3 ASIA B)

Figure 4.32 presents group averaged LF cross correlations between systolic blood pressure and heart rate as a function of time (correlograms) for able bodied (top), paraplegic (middle) and tetraplegic (bottom) studies at rest (left column), in response to tilt (columns 2-5), and recovery from tilt. The magnitudes of the cross-correlation values are color coded according to the color bars on the right of the figure. The lag times (sec) are given on the vertical axes where positive lags correspond to SBP lagging HR. The time in minutes (i.e. progression of the experiment) is plotted along the horizontal axes with respect to the tilt angle change. Able-bodied had strong negative (feedback) and

positive (feed-forward) correlations, blue and red bands respectively, at all stress levels. Paraplegics maintained both feed-back and feed–forward characteristics during increasing stress while tetraplegics had lower values of both characteristics during rest and recovery that essentially disappeared during tilt.

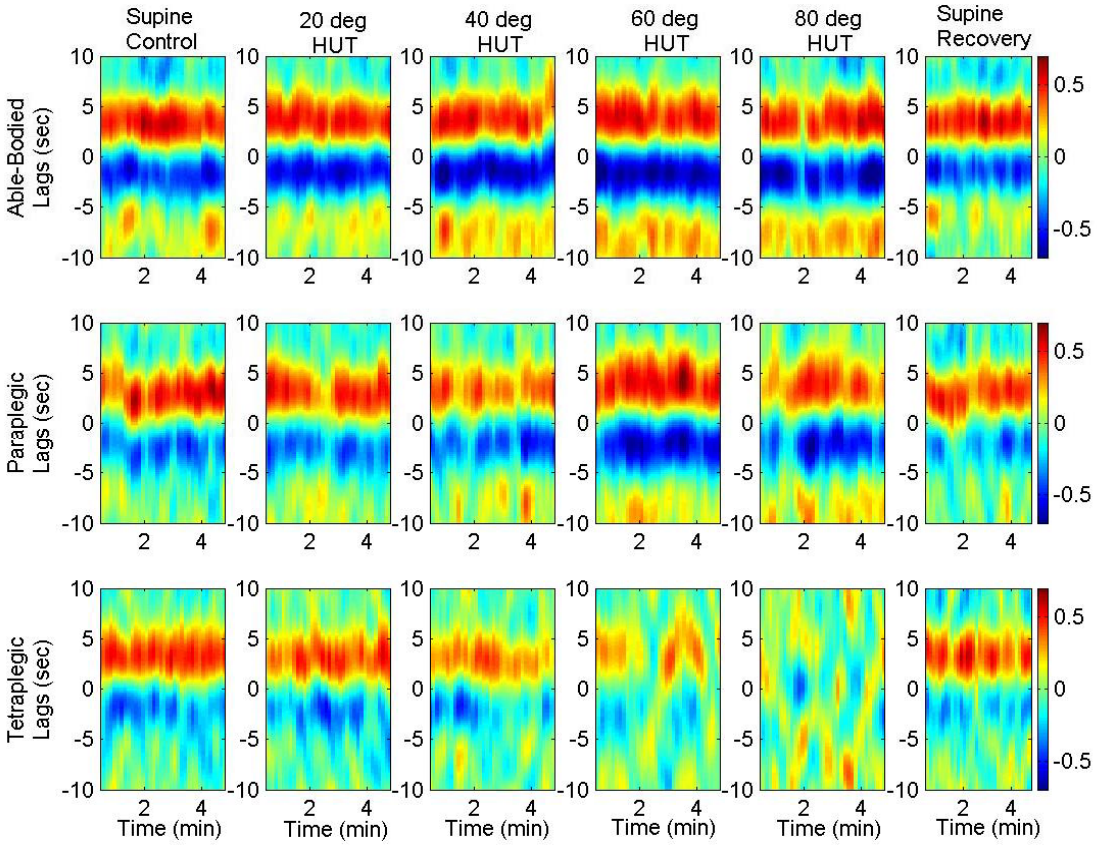


Figure 4.32: Group averaged low frequency (0.04-0.15 Hz) cross correlation between SBP and HR for able bodied (top, n=11), paraplegic (middle, n=5) and tetraplegic (bottom, n=5) subjects at rest (left column), in response to tilt (columns 2-5), and recovery from tilt. The lead/lag times (sec) are given on the vertical axis, and time in minutes (i.e. progression of the experiment) is plotted along the horizontal axis. The strong blue band around –2 sec in the able-bodied group represents feedback characteristics, which also appear on the paraplegic group with less strength under lower orthostatic stress. The diminished strength of the feedback magnitude with increasing orthostatic stress is clearly seen in the tetraplegic group. The red band around 3.5 sec, indicating feed-forward characteristics, remains in the able-bodied, and the paraplegic, but decreases in the tetraplegic groups under increasing orthostatic stress.

Figure 4.33 presents the group averaged HF cross correlation between systolic blood pressure and heart rate for able bodied (top), paraplegic (middle) and tetraplegic (bottom) subjects during supine rest (left column), in response to tilt (columns 2-5), and recovery from tilt. Able-bodied subjects had the strongest blue and red bands at rest and during head up tilt. Paraplegics had weaker correlations than able bodied, but the correlation remained throughout the study. Both correlations declined in tetraplegics with tilt. Respiratory effects may contribute to tetraplegics' systolic blood pressure and heart rate correlations during supine rest, at 20^{o} HUT and supine recovery.

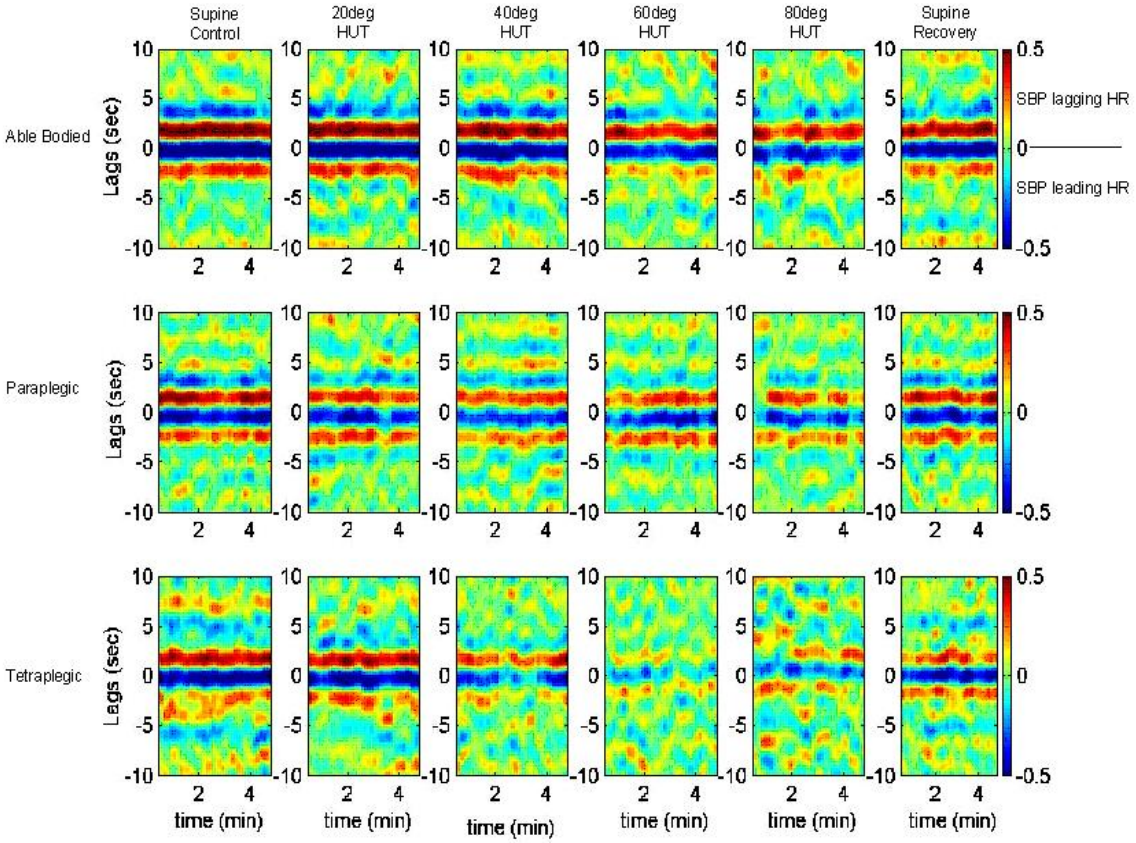


Figure 4.33: High frequency (0.15-0.45 Hz) cross correlation between SBP and HR for able bodied (top, n=11), paraplegic (middle, n=5) and tetraplegic (bottom, n=5) subjects at rest (left column), in response to tilt (columns 2-5), and recovery from tilt. The lead/lag times (sec) are given on the vertical axis, and time in minutes (i.e. progression of the experiment) is plotted along the horizontal axis. The magnitude of the correlation is indicated by the color density; blue represents negative (feedback), red represents positive (feed-forward) correlation. The bar on the right shows the magnitude of the correlation; the darker the color, the stronger the correlation. The last five minutes of data were used at each tilt position. There is a strong blue band around –1sec in AB throughout the study representing negative feedback control, which

also appears in the paraplegic group with less strength. The diminishment in the strength of the feedback magnitude with increasing orthostatic stress is clearly seen in the tetraplegic group. The red band around 1.5 sec remains in the able-bodied and the paraplegic whereas diminishes in the tetraplegic groups.

Indexes of Sympathetic Activity via Cross Correlation Technique

Figure 4.34 shows the average magnitude of the LF negative peak (a), and the magnitude versus its corresponding time lag (from zero to the negative peak) of the cross correlation between systolic blood pressure and heart rate (b). Although the correlation magnitudes for the SCI groups were similar at rest, they did not exhibit increasing magnitude in response to tilt as was the case in able bodied subjects. The strength of the correlation significantly increased in able-bodied at 40^{o}, 60^{o} and 80^{o} HUT, remains in paraplegic, and declines in tetraplegic group (group, tilt, group/tilt interaction, $p < 0.05$). The time lags for reaching the maximum negative correlation points in response to increasing orthostatic stress covered a small range in the able bodied and paraplegic subjects, but occupied different regions in the tetraplegic subjects (group, group/tilt interaction, $p < 0.05$). The tetraplegic group exhibited an erratic time lag behavior, most likely the result of weak (or nonexistent) correlation being dominated by noise and other weakly correlated processes (note the low correlation).

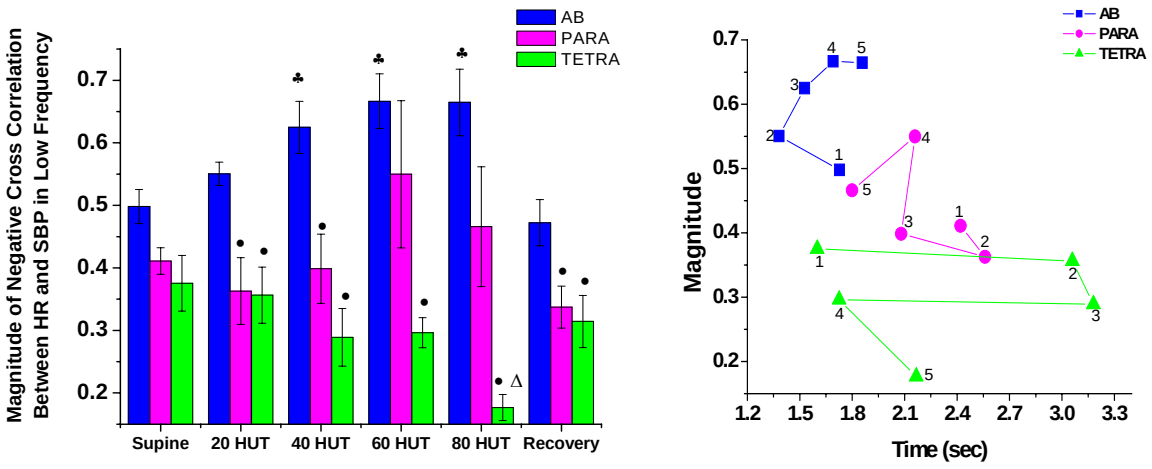


Figure 4.34: Group averaged magnitude of the LF (0.04-0.15Hz) negative peak of the cross correlation between systolic blood pressure and heart rate (a), and group averaged magnitude vs. corresponding time lag of cross correlation between systolic blood pressure and heart rate where systolic blood pressure leads heart rate (b) at

rest and in response to tilt for able-bodied subjects (n=11), paraplegics (n=5) and tetraplegics (n=5). Group, group/tilt interaction, p <0.05); ● significantly different from AB (same stress level), Δ significantly different from paraplegic (same stress level), ♣ significantly different from supine condition (same group). 1: supine control, 2: 20°HUT, 3: 40°HUT, 4: 60°HUT, 5: 80°HUT.

Indexes of Parasympathetic Activity via Cross Correlation Technique

Figure 4.35 shows the group average magnitude of the negative peak (a), and the magnitude versus its time lag (b, from zero to the negative peak) for the cross correlation between systolic blood pressure and heart rate in the HF region. All groups had relatively close values at rest, and significantly decreased their values from supine to 80° HUT. Although, the decrease in correlation magnitude with increase in tilt angle was common in all groups, SCI subjects demonstrated a higher reduction in magnitude than did able-bodied group at higher tilt angles. Resting time lag values were similar (0.2 sec) in able-bodied and tetraplegic groups, and larger in the paraplegic group. The time lags slightly go up in able-bodied and paraplegics but tend to decease in the tetraplegic group with increasing tilt levels (Figure 4.35, b).

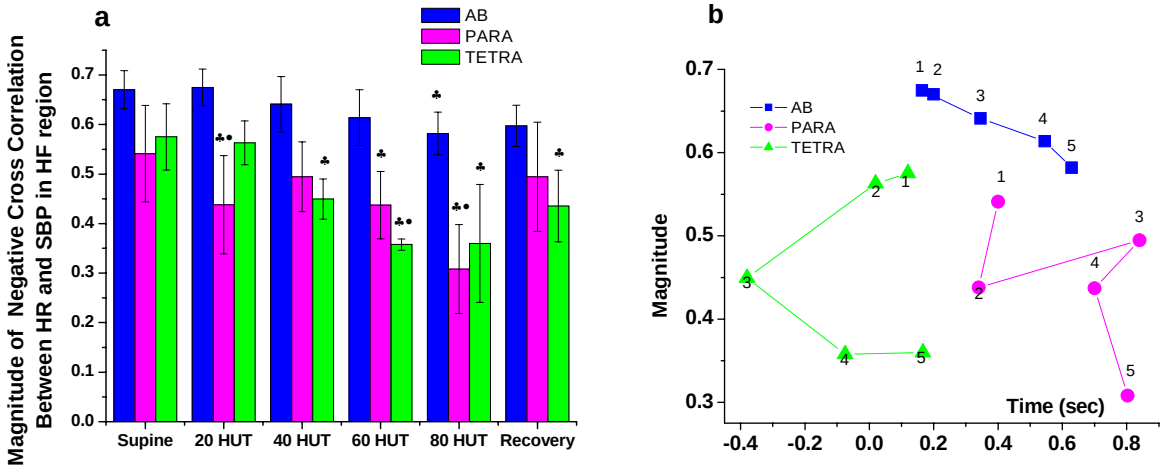


Figure 4.35: Group averaged magnitude of the HF (0.15-0.4Hz) negative peak of the cross correlation between systolic blood pressure and heart rate (a), and group averaged magnitude vs. corresponding time lag of cross correlation between systolic blood pressure and heart rate where systolic blood pressure leads heart rate (b) at rest and in response to tilt for able-bodied subjects (n=11), paraplegics (n=5) and tetraplegics (n=5).. Negative correlation magnitude: group, tilt, p<0.05, time lag: group, tilt, group/tilt interaction, p<0.05).1: supine control, 2: 20°HUT, 3: 40°HUT, 4: 60°HUT, 5: 80°HUT.● significantly different from AB

(same stress level), Δ significantly different from paraplegic (same stress level), ♣ significantly different from supine condition (same group).

Indexes of Low Frequency Feed-Forward Activity via Cross Correlation Technique

Figure 4.36 illustrates the average magnitude of the LF positive peak (a), and the magnitude versus its corresponding time lag (from zero to the positive peak) of cross correlation between SBP and HR (b). The strength of the positive correlation remained in the able-bodied and the paraplegic groups, but significantly decreased in the tetraplegic group with increasing tilt (group, tilt, group/tilt interaction $p < 0.05$). There was little change in time lags (for reaching the maximum positive correlation peaks) in able-bodied in response to increasing tilt. This index in the paraplegic group was significantly lower at supine control, 20°, and 40° deg HUT than in the able-bodied group, and reached the able-bodied value at 60° and 80° HUT. Tetraplegics had comparable values to able-bodied at supine control and significantly increased at 80° HUT. This group also demonstrated increasing high variance around the mean with increasing tilt angle.

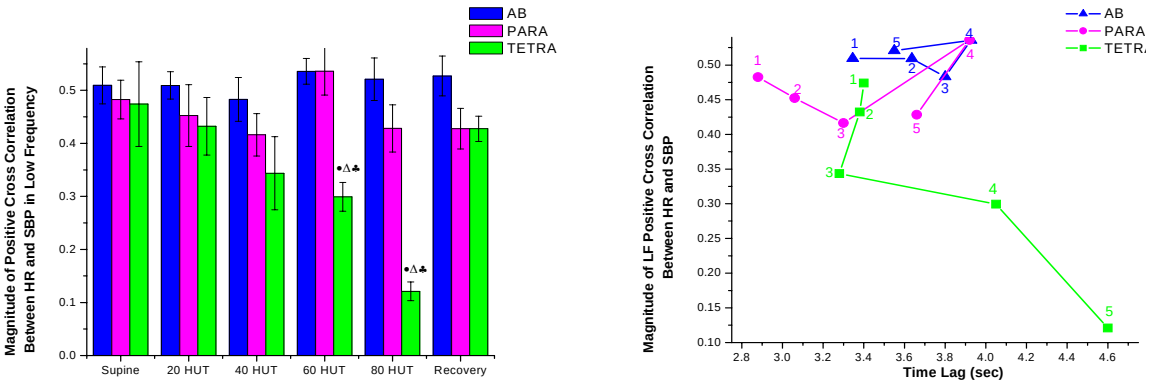


Figure 4.36: Group averaged magnitude (left) and time lag (right) of the LF (0.04-0.15Hz) positive peak of the cross correlation between SBP and HR at rest and in response to tilt is shown on the left (a) for able-bodied subjects (n=11), paraplegics (n=5) and tetraplegics (n=5). Magnitude, group, tilt, group/tilt interaction, time lags, tilt, group/tilt interaction, $p<0.05$; ● significantly different from AB (same stress level), Δ significantly different from paraplegic (same stress level), ♣ significantly different from supine condition (same group). 1: supine control, 2: 20°HUT, 3: 40°HUT, 4: 60°HUT, 5: 80°HUT.

Indexes of High Frequency Feed-Forward Activity via Cross Correlation Technique

Figure 4.37 shows the group average magnitude of the HF positive peak (a), and the magnitude versus its time lag (from zero to the positive peak) for the cross correlation between SBP and HR (b). The strength of the magnitude remained constant from supine to 60° HUT, and significantly decreased at 80° HUT in the able-bodied group. The paraplegic and tetraplegic groups had significantly lower values than able-bodied at each tilt level. The reduction in the strength of the magnitude was significant at 40°, 60° and 80° HUT in the tetraplegic group compared to their supine values (Figure 4.37, a). The time delay showed little decrease in the able-bodied group, but increased in the SCI group with increasing tilt levels (Figure 4.37, b). The tetraplegic group demonstrated bigger time lags than paraplegics at each tilt level except supine control. Positive correlation magnitude: group, tilt, group/tilt interaction, $p < 0.05$, Time lag: tilt, group/tilt interaction, $p < 0.05$.

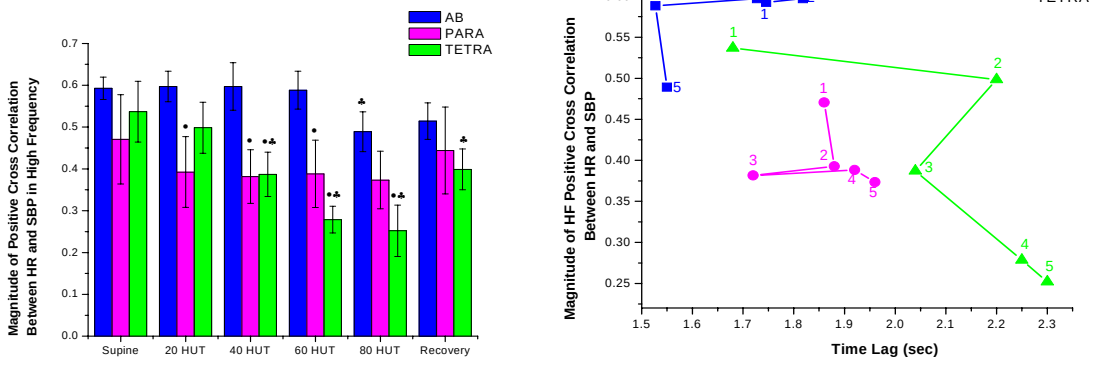


Figure 4.37: Group averaged magnitude (left) and time lag (right) of the HF (0.15-0.45 Hz) positive peak of the cross correlation between systolic blood pressure and heart rate at rest and in response to tilt is shown on the left for able-bodied subjects (n=11), paraplegics (n=5) and tetraplegics (n=5). Group averaged magnitude, group, tilt, group/tilt interaction, $p<0.05$). The time delay, tilt, group/tilt interaction, $p<0.05$. 1: supine control, 2: 20°HUT, 3: 40°HUT, 4: 60°HUT, 5: 80°HUT.● significantly different from AB (same stress level), Δ significantly different from paraplegic (same stress level), ♣ significantly different from supine condition (same group).

The Baroreflex Sequence Technique

Baroreflex Sensitivity Index (ms/mmHg, BRS)

The baroreflex sensitivity index defines the relationship between a change in R-R interval in response to a given change in blood pressure. Baroreflex sensitivity at rest and in response to head-up-tilt is given in Figure 4.38 for all groups. This index decreased with increasing tilt levels in all groups. Baroreflex sensitivity of able-bodied and tetraplegic groups were similar at rest, and significantly decreased at 40^{o}, 60^{o}, 80^{o} HUT from the control and 20^{o} HUT. The paraplegic group had the lowest values at each tilt level.

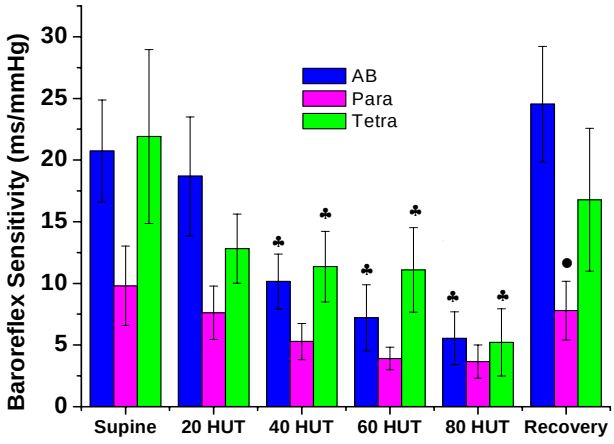


Figure 4.38: Averaged (±SEM) baroreflex sensitivity index for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) in response to head up tilt. Tilt and group/tilt interaction p value ≤ 0.05; ● significantly different from AB (same stress level), ♣ significantly different from supine condition (same group).

The Occurrence of Systolic Blood Pressure Ramps

This index defines the input to the baroreceptors and was calculated as the number of beats involved in generating systolic blood pressure (positive and negative) ramps. It is reported as the percentage of total analyzed beats in a segment. The average (±SEM) percentage of heartbeats involved in positive and negative systolic blood pressure ramps is illustrated in Figure 4.39. The index increased significantly in able-bodied subjects, remained relatively unchanged in paraplegic, and declined in tetraplegic subjects with increasing tilt angles. The index in paraplegics and tetraplegics was significantly lower than in able-bodied subjects at 20^o, 40^o, 60^o and 80^o HUT (group, tilt and group/tilt interaction p value ≤ 0.05)

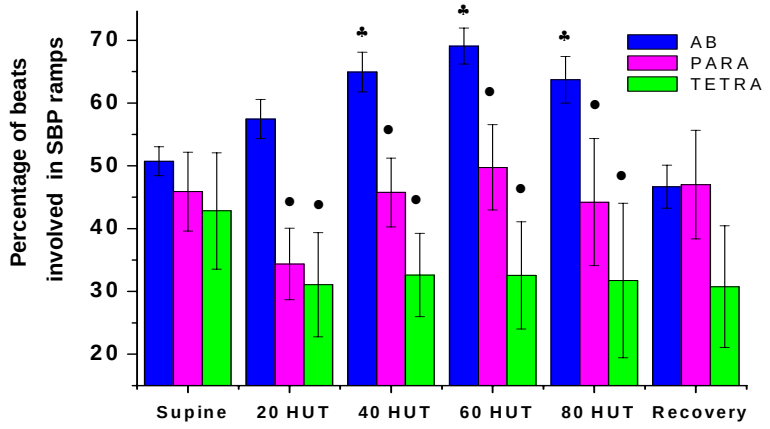


Figure 4.39: Averaged (±SEM) percentage of heartbeats involved in SBP for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects in response to head up tilt. Group, tilt and group/tilt interaction p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from control (same group)

The Occurrence of Baroreflex Sequences

The occurrence of baroreflex sequences, an additional measure of baroreflex activity, was calculated as the number of beats involved in baroreflex sequences. It is reported as the percentage of total analyzed heart beats in a segment. The average (±SEM) percentage of heartbeats involved in baroreflex sequences is illustrated in Figure 4.40. The index increased significantly in able-bodied subjects, remained relatively unchanged in paraplegic, and declined in tetraplegic subjects with increasing tilt angles. Both SCI groups had significantly lower values than the able-bodied group at each tilt position (group, tilt and group/tilt interaction p value ≤ 0.05).

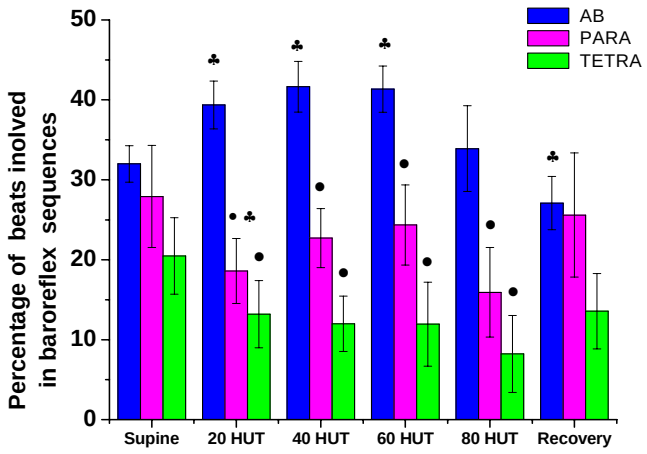


Figure 4.40: Averaged (±SEM) percentage of heartbeats involved in baroreflex sequences for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects in response to head up tilt. Group, tilt and group/tilt interaction p value ≤ 0.05; ● significantly different from AB (same stress level), Δ significantly different from PARA (same stress level), ♣ significantly different from control (same group)

The Baroreflex Effectiveness Index (BEI)

The BEI index is proposed to quantify the number of times that the baroreflex is effective in driving the sinus node (24). It was calculated as the ratio between the total number of baroreflex sequences and the total number of systolic blood pressure positive and negative ramps. The baroreflex effectiveness index, given in Figure 4.41, was greater in the able-bodied group than in the tetraplegic group ($p < 0.05$) and declined with increasing tilt in all groups. Positive and negative BEI values were similar at each level of head-up-tilt.

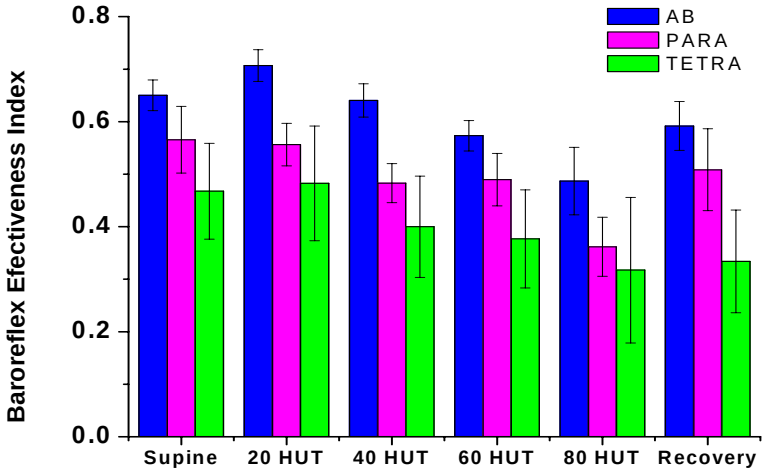


Figure 4.41: Averaged (±SEM) baroreflex effectiveness index for able-bodied (n=11), paraplegic (n=5) and tetraplegic (n=5) subjects in response to head up tilt. Group (TETRA < AB) and tilt effects p value < 0.05.

Chapter 5 : Discussion

The present study examined neural control of the heart and vascular function in able-bodied, paraplegic and tetraplegic subjects during the injured subjects' acute phase of recovery. Orthostatic stress, induced by tilt table, was used to stimulate the cardiovascular control system. This simulation of standing is an accepted effective test for measuring cardiovascular reflexes (71). We had hypothesized that some aspects of the cardiovascular responses to head up tilt would provide early indicators of autonomic damage. The major findings of this study are summarized as below:

- Tetraplegic subjects demonstrated a significant reduction in their ability to regulate blood pressure in response to tilt.

- Spinal cord injured individuals had less dynamic activity in the LF and HF frequency range compared to able-bodied subjects for both blood pressure and heart rate.

- Upper and lower body skin perfusions spectral powers in the LF region in the SCI groups were significantly ($p<0.05$) lower than that of the able-bodied group.

- The tetraplegic group had low heart rate SNS index, and a high heart rate PNS index at the higher tilt levels. These indexes in the paraplegic group were comparable to that of the able-bodied group.

- Spinal cord injury resulted in a significant ($p<0.05$) reduction in the negative cross correlation peak and change in the time delay between fluctuations in systolic blood pressure and heart rate in response to increasing levels of HUT. This reduced correlation occurred in both LF (index of sympathetic activity) and HF (index of parasympathetic activity) regions.

- High levels of spinal cord injury affected the feed-forward relationship between systolic blood pressure and heart rate in LF and HF regions; the magnitude of the positive correlation decreased significantly ($p<0.05$), and the time lags increased with tilt.

- The baroreflex sensitivity index in the tetraplegic group was close to the able-bodied group whereas the index in the paraplegic group was the lowest among three groups. Paraplegics and tetraplegics demonstrated a significantly lower percentage of heartbeats involved in SBP ramps and in baroreflex sequences, and lower baroreflex effectiveness index than able-bodied subjects.

Mean Values

Resting mean blood pressure was not different among the three groups, but significantly decreased in the tetraplegic group with increasing tilt-induced orthostatic stress. Although lower resting mean blood pressures have been reported in tetraplegics (42), our study did not find a significant resting mean blood pressure difference between tetraplegic and able-bodied groups, also reported by others (41). Significant reduction in mean arterial blood pressure in response to head up tilt was also reported for tetraplegic subjects more than one-year post injury (42). In spite of significant increases in heart rate by able-bodied and paraplegic groups, the tilt-induced rise in heart rate in tetraplegics was not significant, and was not sufficient to maintain stable blood pressure in response to HUT. The heart rate increase in all groups is largely vagal withdrawal (41). Paraplegics had higher heart rates, significant in supine control and recovery, than able-bodied, as previously reported (34,35,80,41). One explanation might be that an activation of sympathetic outflow to the heart compensates for the lack of venous return caused by inefficient vascular innervation of splanchnic and lower limb regions (33). The low heart rate at supine and head up tilt in tetraplegic subjects could result from intact parasympathetic and damaged sympathetic outflow to the heart, and vasculature. The

mean stroke volumes in the SCI groups were lower than in the able-bodied group at supine positions and 20^{o} HUT. The mean stoke volume differences between the SCI and able-bodied groups diminished with tilt. Lower stroke volume in paraplegics might be a result of their high heart rate. Mean upper body skin perfusion was well regulated in response to increasing orthostatic stress in the able-bodied and paraplegic groups, indicating intact sympathetic control to the upper body vasculature. However, the paraplegic group had lower values than able-bodied at each tilt level. This might be due to intact upper body sympathetic outflow that compensates for the damaged lower body sympathetic outflow. Mean resting upper body skin perfusion of tetraplegics was close to able-bodied, but significantly decreased with tilt, indicating lack of sympathetic control of the vasculature. Mean lower body skin perfusion was high in the able-bodied, and low in the tetraplegic groups, and significantly decreased with tilt in all groups. Significant decrease in mean lower body skin perfusion with tilt indicates increase in sympathetic outflow to the vasculature in able-bodied group. Since spectral power of lower body skin perfusion of both SCI groups was significantly lower than that in the able-bodied group at each tilt level, the source of decrease in mean lower body skin perfusion might not be due to increased sympathetic outflow, but rather to a greater tilt-induced plasma shift out of the vasculature (29).

Spectral Power

Low frequency spectral power of blood pressure increased significantly ($p < 0.05$) in the able-bodied group in response to HUT. This was an expected result, indicating increased sympathetic activity during orthostatic stress (30,76). Paraplegic spectral power of blood pressure in the LF region was significantly ($p<0.05$) lower than in the able-bodied at each tilt position, and remained fairly constant throughout the study, indicating stable sympathetic activity. Significant tilt-induced reduction of LF spectral power of systolic blood pressure in paraplegic patients (average 11 years post injury) has been reported (80). Since our paraplegics did not show a significant tilt-induced reduction in LF spectral power of blood pressure, the difference might be the result of long-term

lesions. Tetraplegics had the lowest LF power in all groups at each tilt level. The LF spectral power of the tetraplegic group also remained constant during increasing orthostatic stress. The lack of LF spectral power of blood pressure in compete cervical SCI subjects has been reported (42). The very weak power in our tetraplegic group during tilt might represent their mix of complete and incomplete injury status. Spectral power of blood pressure in the frequencies above 0.15 Hz was very small, and was not affected by increasing orthostatic stress in any of the three groups.

The LF spectral power of heart rate increased in the able-bodied group in response to head-up-tilt probably due to increased sympathetic activity (20,42,63). In both SCI groups, spectral powers of heart rate in the LF region were similar, but lower than that of the control group at rest. The paraplegic group was able to maintain LF power, while the tetraplegic group gradually reduced LF power in response to increasing orthostatic stress. Both SCI groups had significantly lower values at 60^{o}, 80^{o} HUT, and supine recovery than the control group. Maintenance of LF spectral power of heart rate in paraplegic subjects was also reported during head-up-tilt (80). In this study, paraplegics had higher LF power at rest, and lower power at tilted positions than did healthy subjects; however, our paraplegic group had lower LF spectral power of heart rate at each tilt position. Low frequency spectral power of heart rate in tetraplegics (minimum 2-month post injury) has been reported to be lower than in healthy subjects at rest and decreased in response to tilt (36) It also has been reported that tetraplegics who had complete traumatic cervical spinal cord injury between C4-C7 (minimum 19-year post injury) demonstrated absent LF power of heart rate (42).

The spectral power of heart rate in the HF region decreased with increasing stress in all three groups due to withdrawal of parasympathetic outflow to the heart. The paraplegic group had lower values than able-bodied and tetraplegic groups at rest; and became significantly lower than able-bodied at 20^{o} 40^{o}, 60^{o}, 80^{o} head-up-tilt. Lower resting and tilted values of spectral power of heart rate have been reported in paraplegics compared to healthy and tetraplegic subjects (20,80). The HF spectral power in the tetraplegic group was close to that of the able-bodied group at supine control, but was significantly lower at 40^{o}, 60^{o}, 80^{o} head-up-tilt, and supine recovery. Comparable results were reported in the study of (42) and (21). These studies reported that able-bodied and

tetraplegics had similar spectral power of heart rate at rest, and underwent similar reduction with increasing orthostatic stress. They did not find significant differences between healthy and tetraplegic subjects during tilt, as we did. Control of power within this frequency range is attributable almost exclusively to parasympathetic nervous activity (e.g. 69). Parasympathetic innervation of the SA-node via the vagus nerve is not interrupted by spinal injury, so these findings were unexpected: we had predicted that SCI subjects would have used HR more effectively, and therefore would have more oscillations in the HF range to stabilize BP in response to an orthostatic challenge.

Spectral power of respiration was decreased by tilt in all three groups. The tetraplegic group had high mean values at each tilt position; however, the variance around the mean was also large at each position.

Heart rate SNS index was calculated as the ratio between spectral power of heart rate in the LF and HF region. The LF/HF ratio represents an estimate of sympatho vagal cardiac control and does not provide information regarding the magnitude of change but rather the reciprocal nature of the two autonomic systems. During head-up-tilt, increases in this index are expected due to shifts in autonomic modulation of augmented sympathetic and attenuated parasympathetic activity. This index was reported to be increased 5 fold in healthy subjects, and 2 fold in paraplegic subjects (80) when subjects moved from supine to 75^{o} HUT. Our able-bodied group increased its index from 1.9±0.3 to 9±2.1, approximately 5 fold change, and the paraplegic group increased its index from 2.7±1.4 to 7.2±2.5 during tilt, approximately 2.5 fold change. This index changed from 1.57±0.3 to 2.9±1 in the tetraplegic group, approximately 1.8 fold increases from rest. Having reasonable intact cardiac SNS modulation, paraplegics exhibited an altered sympatho vagal response to HUT; a similar finding was reported earlier (80). The tetraplegic group demonstrated lower SNS index values than those in able-bodied and paraplegic groups at each tilt level, indicating damage sympathetic outflow to the heart in this group.

The PNS index decreased from 0.57±0.3 to 0.25±0.04, approximately a 0.5 fold reduction in healthy subjects in response to 80^{o} HUT. This index was reduced by 0.58 times in paraplegics, and by 0.7 times in tetraplegics in response to 80^{o} HUT. These

results indicate an altered parasympathetic activity in SCI, that was most pronounced in tetraplegics.

Significantly lower LF spectral power of blood pressure in the SCI groups indicates loss of sympathetic control of the vasculature, which is more significant in tetraplegic subjects. Since paraplegics have presumably intact sympathetic and parasympathetic activity to the heart, attenuation of heart rate power in LH and HF might be due to their decrease in baroreflex sensitivity. Withdrawal of parasympathetic activity in paraplegics during tilt was comparable to able-bodied group, but they exhibited altered sympathetic activity. Withdrawal of parasympathetic activity and increase in sympathetic activity in tetraplegics were lower than in able-bodied subjects in response to tilt, indicating parasympathetic dominance in this group. Increased respiratory variability in SCI may influence the interpretation of spectral power of blood pressure and heart rate.

Cross Correlation

Low Frequency Cross Correlation as an Index of Sympathetic Activity:

The tilt-induced increase in the magnitude of the negative peak of the cross correlation between systolic blood pressure and heart rate represents a progressive increase in sympathetic nerve activity in able-bodied subjects, also previously reported (63). With peripheral vascular and cardiac spinal pathways impaired, paraplegics did not increase their cross correlation magnitude during tilt. Tetraplegics steadily lost correlation during tilt, probably due to loss of both cardiac and peripheral sympathetic pathways. All able-bodied subjects demonstrated strong, constant blue bands at each tilt position indicating strong, active feedback control. Although characterized by lower magnitude and time delay, the blue band was also consistent in all paraplegic subjects except a sixty-year-old subject who lost consistent correlation at higher stress levels. Besides demonstrating very low magnitude and erratic time delays, the negative feedback of tetraplegic subjects occurred only sporadically, indicating that feedback occurred in less than one out of the five minutes of data. Since patients with poor orthostatic tolerance had an increased phase shift between systolic blood pressure and heart rate

fluctuations as well as lower strength correlations (36), an increase in time delay also might contribute to the orthostatic hypotension problem following SCI.

High Frequency Cross Correlation as an Index of Parasympathetic Activity

The tilt-induced decrease in the magnitude of the negative peak of the cross correlation between systolic blood pressure and heart rate represents a progressive withdrawal of parasympathetic outflow that was present in all three groups, but was more pronounced in SCI subjects. Even though both paraplegic and tetraplegic groups had lower magnitude responses compared to able-bodied, paraplegic subjects did maintain feedback control at each tilt level, while tetraplegics increasingly lost control as tilt angles increased. The strong correlation at lower tilt angels in the tetraplegic group may be due to respiration since tetraplegic subjects demonstrated greater breathing fluctuation effects in heart rate and systolic blood pressure (5). Previous studies in able-bodied subjects reported a baroreflex latency of 0.5-0.6 sec (13,68), and significantly shorter latencies (27) in response to different types of stimuli. Another study reported that the time delay between baroreceptor stimulation and oscillations of RR-interval increased from 0.59±0.25 sec to 0.86±0.27 sec as their able-bodied subjects were moved from supine to 60^{o} HUT (45). The time delay in our able-bodied group increased from 0.2±0.07 sec to 0.62±0.16 sec when subjects were moved from supine to 80 deg HUT. The difference between the results of these studies may lie in the different experiment protocols including length and levels of tilt and different data analysis. The time delay in our paraplegic subjects increased from 0.4±0.09 to 0.8±0.24 sec in response to tilt, in the range typical of vagal baroreflex control. The negative peak magnitude and time delay may not accurately represent the correlation between heart rate and systolic blood pressure in tetraplegic subjects due to noise interference with the weak correlation. Although we did our best to identify the negative peak magnitude and time delay values to represent each five-minute correlation, the inconsistencies lead us to conclude that it is more instructive to view the feedback structure of whole segments (Figures 4.30d, 4.31, 4.32, 4.33).

Baroreflex Sequences

The values of an able-bodied baroreflex sensitivity (slope of the RR-Interval vs. systolic blood pressure) fell in the range previously reported for both supine and HUT positions (25,36,42,52,63,81). Baroreflex sensitivity did not differ significantly between able-bodied and tetraplegics, similar to findings reported for able-bodied and tetraplegics studied 12+ months post injury (42,31). Paraplegics had lower baroreflex sensitivity at rest, and at each tilt position than did the other groups. This difference can probably be accounted for by the higher heart rates of paraplegics, a relationship previously established for able-bodied subjects by Abrahamsson (1). Our heart rate and baroreflex sensitivity data also show a similar response in all three groups at rest and during tilt, Figure 5.1.

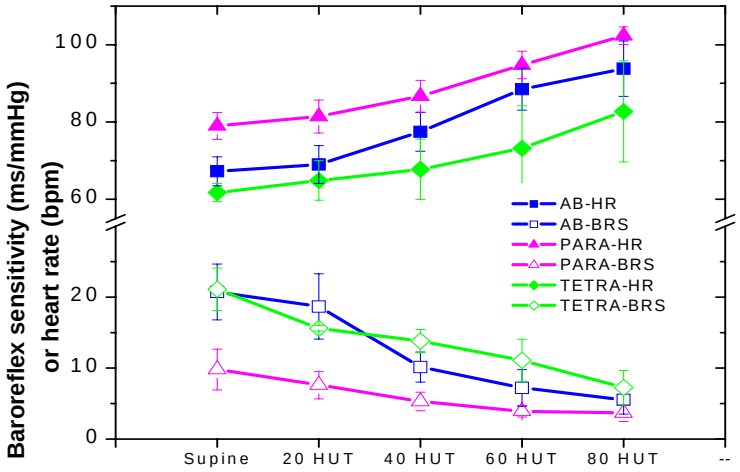


Figure 5. 1: Relationship between heart rate (HR, closed) and baroreflex sensitivity (BRS, open) in three groups at rest and during tilt.

When the natural logarithm of baroreflex sensitivity is plotted against heart rate, an inverse linear relationship can be found, Figure 5.2. Able-bodied and tetraplegic groups had equivalent baroreflex sensitivities at heart rates < 70 bpm, while able-bodied and paraplegic groups demonstrated similar baroreflex sensitivities at heart rates > 75 bpm, indicating that baroreflex differences in response to tilt may be more influenced by heart rate than by SCI, Figure 5.2. These results are consistent with baroreflex sensitivity being strongly a function of parasympathetic outflow with vagal control of heart rate being essential intact after spinal cord injury.

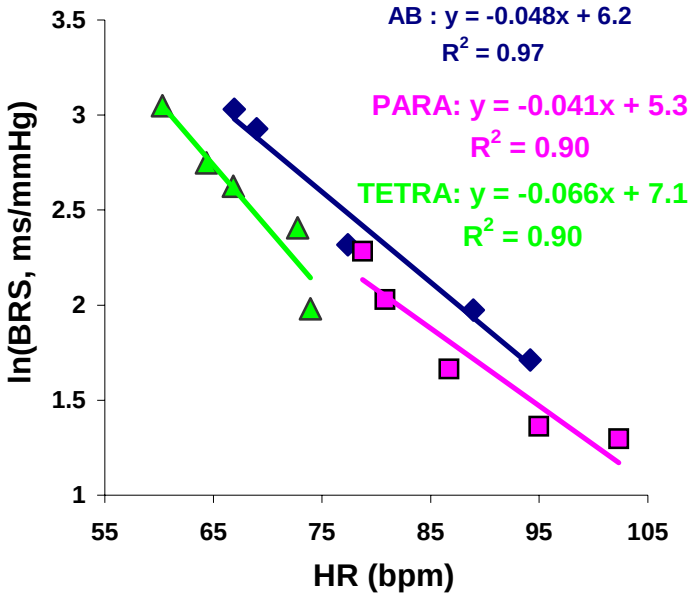


Figure 5. 2: Relationship between heart rate (HR) and the natural logarithm of baroreflex sensitivity ln(BRS)) in three groups during tilt. (AB: Able-bodied, PARA: Paraplegic, TETRA: Tetraplegic

The occurrence of baroreflex sequences in our able-bodied subjects increased significantly from supine to head up tilt (14,36,53). We found a similar, tilt-induced increase in the percentage of beats involved in baroreflex sequences in our able bodied group. In addition, this group demonstrated a tilt-induced increase in the percentage of beats involved in generating SBP ramps. The percentage of heart beats involved in baroreflex sequences in our able-bodied group were in the range reported for a similar able-bodied group during supine rest (32±0.02 %) and 60^{o} HUT (41.3±0.03 %) (14). Both paraplegic and tetraplegic groups had significantly less percentage of beats involved in SBP ramps and baroreflex sequences in response to HUT. Our data therefore support the concept that the stimulus to the baroreflex is diminished by spinal cord injury.

The baroreflex effectiveness index for able-bodied subjects decreased from 65.0±0.03 % at supine to 48.7±0.06 % at 80^{o} HUT as baroreflex sensitivity decreased from 20.7 to 5.53 ms/mmHg, comparable to results of (70). In addition to the lower number of heartbeats involved in SBP ramps and baroreflex sequences, high spinal cord injury resulted in a lower baroreflex effectiveness index, BEI. We did not find significant differences between positive and negative BEI except that positive BEI was slightly higher in supine at rest and negative BEI was slightly higher at 80^{o} HUT in able-bodied and paraplegic groups, opposite to that of tetraplegics.

Since both paraplegic and tetraplegic groups demonstrated a significantly ($p<0.05$) lower percentage of SBP ramps, resulting in significantly ($p<0.05$) lower percentage of baroreflex sequences, and lower baroreflex effectiveness index than the able-bodied group, it is likely that spinal cord injury decreased stimulation of arterial baroreceptors and less engagement of feedback control occurred. These data support the concept that the parasympathetically dominated baroreflex loses some of its capability to regulate heart rate in tetraplegics, and is not stimulated to regulate as powerfully. The mixed sympathetic, parasympathetic innervations of paraplegics, may contribute to the significant decrease in baroreflex sensitivity in that injury, or the higher heart rate may purely account for this effect.

Indexes to assess cardiovascular damage following SCI

Consistent and reproducible assessment scales are necessary to define acutely injured patient deficits and to facilitate communication with caregivers regarding the patient's status (1). The American Spinal Injury Association (ASIA) scale for neurological, and The Functional Independence Measure (FIM) for functional outcome are the most common scales. Besides the deficits in motor and sensory function following SCI, cardiovascular problems known to arise from sympathetic nervous system dysfunction are also common in acute SCI, especially those occurring in the cervical region. Despite these problems, there is no assessment test available to identify patient's cardiovascular deficits following SCI. In this study, we attempted to discriminate able-bodied from SCI, and paraplegic from tetraplegic using cardiovascular variables in response to tilt. In that regard, spectral power of blood pressure and heart rate in the LF region, the magnitude and time delay of cross correlation between heart rate and systolic blood pressure in LH and HF regions become major candidates for diagnostic indicators of the level of autonomic injury and subsequent recovery from injury.

Limitations of the study

A most challenging part of our study entailed recruiting SCI subjects immediately following injury. In addition, the complexity of classifying the injury contributed to large variability among subjects within the same group, such as complete or incomplete injury and different levels of injury. Also, spinal cord injured subjects were under different types of medications that might affect their short-term cardiovascular control mechanisms. Our SCI subjects might have been still in spinal shock, which is common in acute phase of injury. Increased respiratory variability in SCI may influence the interpretation of spectral power of blood pressure and heart rate. The results of hormonal changes and intra to extra vascular fluid shifts that are not reported here may shed further light on SCI effects on sympathetic and parasympathetic activity.

Chapter 6 : Conclusions

In this study, we attempted to quantify the neural control of cardiovascular function deficits following SCI. The LF spectral power of blood pressure and heart rate increased with tilt in the able-bodied group, remained unchanged in the paraplegic group and decreased in the tetraplegic group. The HF spectral power of heart rate decreased in all three groups. In respect to tilt, the peak cross correlation between systolic blood pressure and heart rate in the LF region was greatest in the able-bodied group, and significantly ($p<0.05$) increased during HUT in that group, remained approximately constant in the paraplegic group, and declined in the tetraplegic group. The peak cross correlation in the HF region significantly ($p<0.05$) decreased with tilt in all groups and was lower in SCI than in able-bodied at each tilt level. Both paraplegic and tetraplegic subjects demonstrate a lower percentage of systolic blood pressure ramps, baroreflex sequences, and lower baroreflex effectiveness indexes than able-bodied subjects. It is likely that spinal cord injury decreased stimulation of arterial baroreceptors and that less engagement of feedback control occurred. These data support the concept that the parasympathetically dominated baroreflex loses little of its capability to regulate heart rate in tetraplegics, but is not stimulated to regulate as often. The mixed sympathetic, parasympathetic innervations of paraplegics, may contribute to the significant decrease in baroreflex sensitivity in that injury, or higher heart rate may purely account for this effect. Moreover, the increased time delay in LF cross correlation between heart rate and systolic blood pressure might contribute to the orthostatic hypotension following spinal cord injury. Our data provide strong evidence that the pathways utilized to evoke baroreflex regulation of heart rate are compromised by spinal cord injury and this loss may be a major contributor to the decrease in orthostatic tolerance following injury.

Chapter 7 : Future Work

The SCI subject in the acute phase of recovery should be followed in his/her chronic phase of injury to quantify for further improvement or worsening of his/her condition**.** Recruiting spinal cord injured patients with the same level of lesion could be beneficial to identify cardiovascular deficits in certain injured groups. In addition to baroreflex sequences, nonbaroreflex sequences in able-bodied, paraplegic and tetraplegic groups may give additional important information on cardiovascular control following SCI. Longitudinal follow up studies from the same subjects would be beneficial to validate the proposed indexes.

Chapter 8 : Appendices

Appendix A:

Medications that could possibly affect data collection:

Drug	Classification	Can cause	Used by Subject
Hydrocodone/acetaminophen	narcotic	hypotension	4
Baclofen	skeletal muscle relaxant	hypotension	4,5
Oxycontin	narcotic	hypotension	5
Methadone	opiate analgesic	bradycardia, change in BP	8
Percocet	narcotic	hypotension	8, 13, 14
Zanaflex	skeletal muscle relaxant	hypotension	8
Lasix	Diuretic	Fluid loss	8
HCTZ	Antihypertensive/diuretic	hypotension/fluid loss	8, 15
Ritalin	cerebral stimulant	tachycardia, changes in BP	12
Dantrium	skeletal muscle relaxant	hypotension	4
Lorcet	narcotic	hypotension	5
Sudafed	decongestant	hypertension	14
Theophylline	spasmolytic- relaxes smooth muscle of the respiratory system	sinus tachycardia, hypotension, fluid retention	14
Zestril	Antihypertensive	hypotension	15

Appendix B:

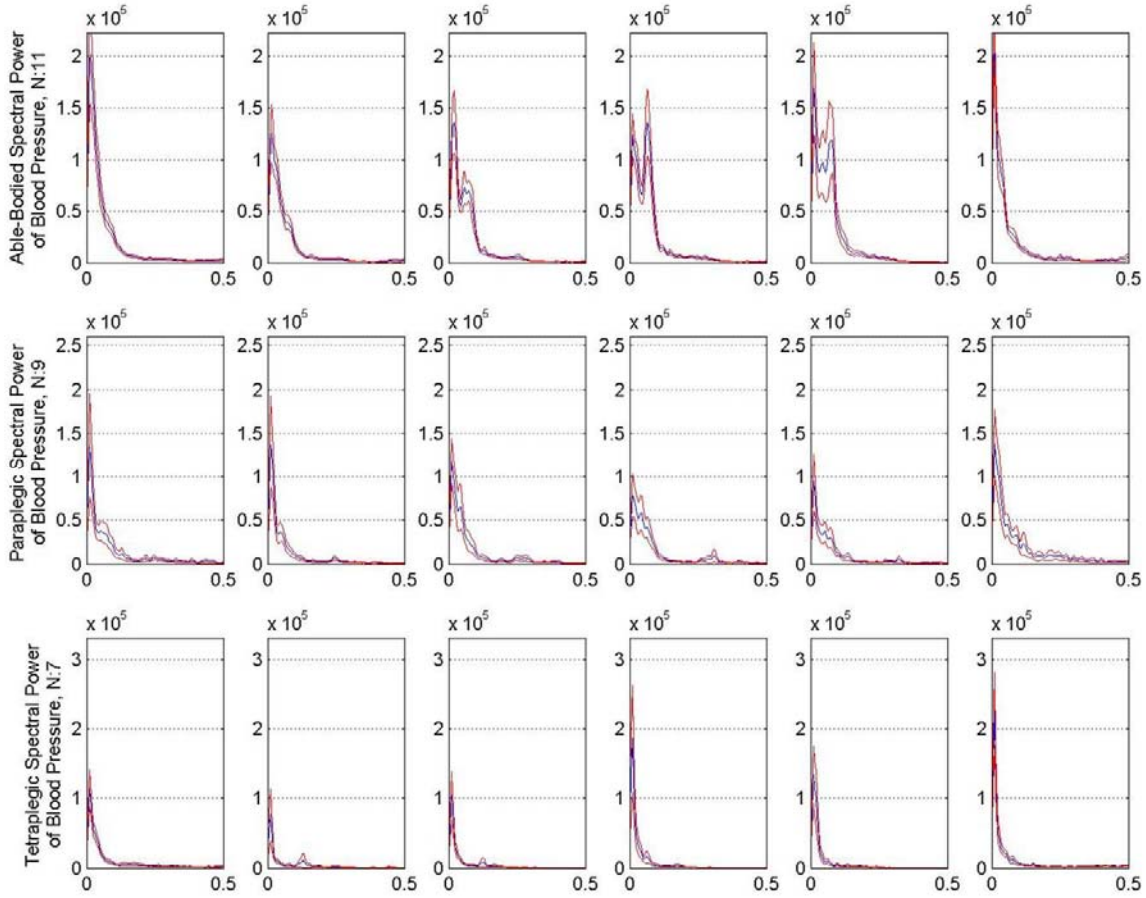


Figure 8.1: Mean (±SEM) spectral power of blood pressure in response to head-up-tilt in three groups. First column is supine control, the next four columns are 20, 40, 60, and 80 deg HUT, and the last column is supine recovery.

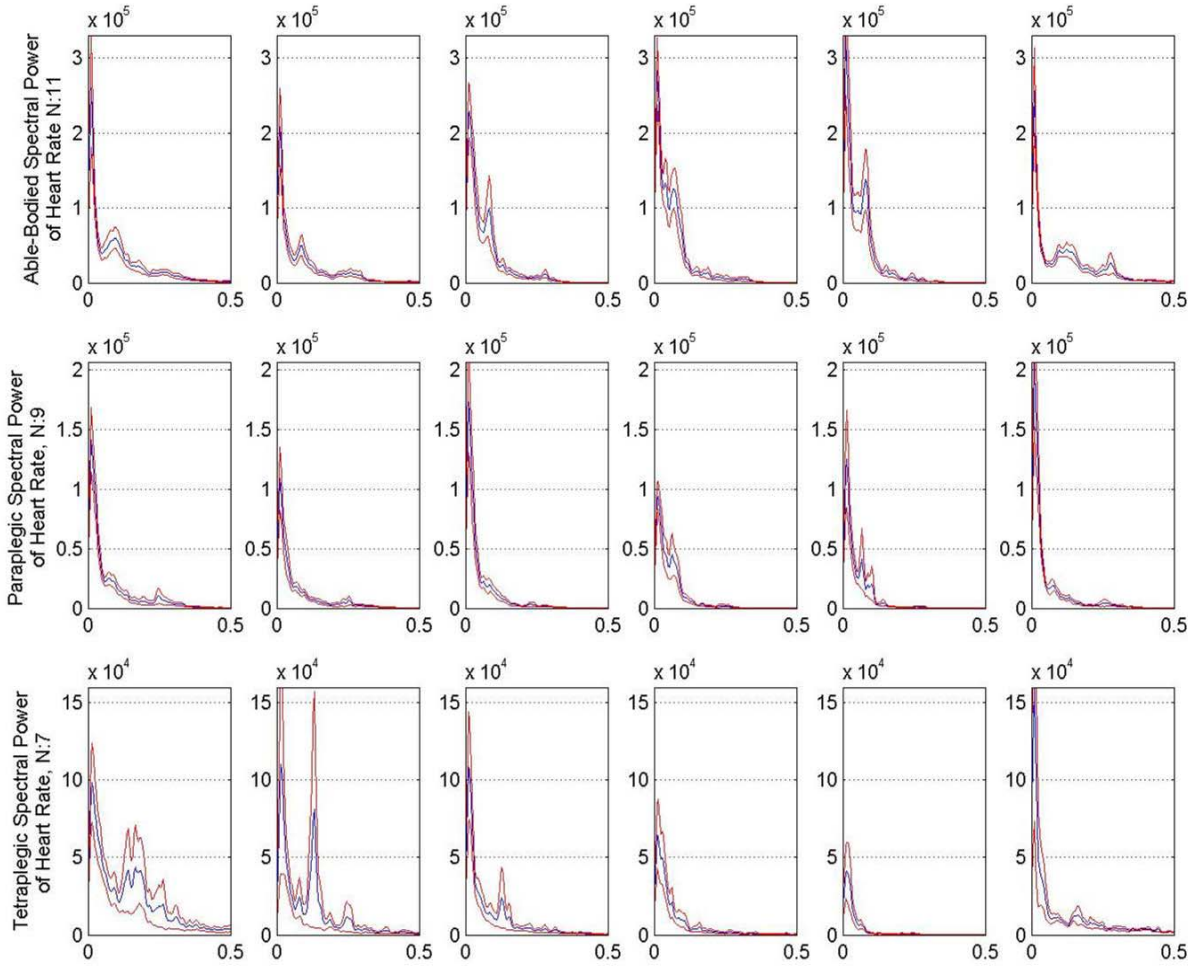


Figure 8.2: Mean (±SEM) spectral power of heart rate in response to head-up-tilt in three groups. First column is supine control, the next four columns are 20, 40, 60, and 80 deg HUT, and the last column is supine recovery.

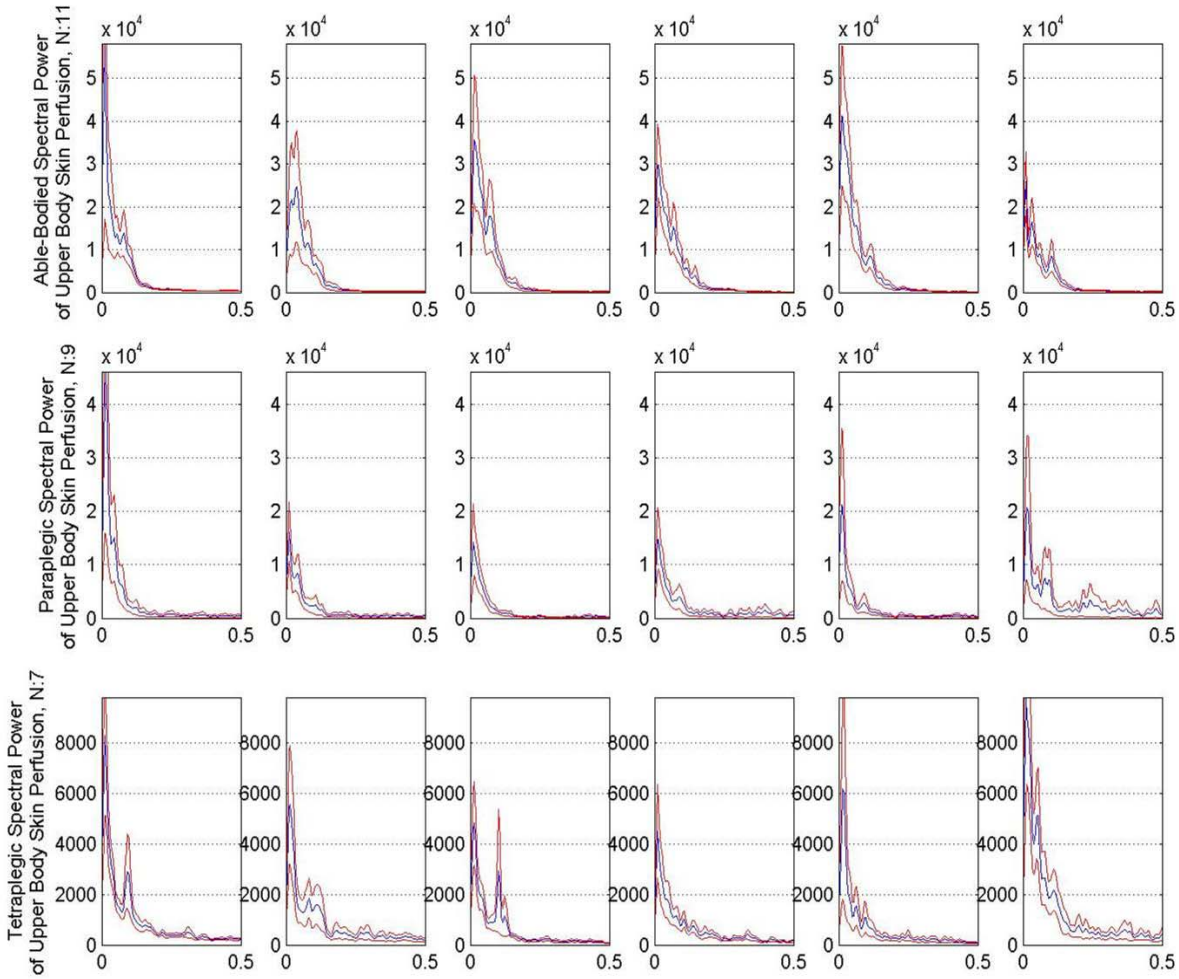


Figure 8.3: Mean (±SEM) spectral power of upper body skin perfusion in response to head-up-tilt in three groups. First column is supine control, the next four columns are 20, 40, 60, and 80 deg HUT, and the last column is supine recovery.

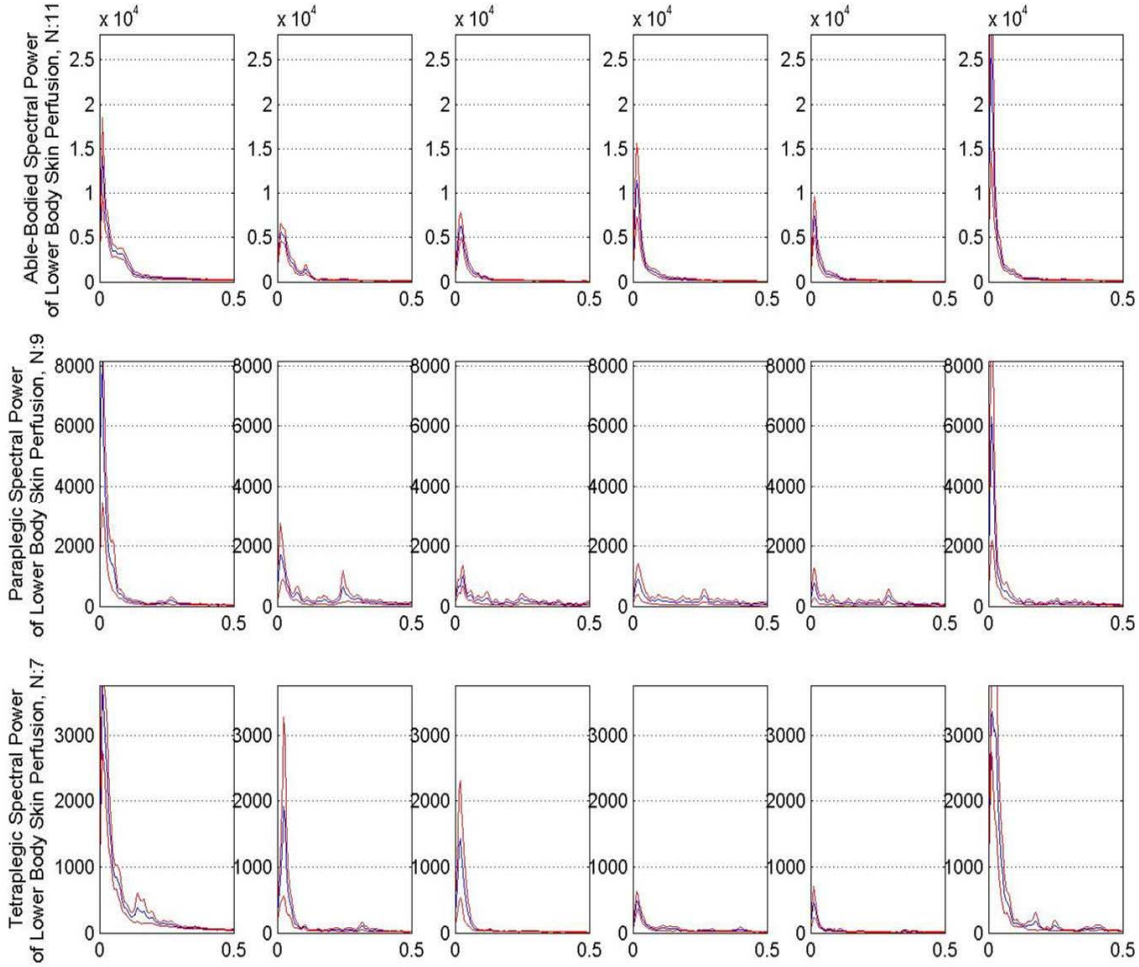
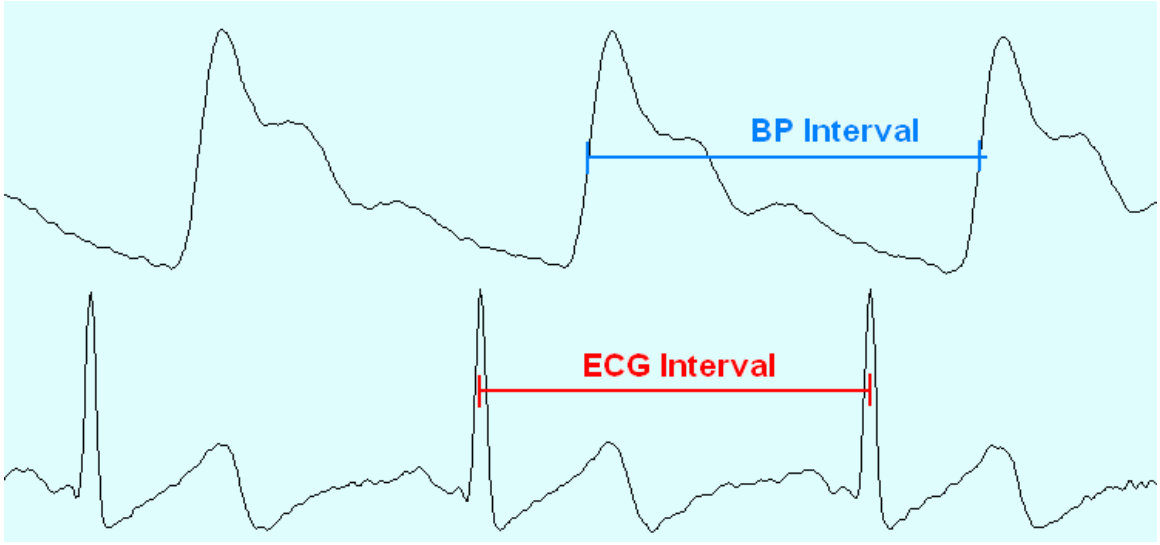


Figure 8.4: Mean (±SEM) spectral power of lower body skin perfusion in response to head-up-tilt in three groups. First column is supine control, the next four columns are 20, 40, 60, and 80 deg HUT, and the last column is supine recovery.

Appendix C:

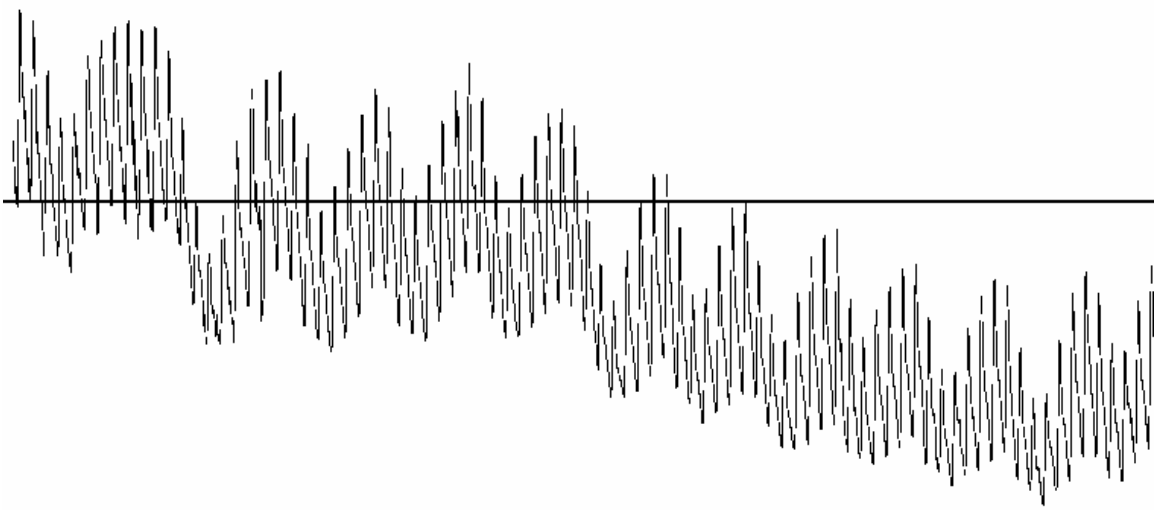
Calculation of Heart Rate from blood pressure and ECG by ViiSoftware Browser

1. Heart rate (HR) is calculated as the reciprocal of the pulse-interval.
2. The beginning and end of a pulse interval is determined from an ECG or pulsatile blood-pressure (BP) signal by determining when either signal crosses a reference value while moving in a positive direction. That is when the signal exceeds the reference going from smaller to larger values.
3. The figure below shows both an ECG and a BP signal and shows the determination of the pulse intervals.

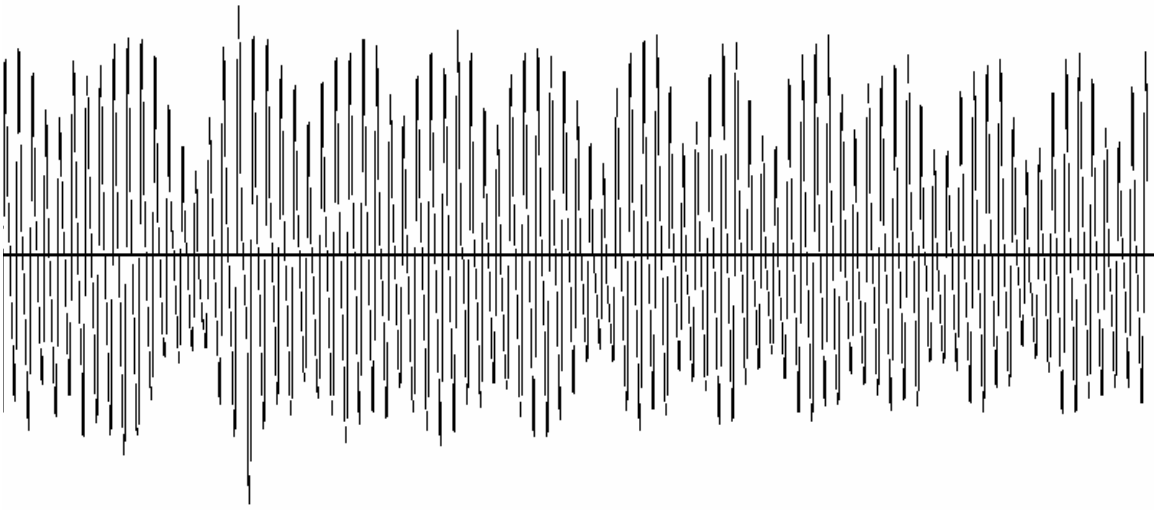


The blue line represents the reference for the blood-pressure signal whereas the red line the reference for the ECG. The length of the blue and red lines represents the pulse-interval (in units of time). Note the values calculated using the ECG or BP signals are not identical but over any length of time will be essentially the same.

4. A problem with BP is that its mean value varies so that selecting a reference value is problematic. The figure below shows a wandering BP signal and a failed attempt to set a suitable reference.



To overcome this problem the ViiSoftware Browser high-pass-filters the BP signal. The figure below shows the same BP signal after high-pass filtering. Note that setting a reference value is now not difficult.



In addition to the high-pass filter the signal is usually low-pass filtered to remove potentially high-frequency oscillations that could cause erroneously triggers and incorrect pulse-interval.

The ECG signal often does not need filtering but as a default the program filters the ECG signal.

When the signals are high pass filtered the mean value is close to zero. Hence the default value for the reference is zero although it can be changed with user input.

5. A potential problem in calculating HR is false triggers. A large BP dicrotic-notch or large ECG T-wave can cause such triggering. A parameter HR-limit is used to circumvent harmonic false triggers. The parameter in raw AD-units defines a dead-space after triggering in which a new trigger cannot occur.

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