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Loss of Sympathetic Control of Cardiovascular Function Following Spinal Cord Injury

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ABSTRACT OF THESIS

Loss of Sympathetic Control of
Cardiovascular Function Following Spinal Cord Injury

Cardiovascular control in the human is significantly impaired after spinal cord injury (SCI) having a direct effect on the sympathetic nervous system (SNS) causing an inability to regulate vasoconstriction below the level of the lesion. The effects of SCI on the two major components of blood pressure regulation, control of plasma volume and neural control of the heart and peripheral vasculature are poorly understood. In particular, no index to diagnose disorders to autonomic control of the heart and vasculature has been developed. The present study primarily utilized noninvasively acquired, easily accessible variables that may have promise as indicators of autonomic activity for assessing the level of autonomic injury and recovery of visceral control following SCI. The most significant results and the clearest differences between the three groups (able-bodied, paraplegic and tetraplegic) were evident in spectral analysis obtained in the frequency domain: Arterial blood pressure and lower body (at a region on the shin) skin perfusion spectral power in the low frequency (LF) region are of significance. These variables could be good discriminators of the three groups, as well as show level of SCI and autonomic function.

Keywords: Spinal cord injury, cardiovascular function, skin perfusion, autonomic activity, sympathetic control

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Loss of Sympathetic Control of Cardiovascular Function Following Spinal Cord Injury

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The Graduate School

University of Kentucky

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THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science in Biomedical Engineering in the
Graduate School at the University of Kentucky

By

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Lexington, Kentucky

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Lexington, Kentucky

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Chapter One

Introduction

Cardiovascular control in the human is significantly impaired after spinal cord injury (SCI) (Krassioukov 1999). The sympathetic nervous system (SNS) may be seriously impaired causing an inability to regulate vasoconstriction in the arms, legs and splanchnic area below the level of the lesion (Houtman 2000). Cardiovascular control in humans with high spinal cord lesions is dissociated from any cerebral or medullary regulatory component. These individuals form a human physiological model in whom the afferent, central, and vagal efferent components of the baroreflex arc are intact, but where the spinal and peripheral sympathetic nervous system is isolated (Rowell 1993). Impairment of cardiovascular regulation following SCI has short and long-term impact on the recovery of the individual. In the short-term, the patient's ability to participate in rehabilitation therapy is limited and in-patient stay is increased. Enhancing the recovery of cardiovascular control could provide significant benefit to SCI patients and their long- term quality of health. The long-term adaptive mechanisms are still controversial, probably involving multiple neurological, endocrine, renal, cardiovascular and hemodynamic factors. These factors include inhibition of vagal tone, plasma catecholamine levels, sensitivity of vascular beds to catecholamines, stretch reflexes in blood vessels, spinal blood pressure reflexes, renin-angiotensin system, aldosterone and plasma volume changes. Individual differences may also interact with these various mechanisms, further complicating the issues (Figoni 1984). Research is needed to clarify these adaptive mechanisms, as well as to investigate the physiological effects of SCI on the human body.

The effects of SCI on the two major components of blood pressure regulation, control of plasma volume and neural control of the heart and peripheral vasculature are poorly understood. In particular, no index to diagnose disorders to autonomic control of the heart and vasculature has been developed. A broad, overall objective of this SCI research at the University of Kentucky's Center for Biomedical Engineering is to characterize the level of autonomic damage after injury so that indices can be developed to monitor the rate of recovery of autonomic and volume regulatory control during rehabilitation.

At the core of this SCI research there exists both a basic science and a clinical aim. The basic science aim addresses the issue of quantifying blood pressure regulation in able-bodied (AB) and SCI subjects with respect to:

1. Neural regulation of cardiac and vascular function.
2. Hormonal regulation of cardiac and vascular function.
3. Tilt-induced fluid volume shifts to assess both intravascular pooling and extravascular filtration.

The clinical aim of this SCI research is to develop a protocol (using the parameters identified in the basic science aim) to diagnose disorders of cardiovascular regulation in individuals with SCI and assess rehabilitation therapies.

This thesis will address both neural and hormonal mechanisms, their function under normal conditions and what determines the activity or lack-there-of post-SCI because following SCI, the sympathetic chain at the spinal cord is severed at some level leading to disruptions in autonomic control below the level of injury. These autonomic disruptions have a great effect on the cardiovascular system and are a major contributing factor to orthostatic intolerance post-SCI. Circulating hormones have elevated concentrations due either to attempts to compensate for loss of neural control or due to loss of inhibition of their release. However, these increased hormonal levels (mainly PRA) are thought to accelerate the development of arthersclerosis in the vasculature.

The primary goal of this thesis is to increase understanding of blood pressure regulation by indirect assessment of autonomic function. A secondary goal is that the results of this thesis may be used to develop more effective means to assess and promote recovery from orthostatic intolerance in SCI patients in the weeks and months following their injury. This research utilizes primarily noninvasively acquired, easily accessible variables that are promising indicators of autonomic activity to assess level of autonomic injury and recovery of visceral control following SCI. From what will be a large pool of parameters, variables such as arterial blood pressure, heart rate, skin blood flow (in the upper and lower body), stroke volume and cardiac output will be acquired and analyzed in both the time and frequency domain. Special emphasis will be placed on skin blood flow for reasons described below. It is envisioned that these experiments will provide the database for other investigators to develop an optimal index of autonomic activity. Such an index would allow for the development of practical protocols that could be conducted in a clinical setting.

Chapter Two

Physiological Background

As mentioned earlier, the focus of this research is to explore the effects of spinal cord injury on blood pressure regulation with special emphasis on the contribution of skin perfusion in helping to better understand the regulatory process. The following section provides the necessary background in anatomy and physiology of the neural and circulatory systems in order to develop experiments for this study.

Anatomy and Physiology of the Spinal Cord

The spinal cord is a 45 cm long slender cylinder of nerve tissue in adults measuring ~two cm in diameter that extends from the brain stem. The spinal cord exits through the *foramen magnum* in the base of the skull and is enclosed by the protective vertebral column as it descends through the vertebral canal (refer to figure 5.30 in Sherwood, Lauralee, Human Physiology: From Cells to Systems. 2001). The vertebral canal works as the main support for the spinal cord and the nerve pathways that carry information from the arms, legs, and the rest of the body, and carries signals from the brain to the body (Sherwood 2001).

Paired spinal nerves emerge from the spinal cord through spaces formed between the bony, wing-like arches of adjacent vertebrae (refer to figure 5.30 in Sherwood, Lauralee, Human Physiology: From Cells to Systems. 2001). The spinal nerves are named according to the region of the vertebral column from which they emerge (refer to Figure 5.31 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001): there are eight pairs of cervical (neck) nerves (C_1-C_8), twelve thoracic (chest) nerves (T_1-T_{12}), five lumbar (abdominal) nerves (L_1-L_5), five sacral (pelvic) nerves (S_1-S_5), and one coccygeal (tailbone) nerve (Sherwood 2001).

Spinal nerves connect with each side of the spinal cord by a dorsal root and a ventral root (refer to figure 5.32 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001). Afferent fibers carrying incoming signals enter the spinal cord through the dorsal root and efferent fibers carrying outgoing signals leave through the ventral root. The cell bodies for the afferent neurons at each level are clustered together in a dorsal root ganglion. The cell bodies for the efferent neurons originate in the gray matter and send axons out through the ventral root. The dorsal and ventral roots at each level join to form a spinal nerve that emerges from the vertebral column. A spinal nerve contains both afferent and efferent fibers traversing between a particular region of the body and the spinal cord (Sherwood 2001).

Although there are some slight regional variations, the cross-sectional anatomy of the spinal cord is generally the same throughout its length (refer to figure 5.32 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001). The "gray matter" in the spinal cord forms a butterfly-shaped region on the inside and is surrounded by the outer "white matter." As in the brain, the cord gray matter consists primarily of neuronal cell bodies and their dendrites, short interneurons and glial cells. The white matter is organized into tracts, some ascending tracts (spinal cord to brain) that transmit to the brain signals derived from afferent input and descending tracts (brain to spinal cord) that relay messages from the brain to efferent neurons (Sherwood 2001).

The Autonomic Nervous System

The human nervous system is more than the brain (figure 2.1). The brain and the spinal cord make up the central nervous system (CNS), and information is brought to and from the CNS by means of an enormous network of nerves that make up the peripheral nervous system. The peripheral nervous system is divided into the somatic nervous system, which controls organs under voluntary control (mainly muscles) and the autonomic nervous system (ANS), which regulates individual organ function and homeostasis, and for the most part is not subject to voluntary control. It is also known as the visceral or automatic system (Sherwood 2001).

The ANS is predominantly an efferent system transmitting impulses from the central nervous system (CNS) to peripheral organ systems. Its effects include control of heart rate and force of contraction, constriction and dilation of blood vessels, contraction and relaxation of smooth muscle in various organs and secretions from exocrine and endocrine glands. Autonomic nerves constitute all the efferent fibers, which leave the CNS, except those which innervate skeletal muscle. There are some afferent autonomic fibers, which are concerned with the mediation of visceral sensation and the regulation of vasomotor and respiratory reflexes, for example the baroreceptors and chemoreceptors in the carotid sinus aortic arch, which are important in the control of heart rate, blood pressure and respiratory activity (Sherwood 2001). Reflex responses to autonomic efferent fibers can cause contraction of smooth muscle in certain organs (blood vessels and lungs) and can influence the function of the heart (Mathias 1992).

The ANS is divided into two separate divisions called the parasympathetic and sympathetic nervous systems, on the basis of anatomical and functional differences. Both of these systems consist of myelinated preganglionic fibers, which make synaptic connections with

unmyelinated postganglionic fibers, and it is the latter that innervate the effector organ. Sympathetic nerve fibers originate in the thoracic and lumbar regions of the spinal cord. 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 (Sherwood 2001). Long postganglionic fibers originating in the ganglion terminate on the effector organ. Parasympathetic preganglionic fibers arise from the cranial (brain) and sacral (lower spinal cord) areas of the CNS. These 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 (Sherwood 2001). Most organs are innervated by fibers from both divisions of the ANS (refer to figure 7.3 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001) and the influence is usually opposing (e.g. stimulating the vagus nerve slows the heart, whilst stimulating sympathetic nerves increases heart rate and contractility).

Anatomy of the Circulatory System

The circulatory system contributes to homeostasis by serving as the body's transport system. The circulatory system consists of the heart, blood vessels and the blood. The heart serves as the pump that establishes the pressure gradient needed for blood (the transport medium within which materials being transported are dissolved or suspended) to flow to the tissues. The blood vessels transport and distribute blood pumped through them by the heart to meet the body's need for oxygen and nutrient delivery, waste removal and hormonal signaling (Sherwood 2001).

The blood vessels of the circulatory system are made up of a high-pressure arterial network and a low-pressure venous network. The arterial system is composed of a complex series of arteries, arterioles and capillaries and the venous system is composed of venules and veins (refer to figure 10.20 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001). The arterial network is used to distribute oxygen and nutrients to the organs and systems of the body, while the venous system is used to carry blood back to the heart. The highly elastic arteries transport blood from the heart to the tissues and serve as a pressure reservoir to continue driving blood forward when the heart is relaxing and filling. The amount of blood that flows through a given tissue (refer to figure 10.1 in Sherwood, Lauralee. Human Physiology: From Cells to Systems. 2001) depends on the blood pressure perfusing the organ and on the caliber of

the highly muscular arterioles that supply the tissue. Arteriolar tone is subject to control (neural and local) so that the distribution of cardiac output can be constantly readjusted to best serve the body's needs at the moment (Sherwood 2001). For example, during exercise, some of the blood that normally flows through the digestive organs or kidneys is diverted to skeletal muscles in order to meet metabolic needs. Likewise, blood flow is redistributed to the skin during heat exposure in order to keep inner core temperature at a reasonable level. Indirect evidence suggests that heated human skin comprises one of the largest venous reservoirs into which blood volume will accumulate when blood flow is high (Rowell 1993). Therefore skin and its ability to receive redistributed blood to the peripheral segments of the body plays a very important role in maintaining adequate temperature stability.

Anatomy of the Cutaneous Circulation

The skin is a large organ, weighing as much as two kg in an average-size human with 1.8m^2 surface area. It is our waterproof coating, vapor barrier, protection from mechanical injury, and our thermal insulation together with underlying subcutaneous adipose tissue. Its role as a heat exchanger and insulator stems from its location on the body surface and its dense system of capillary loops that empty into a capacious subpapillary venous plexus (Rowell 1993). The cutaneous blood supply is a microcirculatory bed composed of three segments-arterioles, arterial and venous capillaries, and venules.

Large Fluid Reservoir: Indirect evidence suggests that heated human skin comprises one of the largest venous reservoirs. When maximally vasodilated, skin can receive as much as 7-8 L/min of blood, competing largely with skeletal muscle for cardiac output (Rowell 1993). Many factors influence blood pressure regulation, however the large volume capacity of skin vascular beds makes studying the cutaneous circulation and skin perfusion very attractive.

Neural control: All cutaneous resistance vessels receive tonic outflow from sympathetic vasoconstrictor fibers. The first demonstration of tonic vasoconstrictor activity was made in 1852 by Claude Bernard, who saw that cutting the nerves supplying a rabbit's ear caused an increase in its blood flow. The same result can be attained by surgical section or pharmacological blockade of sympathetic nerves supplying human skin (Rowell 1993). When all vasoconstrictor tone is withdrawn, skin blood flow is approximately doubled (Shepherd, 1963). Tonic vasoconstrictor activity decreases with rising body temperature and skin temperature. Blood flow to nonacral skin (limbs and body trunk) is controlled by these fibers in

cool environments, but tone is minimal in neutral environments (Rowell 1993). Regulation of sympathetic vasoconstrictor activity is accomplished by increasing or decreasing the firing rate above or below the tonic level in these sympathetic fibers (Mathias 1988). The vasoconstrictor activity of cutaneous vessels caused by neural sympathetic outflow allows us to make an attempt to diagnose the degree of autonomic dysfunction in SCI patients.

A rationale for using skin blood flow as one of the parameters for assessing blood pressure regulation

There are many reasons to study the cutaneous circulation:

- *One of the largest reservoirs for fluid in the body*
  - At rest, total skin blood flow between 200 & 500 mL/min (Rowell 1993)
  - At rest, total skin blood volume ~3000 mL (Rowell 1993)
  - Skin can receive as much as 7000-8000 mL/min when "maximally" vasodilated by whole body heating (Rowell 1993)
- *Under neural control*
  - Skin appears to be second only to skeletal muscle in its capacity to receive high blood flows at normal perfusion pressure (Rowell 1993)
  - Competes with skeletal muscle for cardiac output during exercise (Rowell 1993)
- *Experimental advantages*
  - Studied non-invasively
  - Easily accessible

The aforementioned skin properties create a great opportunity to use skin perfusion and cutaneous circulation to analyze blood pressure regulation in AB subjects and diagnose decrements in blood pressure regulation in SCI patients.

Assessment of Autonomic Dysfunction Using Skin Blood Flow

Skin blood flow fluctuations around 0.1 Hz are thought to be indicative of autonomic control of the cutaneous vasculature (Crandall 1998) [(throughout this document skin blood flow will also be referred as microvascular blood flow, cutaneous circulation and skin perfusion)]. Skin circulation largely depends on neurogenic influences and metabolic needs and skin vasomotor reflexes are studied to detect focal abnormalities of autonomic function (Bernardi 1989). Although, rhythmical variations have been described in human skin blood flow,

quantitative comparison between skin blood flow fluctuations and phasic changes of autonomic tone are rare (Bernardi 1989). Heart rate fluctuations are largely dependent on autonomic influences, which can be easily described and quantified by spectral analysis techniques (Bernardi 1989). Low-frequency (LF; 0.1 Hz) oscillations, considered a marker of sympathetic activity in heart rate and blood pressure, in the skin circulation are also modified by changes in sympathetic tone, suggesting that oscillations in microsvascular blood flow may be controlled by both central and local mechanisms (Bernardi 1997).

As a result of SCI, descending spinal sympathetic pathways are disrupted, possibly severed (Curt 1995). It has been shown that SCI results in profound changes within the affected limbs, both in the upper and lower body, dependent upon the level of injury. I hypothesize that low frequency spectral power of skin blood flow fluctuations in the upper and lower body will be significantly larger in AB subjects than in paraplegic and tetraplegic subjects. These data can then be used to assess the relationship between autonomic nervous control and local cutaneous circulation. Post-SCI, peripheral circulatory adaptations, indicative of autonomic dysfunction, may largely contribute to the increased risk of cardiovascular disease in SCI patients. By studying these peripheral adaptations in SCI patients, the level of autonomic dysfunction in SCI subjects can be quantified.

The driving force for cardiovascular research following SCI:

1. Diminished cardiovascular control presents significant health risks and obstructs effective rehabilitation in individuals with SCI.
2. The nature of the effects of SCI on the autonomic nervous system are poorly understood
3. An improved understanding of the mechanisms of cardiovascular control may

facilitate optimization of rehabilitation practices for SCI subjects. This information may be particularly important as new techniques for spinal cord regeneration and repair are developed.

Impaired Cardiovascular Control in SCI: Background and Significance

Background: SCI results in immediate derangement in cardiovascular control with associated acute and chronic consequences. The dysfunction of the sympathetic nervous system (SNS) after acute SCI results in hypotension (decrease in blood pressure), bradycardia (decrease in heart rate), autonomic dysreflexia (surges in blood pressure), and, rarely, cardiac arrest. Hypotension is the first observed manifestation of autonomic dysfunction following SCI. Autonomic dysreflexia occurs, almost exclusively, in SCI subjects with high level of injury after six months

post-injury. Acute manifestations of alteration of SNS activity typically resolve in the first few weeks, but orthostatic hypotension and low blood pressure persist for months and, in some patients, may persist for years (Garstang 2001).

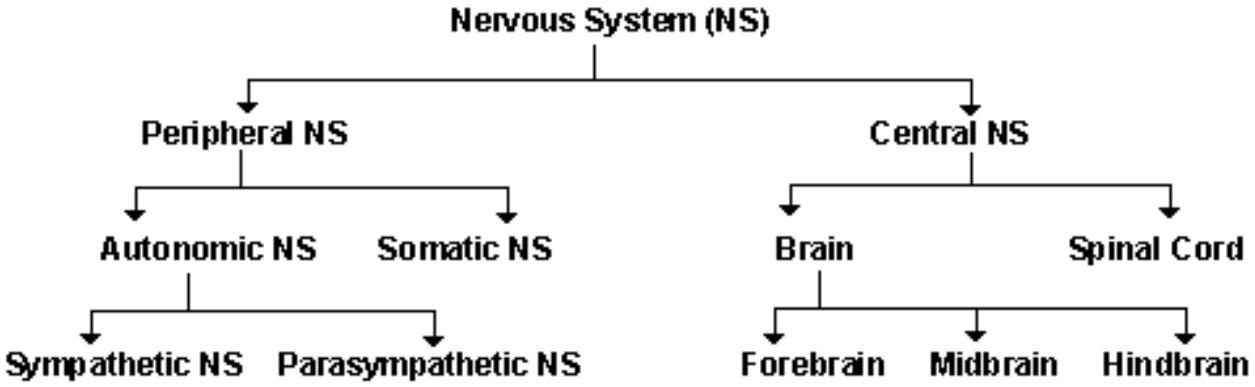
Pathophysiology: Immediately after SCI, an acute rise in blood pressure occurs. This phenomenon has been shown in experimental studies to be caused by release of epinephrine from the adrenal glands and by pressor response from mechanical disruption of vasoactive neurons and tracts in the cervical and upper thoracic spinal cord resulting in additional outpouring of norepinephrine (Garstang 2001). This brief response is followed by a period of decreased SNS activity because of interruption of the descending sympathetic tracts. Lack of supraspinal input develops, causing cutaneous vasodilatation, lack of sympathetic vasoconstrictor activity, and absent sympathetic input to the heart. Clinically, the patient with SCI is susceptible then to hypothermia, hypotension, and bradycardia from lack of sympathetic input and unopposed vagal tone (Garstang 2001).

Frequency: Annual incidence of SCI in the U.S. is approximately 40 cases per million population, or approximately 11,000 new cases each year (there are approximately 250,000 people in the U.S. living with SCI) (Lali 2001, Garstang 2001). Of these, 51.7% have tetraplegia (i.e. a level of injury at the cervical, C_1 to C_8, spinal cord), and 46.7% have paraplegia (i.e. a level of injury at the thoracic, T_1-T_{12}, lumbar, L_1-L_5, or sacral, S_1-S_5, regions of the spinal cord). The most frequent neurologic category is incomplete tetraplegia (29.5%), followed by complete paraplegia (27.9%), incomplete paraplegia (21.3%), and complete tetraplegia (18.5%) (Lali 2001, Garstang 2001).

The loss of autonomic control of cardiac and vascular regulatory mechanisms is dependent on the severity and level of injury to the spinal cord (Grimm 1995). Of the patients with severe cervical injuries in the C_1 to C_8 region of the spinal cord that are diagnosed with ASIA A or ASIA B (analyzed with the American Spinal Cord Injury Association [ASIA] scale) up to 100% develop bradycardia, 68% are hypotensive, 35% require pressors, and 16% have primary cardiac arrest (Garstang 2001). Of those with milder cervical injuries (incomplete grades of ASIA C or ASIA D), 35-71% develop persistent bradycardia, and some have hypotension or require medication with pressor agents. Patients with thoracolumbar injuries experience bradycardia 13-35% of the time and rarely experience other cardiovascular problems (Garstang 2001). Only SCI patients with level of injury above T_6, the level of major outflow

from the sympathetic chain are affected. However, patients with injuries below T_6 are only affected by loss of local muscle tone that can result in increased lower extremity venous pooling.

Figure 2.1: Breakdown of the nervous system



Chapter Three

Methods

Subjects

There were 11 AB (control group: eight male, three female) subjects studied once, three male paraplegic (lesions between T_{10} and T_{12}) and three male tetraplegic (lesions between C_3 and C_4) patients between the ages of 18-45 studied up to eight times each during the first year post-injury. 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, nine and 12 months post-injury) were performed at the General Clinical Research Center (GCRC) at the University of Kentucky. For the studies at the GCRC, the subjects (both AB 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. The following conditions excluded any subjects: 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.

None of the participants had any previous cardiovascular-related disease and only a few of the AB subjects took any medication likely to affect the cardiovascular system (a list of medications likely to affect data collection can be found in Appendix G). All the SCI patients wore TED hose and abdominal binders during the study. Some SCI patients were on blood pressure medication and some were on medications to treat muscle spasms (list of medications can be found in Appendix G). One tetraplegic and two paraplegic patients had sustained complete injuries (ASIA A), two tetraplegic patients had some sensitivity below the level of lesion (ASIA B) and one paraplegic patient had some motor control below the level of the lesion that was of such poor quality that it could not be used functionally (ASIA C). A physician, using the American Spinal Cord Injury Association (ASIA) scale (Appendix A) to assess the severity of the spinal cord injury, diagnosed all SCI patients during the acute phase of injury before the SCI patients participated in the study. All participants were familiarized with the study protocol and signed an informed consent form before experimental data were collected. All subject information can be found in Appendix B**.**

Protocol

All subjects were studied at least one hour post-prandial and refrained from alcohol and caffeine at least 24 hours before the study. The subjects consumed a fat free breakfast, as to not interfere with data and hormonal analysis. AB subjects emptied their bladder 30 min before the study and SCI subjects had bladder catheterization. After arriving at the tilt site (Physical Therapy Clinic at CHRH or GCRC), the subjects were acquainted with instrumentation and experimental procedures and then rested supine on the tilt table. An IV cannula was inserted in an antecubital vein to obtain blood for hormonal analysis. The non-invasive instrumentation, described below, was applied while the subject was 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. All subjects underwent a provocative head-up-tilt (HUT) test used to elicit a cardiovascular response. A HUT test was used to test for baroreflex activity, bradycardia, hypotentsion, orthostatic intolerance, hormone responses, fluid volume shifts and regulation. More specifically, a HUT test is a well-known maneuver that is able to produce a generalized sympathetic activation. For the present study, a HUT is utilized to elicit heart rate, arterial pressure, and skin blood flow responses that are then used to assess sympathetic activity and level of autonomic damage in SCI.

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 about 10 min. The last phase, the recovery period, consisted of one min at 20^{o} HUT and up to seven min in the supine position (a typical protocol can be found in figure 3.1). During the tilt, members of the research and clinical team continuously monitored the alertness of the subject and the hemodynamic variables. If the subjects developed syncopal symptoms (signs of fainting) during any part of the study, they were brought to a supine position and the recovery phase began. Blood samples for hormonal assay were taken at the end of supine control, 20^{o}, 40^{o}, 60^{o}, 80^{o} HUT and recovery.

Acquired Variables

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

Arterial Blood Pressure: 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 (Additional information on the Portapres and the Penaz principle can be found in the additional instrumentation background in Appendix

C). Manual arterial blood pressure measurements were taken at the beginning of supine control and at the end of the recovery period with an AND 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, dZ/dt, dZ/dt respiration, cardiac output and stroke volume through an EXT-TEBCO Module (Hemo Sapiens, Sedona, AZ) (Additional information on TEBCO can be found in Appendix C).

Skin Perfusion and Concentration of Moving Cells: 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) using the Laser Doppler flowmetry technique (Additional information on the Perimed and the Laser Doppler flowmetry technique can be found in Appendix C).

Calf Circumference: 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.

Eleven mL of venous blood was 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 the 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. A set of data (in the process of being collected and analyzed) from the AB control group and the SCI groups were evaluated.

Data Acquistion

All data was acquired at 250 Hz and saved as a LABVIEW file to a Dell Inspiron 4100. Calibration files were created for all variables and saved as separate files for future reference in case the data acquisition laptop were to crash. A data file was then created, in which all acquired data was stored and saved. After the study, the data were stripped and copied from the data acquisition computer, converted to a binary file, then to a raw (.raw) file in order to be observed in a data playback browser program written by Dr. David Brown of the University of Kentucky. Large peaks and anomalies were removed from all the acquired variables and saved as a

modified (.mod) file. Heart rate was then calculated using Dr. Brown's Browser Program and correctly aligned in time with all the other variables. Finally, all 16 channels of data were down-sampled to 5 Hz using Dr. Brown's Browser Program and converted to a MATLAB (.mat) file for data analysis.

Data Analysis

All data analysis was done with MATLAB, Dr. Brown's Browser Program, Microsoft Excel, PowerPoint and Word.

Mean Value Analysis: Using MATLAB and Excel in the time domain, a mean value analysis was conducted on the last 5 min (1500 data points) of data at each level of the protocol (supine control, 20^{o}, 40^{o}, 60^{o}, 80^{o} HUT and recovery). Before conducting mean value analysis, the data in question were low-pass filtered (LPF) with the low-pass cutoff equal to 0.5 Hz. The LPF was initialized with the MATLAB function "fir1" using a 100^{th} order finite impulse response filter and filtering was carried out using the MATLAB "filtfilt" function (Additional information on the fir1 and filtfilt MATLAB functions can be found in Appendix D). An LPF was used to preserve the low-frequency data, while stripping out high-frequency information.

Cardiac output was found by multiplying heart rate and stroke volume.

Cardiac output = Heart rate * Stroke volume (1)

Assuming the central venous pressure to be sufficiently small so as not to be considered in the pressure drop calculation across the circulation. Total peripheral resistance was calculated as:

Total peripheral resistance, TPR = (Mean arterial pressure – 0) / Cardiac output (2)

Spectral Power Analysis: Using MATLAB and Excel in the frequency domain, a power spectral density estimate was conducted on the last 5 min (1500 data points) of data at each level of the protocol (supine control, 20^{o}, 40^{o}, 60^{o}, 80^{o} HUT and recovery). The data were filtered using an LPF and the above LPF methods and parameters. The data were linearly detrended and the power spectral density was found using the MATLAB function "psd." A 1024 point Fast Fourier Transform (FFT) was used to obtain the power spectrum and a 500 point Hanning Window with 250 points of overlap was used to decrease leakage of the power spectrum. Power spectral density estimates were analyzed in three frequency regions:

- Very low frequency region (0.01-0.04 Hz), thermal domination of regulation
- Low frequency region (0.04-0.15 Hz), sympathetic domination of regulation

- High frequency region (0.15-0.4 Hz), parasympathetic domination of regulation

Autonomic balance was estimated based on the following indicies:

$$\text{SNS spectral index} = \text{LF power} / \text{HF power} \quad (3)$$

$$\text{PNS spectral index} = \text{HF power} / \text{Total power (VLF + LF + HF)} \quad (4)$$

Cross Correlation Analysis: Using MATLAB and Excel in the frequency domain, a cross correlation analysis was conducted on the last 5 min (1500 data points) of data at each level of the protocol (supine control, 20^{o}, 40^{o}, 60^{o}, 80^{o} HUT and recovery). For low-pass analysis, the data were filtered using a low-pass Butterworth filter with cutoff coefficients equal to 0.04 and 0.15 Hz. For high-pass analysis, the data were filtered using a high-pass Butterworth filter with cutoff coefficients equal to 0.15-0.4 Hz. Cross correlation analysis provides a measure of the correlation and phase relationships between two signals in the frequency domain. The existence and location of cross correlation peaks provide indications of sympathetic and parasympathetic influences that are shared by cardiovascular variables and may indicate commonalities in control mechanisms.

Cross correlation is an engineering tool used to study the coordination of two signals. One signal is defined as the stationary or reference signal and the other signal is the sliding signal. The autocorrelation of the two signals is calculated as the sliding signal moves through the reference signal. An autocorrelation of one is perfect correlation, i.e. the signals are identical, and an autocorrelation of zero is the worst that the two signals can correlate. Negative and positive cross correlation peaks are calculated, where a positive peak indicates a point at which the two signals are increasing simultaneously or decreasing simultaneously. A negative peak designates a point at which one signal is increasing and the other is decreasing. In addition to positive and negative cross correlation peaks, lag times are calculated at each of the positive and negative peaks. Negative and positive cross correlation peaks that occur closest to a lag time of zero seconds are the peaks that are thought to indicate the most significance. An autocorrelation of one is considered to be ideal, although this phenomenon is rare in a physiological environment. The magnitude of positive and negative cross correlation peaks of 0.5 and –0.5, respectively, are typical with correlations involving skin blood flow. In AB subjects these maximum positive and negative cross correlation peaks are used as the gold standard against which paraplegic and tetraplegic subjects will be compared.

Statistics

Differences within and between the three groups (AB, Paraplegic and Tetraplegic) during supine control, the four levels of HUT and recovery were tested for significance using a two factor Analysis of Variance (ANOVA) using SPSS statistical software. The within factor was used to indicate a tilt affect among the groups. The between factor was used to indicate differences between the three groups. A p value ≤ 0.05 was considered to indicate statistical significance. Results were expressed as mean and standard error. Statistical significance for all analyzed variables are shown in tables, not figures. Note: throughout the present study, the paraplegic sample size of five indicates five studies from three subjects and the tetraplegic sample size of six indicates six studies from three subjects.

Dr. Helena Truszczynska from the University of Kentucky assisted with the repeated measures ANOVA statistical design and analysis.

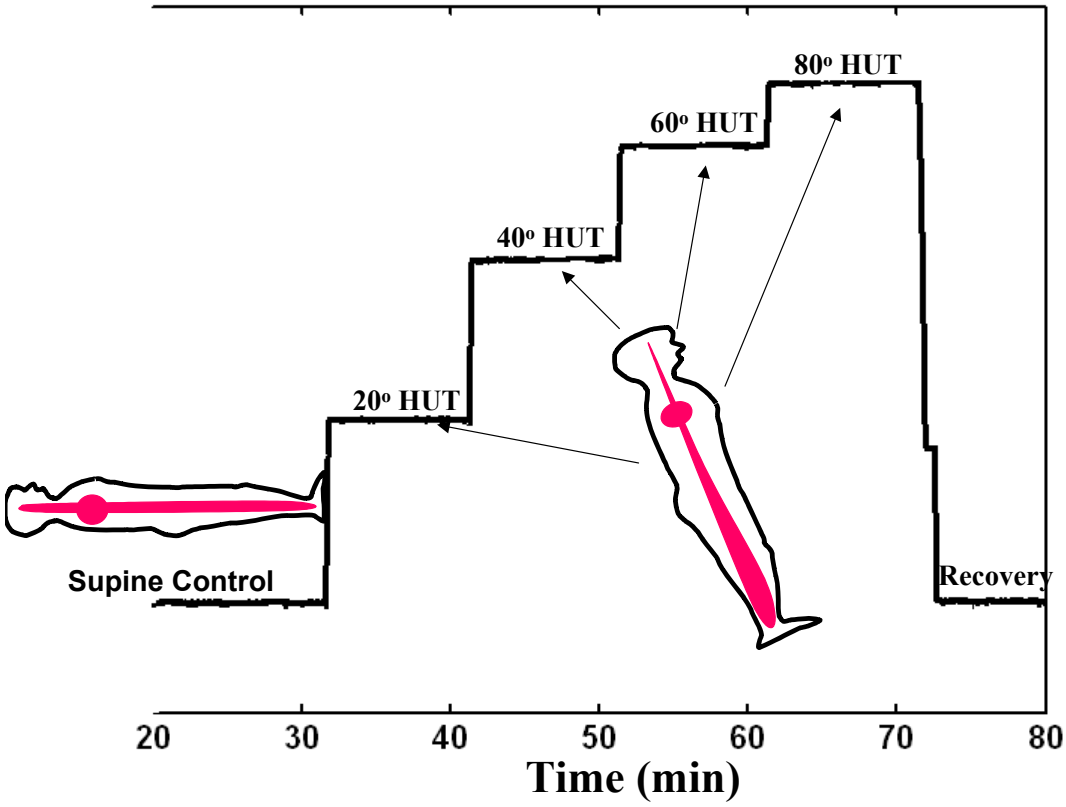
Table 3.1: Information on SCI ASIA scores

Subject	Level of Injury	Severity of Injury	Assessment Date	Times studied
11 AB subjects	AB	AB	N/A	One time per subject
Tetraplegic subject 1	C3	ASIA B	2/5/2002	Six
Tetraplegic subject 1	C3	ASIA C	2/28/2004	Six
Tetraplegic subject 1	C4	ASIA D	11/7/2002	Six
Tetraplegic subject 1	C4	ASIA D	3/27/2003	Six
Tetraplegic subject 2	C3	ASIA A	1/17/2003	Two
Tetraplegic subject 2	C4	ASIA A	3/15/2003	Two
Tetraplegic subject 3	C4	ASIA B	8/20/2003	Four
Tetraplegic subject 3	C4	ASIA C	3/16/2004	Four
Paraplegic subject 1	L1-L3	ASIA A	3/26/2002	Eight
Paraplegic subject 1	T12	ASIA C	6/3/2002	Eight
Paraplegic subject 1	L1	ASIA A	10/1/2002	Eight
Paraplegic subject 1	T12	ASIA A	1/16/2003	Eight
Paraplegic subject 1	T12	ASIA C	2/11/2003	Eight
Paraplegic subject 2	T10	ASIA A		Three
Paraplegic subject 3	T12-L1	ASIA A		Once

Table 3.2: Channel listing with calibrations & units

Channel	Signal	Voltage (V)	Engineering Units	
			Value	Units
0	AP	[0 2]	[0 200]	mmHg
1	ECG (analog)	No calibration	No calibration	unitless
2	$_{\Delta}Z$	[0 0.98 1.95 4.88]	[0 50 100 250]	unitless
3	$_{\Delta}Z/_{\Delta}T$	[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]	unitless
7	$_{\Delta}Z/_{\Delta}T_{resp}$	[0 0.98 1.95 4.88]	[0 50 100 250]	unitless
8	***Resp. rate***	[0 0.5 1 1.5]	[0 10 20 30]	breaths/min
9	RF	±0.35	±10, 0	cm/sec
10	CC	[0 0.025], [0 0.25]	[0 0.1], [0 1]	%
11	Tilt Angle	[0.62 3.2]	[0 90]	degrees
12	SP1	[0 1]	[0 100]	perfusion units
13	CMBC1	[0 1]	[0 100]	concentration units
14	SP2	[0 1]	[0 100]	perfusion units
15	CMBC2	[0 1]	[0 100]	concentration units

Figure 3.1: Standard protocol with supine control, four levels of HUT and recovery



Chapter Four

Results

Typical hemodynamic responses to HUT are shown for one AB and one tetraplegic subject in figure 4.1. The cardiovascular variables of interest (heart rate, arterial pressure, stroke volume, upper and lower body skin perfusion and calf circumference) exhibit dissimilarities between the two subjects. Arterial pressure and heart rate were well maintained in the AB subject but not in the tetraplegic subject. Upper and lower body skin perfusion were more affected by HUT in the AB subject because in the tetraplegic subject skin perfusion in the upper and lower body was low during control and remained low during HUT.

When considering the responses for the AB and paraplegic groups, arterial blood pressure (figure 4.1a) was similar for the group of AB and paraplegic subjects during supine control, four levels of HUT and recovery; however, there was much variability in the tetraplegic group. Due to diminished cardiovascular control, orthostatic hypotension was common in SCI (figure 4.1b).

Mean values and spectral power of arterial blood pressure, heart rate and upper and lower body skin perfusion were used to test for differences between AB and SCI (paraplegic and tetraplegic) subjects. For all mean and spectral power results shown from the three groups, five minutes of data were used to analyze supine control, four levels of HUT (20^{o}, 40^{o}, 60^{o}, 80^{o}) and recovery periods. A typical mean arterial blood pressure trace (i.e. pressure average per cardiac cycle and downsampled to 5 Hz) with the spectral power from five minutes of supine control (insert) in one AB subject is shown in figure 4.2. Figure 4.2 shows five min of arterial pressure during control and the spectral power produced from the arterial pressure signal-the peak in the LF region is indicative of sympathetic activity. Arterial blood pressure group results analyzed in the time and frequency domains (figure 4.2a and table 4.2) further illustrate arterial pressure differences among the three groups. Arterial pressure spectral power in the VLF and HF regions do not show any great differences among the three groups, however, arterial pressure spectral power in the LF region is an excellent discriminator ($p<0.05$) among the three groups. Arterial pressure spectral power in the LF region is larger in the AB than the SCI groups and spectral power increases with increasing HUT in AB but decreases in SCI. For illustrative purposes, AB, paraplegic and tetraplegic group averaged arterial pressure spectral power figures are shown in Appendix E.

Heart rate raw data (downsampled to 5 Hz) with the mean and spectral power from five minutes of supine control in one AB subject is shown in figure 4.3-the peak in the LF region is indicative of sympathetic activity and the peak in the HF region is indicative of parasympathetic activity. In AB subjects, the LF peak increases and the HF peak decreases with increasing levels of HUT. Heart rate group results analyzed in the time and frequency domains (figure 4.3a and table 4.3) further illustrate heart rate differences among the three groups. Mean heart rate increases with increasing HUT in all three groups, however tetraplegic subjects have lower values of heart rate at all levels of HUT. Heart rate spectral power in the VLF and LF regions is greatest in the AB group, as it increases with increasing HUT, however in the paraplegic and tetraplegic groups heart rate spectral power in these regions decreases with increasing HUT. Heart rate spectral power in the HF region is greatest in the AB group and is marked by decreases with increasing HUT in all three groups. For illustrative purposes, AB, paraplegic and tetraplegic group averaged heart rate spectral power figures are shown in Appendix E.

Upper body skin perfusion raw data (downsampled to 5 Hz) with the mean and spectral power from five minutes of supine control (insert) in one AB subject is shown in figure 4.4. Most of the spectral power is in the LF region, which is indicative of sympathetic activity to the skin arterioles controlling blood flow in the forearm. There is very little power in the HF region, which shows that skin blood flow in the forearm is not under much parasympathetic control. Upper body skin perfusion group results analyzed in the time and frequency domains (figure 4.4a and table 4.4) further illustrate upper body skin perfusion differences among the three groups. Mean upper body skin perfusion tended to decrease with increasing HUT in all three groups, with paraplegic subjects having the highest perfusion values. Upper body skin perfusion spectral power in the VLF, LF and HF regions in the AB groups remains relatively constant with increasing HUT. Paraplegic subjects exhibit the largest, non-significant, values of spectral power, while the tetraplegic subjects exhibit the lowest values of spectral power in the VLF, LF and HF regions. For illustrative purposes, AB, paraplegic and tetraplegic group averaged upper body skin perfusion spectral power figures are shown in Appendix E.

Lower body skin perfusion raw data (downsampled to 5 Hz) with the mean and spectral power from five minutes of supine control (control) in one AB subject is shown in figure 4.5. Most of the spectral power is in the LF region, which is indicative of sympathetic activity to the skin arterioles controlling blood flow in the shin. Lower body skin perfusion group results

analyzed in the time and frequency domains (figure 4.5a and table 4.5) further illustrate the lower body skin perfusion differences among the three groups. Mean lower body skin perfusion decreases with increasing HUT in all three groups, however the AB group has a greater perfusion than the SCI groups. Lower body skin perfusion spectral power in the VLF and LF regions decrease with increasing HUT in all three groups, however the AB group maintains the greatest ($p<0.05$ in LF region) spectral power in these regions for every level of HUT. Lower body skin perfusion spectral power in the LF region is an excellent approach that can be used to discriminate among the three groups and assess level of autonomic damage following SCI. Lower body skin perfusion spectral power in the HF region has a tendency to decrease with increasing HUT in all three groups. For illustrative purposes, AB, paraplegic and tetraplegic group averaged lower body skin perfusion spectral power figures are shown in Appendix E.

In order to assess cardiac function, the coordination or correlation of heart rate and arterial blood pressure signals was conducted. Cross correlation of heart rate and arterial pressure in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.6. Cross correlation negative and positive peaks, negative and positive lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.6a and table 4.6. As mentioned in the methods section, a negative peak designates a point at which arterial pressure is increasing as heart rate is decreasing or vice versa and a positive peak indicates a point at which both signals are increasing or decreasing together. In AB subjects, arterial pressure and heart rate have a negative cross correlation magnitude of –0.4 during supine control and increases to –0.5 with HUT. AB and paraplegic subjects have a negative cross correlation lag time of ~2.2 seconds for supine control, all levels of HUT and recovery, while tetraplegic subjects have a lag time a ~1.8 seconds for the entire protocol. In paraplegic and tetraplegic subjects, the negative cross correlation peak is –0.2, increases to –0.4 in paraplegic and decreases to –0.03 in tetraplegic subjects with increasing levels of HUT. AB subjects have a positive cross correlation lag time of ~two seconds during supine control and decreases to ~1.5 seconds with increasing HUT, while paraplegic subjects maintain a lag time of ~1.5 seconds and tetraplegic subjects have a lag time of ~1.25 seconds during control and decreased to 0.25 seconds during the 80^{o} HUT. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of heart rate and arterial pressure are shown in Appendix F.

Cross correlation of arterial pressure and upper body skin perfusion in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.7. Cross correlation positive and negative peaks, positive and negative lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.7a and table 4.7. In AB subjects the magnitude of the positive cross correlation between upper body skin perfusion and arterial pressure is 0.3 during control and increases to 0.4 at the highest degree of HUT. Paraplegic and tetraplegic subjects had a magnitude of 0.4 and 0.3, respectively, during control and decreased to 0.15 and 0.18, respectively, during the highest degree of HUT. Upper body skin perfusion lagged arterial pressure in all groups, however the lag times were minimal. In AB subjects the magnitude of the negative cross correlation was –0.4 during control and decreased to –0.3 at the highest degree of HUT. In paraplegic subjects the magnitude of the negative correlation was –0.3 and decreased to –0.1 at the highest degree of HUT, whereas tetraplegic subjects maintained a magnitude of –0.2 for the entire protocol. Upper body skin perfusion led arterial pressure in all three groups: four seconds in AB, five to six seconds in paraplegic and seven seconds in tetraplegic subjects. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of arterial pressure and upper body skin perfusion are shown in Appendix F.

Cross correlation of heart rate and upper body skin perfusion in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.8. Cross correlation positive and negative peaks, positive and negative lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.8a and table 4.8. In AB, paraplegic and tetraplegic subjects the magnitude of the positive cross correlation was 0.4, 0.4 and 0.35, respectively, during control and decreased to 0.35, 0.2 and 0.1, respectively, at the highest level of HUT. In all cases, upper body skin perfusion led heart rate and the lead times were minimal and not significant. In AB, paraplegic and tetraplegic subjects the magnitude of the negative cross correlation was –0.35, -0.25 and –0.2, respectively, during control and decreased to –0.25, -0.2 and –0.05, respectively, at the highest level of HUT. In all cases, upper body skin perfusion led heart rate: in AB seven seconds during control and five seconds at the highest level of HUT, in paraplegic subjects seven seconds during control and three seconds at the highest level of HUT and tetraplegics had a lead time of six seconds for the entire HUT. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of heart rate and upper body skin perfusion are shown in Appendix F.

Cross correlation of arterial pressure and lower body skin perfusion in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.9. Cross correlation positive and negative peaks, positive and negative lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.9a and table 4.9. In AB, paraplegic and tetraplegic subjects the magnitude of the positive cross correlation was 0.35, 0.4 and 0.25, respectively, during control and increased to 0.4 in AB, but decreased to 0.2 for paraplegic and tetraplegic at the highest level of HUT. In all cases, lower body skin perfusion lagged arterial pressure and the lag times for AB were ~two seconds for all levels of HUT. In paraplegic subjects, lower body skin perfusion lagged arterial pressure by two seconds during control but led arterial pressure by two seconds during the highest level of HUT. In tetraplegic subjects, lower body skin perfusion led arterial pressure by ~0.2 seconds during control and ~two seconds during the highest level of HUT. In AB, paraplegic and tetraplegic subjects the magnitude of the negative cross correlation was –0.35, -0.25 and –0.15, respectively, during control and decreased to –0.28, -0.18 and –0.15, respectively, at the highest level of HUT. In all cases, lower body skin perfusion led arterial pressure: in AB ~five seconds during all levels of HUT, in paraplegic subjects ~four seconds during all levels of HUT and tetraplegics had a lead time of ~four seconds during control to ~six seconds for the highest level of HUT. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of arterial pressure and lower body skin perfusion are shown in Appendix F.

Cross correlation of heart rate and lower body skin perfusion in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.10. Cross correlation positive and negative peaks, positive and negative lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.10a and table 4.10. In AB, paraplegic and tetraplegic subjects the magnitude of the positive cross correlation was 0.4, 0.28 and 0.32, respectively, during control and decreased to 0.32, 0.15 and 0.15 at the highest level of HUT. Lower body skin perfusion lagged heart rate in AB subjects by 0.25 seconds during control and one second during the highest level of HUT. In paraplegic and tetraplegic subjects, lower body skin perfusion led heart rate by two and 2.25 seconds, respectively, during control and lagged heart rate by 0.25 seconds during the highest level of HUT. In AB, paraplegic and tetraplegic subjects the negative cross correlation magnitude was –0.2, -0.15 and –0.18, respectively, during control and increased to –0.33 in AB, but decreased to –0.1 in paraplegic and tetraplegic subjects

during the highest degree of HUT. Lower body skin perfusion led heart rate by ~four seconds in AB, ~six seconds in paraplegic and ~five seconds in tetraplegic subjects. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of heart rate and lower body skin perfusion are shown in Appendix F.

Cross correlation of upper and lower body skin perfusion in the LF and HF regions during five minutes of supine control in one AB subject is shown in figure 4.11. Cross correlation positive and negative peaks, positive and negative lag times in the LF region for AB, paraplegic and tetraplegic groups are shown in figure 4.11a and table 4.11.

In AB, paraplegic and tetraplegic subjects the positive cross correlation magnitude was 0.4, 0.32 and 0.2 (significant group effect, $p<0.05$), respectively, during control and decreased to 0.3, 0.2 and 0.15 during the highest level of HUT. In AB subjects, lower body skin perfusion led upper body skin perfusion by 0.25 seconds during control but lagged upper body skin perfusion by ~two seconds during the highest level of HUT. In paraplegic subjects lower body skin perfusion lagged upper body skin perfusion by ~0.5 seconds during control and led upper body skin perfusion by ~1.5 seconds during the highest level of HUT. In tetraplegic subjects, the minimal lead and lag times were variable and largely dependent on the level of HUT. In AB, paraplegic and tetraplegic subjects the negative cross correlation magnitude was -0.3, -0.2 and –0.1, respectively, during control and decreased to –0.15 in paraplegic subjects but remained constant in AB and tetraplegic subjects during the highest level of HUT. Lower body skin perfusion lagged upper body skin perfusion by ~six, six and seven seconds, respectively, in AB, paraplegic and tetraplegic subjects. For descriptive purposes, AB, paraplegic and tetraplegic group averaged cross correlation of upper and lower body skin perfusion are shown in Appendix F.

Plasma volume shifts out of the intravascular space, into the interstitial space are shown for AB, paraplegic and tetraplegic groups in figure 4.12. Plasma volume shifts, a natural effect of HUT, is greater in tetraplegic than paraplegic than the AB group. The larger shift of plasma volume out of the vascular space in the SCI groups is indicative of a leaky vascular system and could also be a contributor to orthostatic hypotension. Plasma volume shifts, % change per minute, were calculated from changes in hematocrit and total proteins using only those samples taken before and after the HUT. These tilt-induced changes indicate that SCI subjects were less effective regulators of circulating plasma than were AB subjects, even though SCI subjects wore support stockings during the study.

Plasma renin activity (PRA), an index of the body's attempt to regulate plasma volume, was dramatically higher in SCI than AB subjects (figure 4.13). With increasing levels of HUT, AB demonstrate small gradual increases, while SCI subjects display erratic behavior of PRA. In AB subjects, PRA rose from levels below 1 ng/mL/hr to about 4 ng/mL/hr with increasing levels of tilt, however SCI subjects had resting levels ranging from 2-16 ng/mL/hr rising to over 60 ng/mL/hr with tilt.

Indexes of sympathetic activity, epinephrine (figure 4.14) and norepinephrine (figure 4.15), are illustrated for AB and SCI subjects. AB have lower initial concentrations of epinephrine and norepinephrine and exhibit gradual increases with increasing levels of HUT of both epinephrine and norepinephrine when compared to SCI. SCI subjects demonstrate erratic behavior of epinephrine and norepinephrine with increasing levels of HUT, indicating a possible lack of controlled release of hormones from the adrenal medulla or a possible lack of end organ effect caused by disrupted receptors (discussed in more detail in chapter five).

Response to Results

There are many results presented at this point, however only some are of importance. The clearest differences between the three groups were evident in spectral analysis obtained in the frequency domain: Arterial blood pressure and lower body skin perfusion spectral power in the LF region are of significance. These variables analyzed in the LF region show differences among the three groups that could be good discriminators of the three groups, as well as show level of SCI and autonomic function. Arterial pressure in the LF region provides a significant group and group by HUT interaction. AB and tetraplegic, as well as paraplegic and tetraplegic have a significant group interaction. Lower body skin perfusion analyzed in the LF region gave a significant group and a significant HUT effect. Other variables have scattered significance, albeit, not as important as arterial pressure and lower body skin perfusion.

A more complicated measure to assess the level of SCI and autonomic function is to use the engineering tool of cross correlation. Cross correlation can be applied to arterial blood pressure, heart rate, upper and lower body skin perfusion to assess the coordination of arterial pressure with upper and lower body skin perfusion and then to assess the correlation of heart rate with upper and lower body skin perfusion.

Additional measures of autonomic function are present in hormonal analysis. The behavior of PRA, epinephrine and norepinephrine are excellent indicators of erratic, uncontrolled

release of hormones and may provide discriminants of levels of injury once data analysis is complete. These vasoactive hormones may also provide an early indication of future vascular damage due to loss of controlled release. The behavior of hematocrit and total proteins with HUT was also a good indicator of the larger amount of fluid shifted out of the vasculature in SCI subjects. This index of fluid shifts may provide an index of future orthostatic hypotension problems that SCI subjects may experience.

During Control, 20°, 40°, 60° HUT: AB (n=11), Paraplegic (5 studies from 3 subjects), Tetraplegic (6 studies from 3 subjects)
Due to pre-syncope: 80° HUT data excluded from statistical analysis: AB (n=7), Paraplegic (n=5 studies from 3 subjects),Tetraplegic (n=5 studies from 3 subject)
Post hoc pairwise comparisons are made if group by tilt interaction is significant:
♣ different from AB at p≤0.05 level (indicates Group and Group x HUT effects)
∗ different from Tetraplegic at p≤0.05 level (indicates Group and Group x HUT effects)
♦ difference from control is significant at p≤0.05 level (indicates overall HUT effect)

Table 4.1: Stroke volume, cardiac output & total peripheral resistance for AB, paraplegic & tetraplegic during supine control, 20°, 40°, 60°, 80° HUT and recovery.

Stroke volume (mL)-HUT effect (p<0.001)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	118 ± 8	106 ± 9♦	89 ± 7♦	75 ± 6♦	70 ± 6	115 ± 10
Paraplegic	104 ± 9	93 ± 6♦	84 ± 4♦	77 ± 2♦	68 ± 2	95 ± 4
Tetraplegic	109 ± 15	94 ± 10♦	77 ± 17♦	82 ± 10♦	70 ± 11	127 ± 18
Cardiac output (L/min)-HUT effect (p<0.027)						
AB	7 ± 0.3	7 ± 0.3♦	6 ± 0.3♦	6 ± 0.3♦	6 ± 0.5	7 ± 0.4♦
Paraplegic	8 ± 0.8	7 ± 0.6♦	7 ± 0.4♦	7 ± 0.3♦	7 ± 0.3	8 ± 0.7♦
Tetraplegic	7 ± 1	6 ± 1♦	6 ± 1♦	6 ± 1♦	6 ± 1	6 ± 1♦
Total peripheral resistance (mmHg/(L/min))-HUT effect (p<0.034)						
AB	11 ± 0.5	12 ± 0.7	13 ± 0.7	14 ± 0.7♦	15 ± 1.3	13 ± 0.9♦
Paraplegic	10 ± 2	11 ± 2	11 ± 1	11 ± 1♦	13 ± 2	11 ± 2♦
Tetraplegic	16 ± 3	13 ± 1	14 ± 1	13 ± 3♦	16 ± 5	18 ± 4♦

During Control, 20°, 40°, 60° HUT: AB (n=11), Paraplegic (5 studies from 3 subjects), Tetraplegic (6 studies from 3 subjects)

Due to pre-syncope: 80° HUT data excluded from statistical analysis: AB (n=7), Paraplegic (n=5 studies from 3 subjects),Tetraplegic (n=5 studies from 3 subject)

Post hoc pairwise comparisons are made if group by tilt interaction is significant:

♣ different from AB at p≤0.05 level (indicates Group and Group x HUT effects)

∗ different from Tetraplegic at p≤0.05 level (indicates Group and Group x HUT effects)

♦ difference from control is significant at p≤0.05 level (indicates overall HUT effect)

Table 4.2: Arterial Pressure (AP) Group Results (Mean ± SEM)						
Mean Arterial Pressure, MAP (mmHg)--HUT, Group x HUT effects (p<0.0001)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	74.5 ± 3.2	78 ± 3.6	79.2 ± 4	81.8 ± 4	84.5 ± 3.8	80 ± 3
Paraplegic	70.3 ± 9.4	74.9 ± 8	76.6 ± 6	77.9 ± 7	85.2 ± 8.7	84 ± 8
Tetraplegic	80.9 ± 5.3	70.9 ± 7	70 ± 7	68.6 ± 5	68 ± 9	93 ± 6
VLF (0.01-0.04 Hz) in AP (mmHg^2/Hz)—No Significant effects						
AB	139.2 ± 40	112.2 ± 26	128.4 ± 28	83.6 ± 9	118 ± 36	120.2 ± 21
Paraplegic	122.6 ± 81	77.9 ± 36	186 ± 123	77.3 ± 34	42.5 ± 9	83.4 ± 29
Tetraplegic	45.6 ± 3	24 ± 9	42.3 ± 5	65 ± 19	47.7 ± 21	79.3 ± 25
LF(0.04-0.15 Hz) in AP (mmHg^2/Hz)—Group (p<0.004), Group x HUT (p<0.04) effects						
AB	30.8 ± 4.1	30.8 ± 4.4	41.6 ± 5.3	48 ± 7	68.6 ± 23.6	28.5 ± 3.9
Paraplegic∗	44.8 ± 19.7	20 ± 7	38.8 ± 19∗	21 ± 5♣	15.4 ± 2.8	27 ± 13.4
Tetraplegic♣	8.9 ± 3♣	5.1 ± 3.3♣	6.4 ± 3♣	8.6 ± 1.2♣	5 ± 2.1	10.4 ± 2♣
HF(0.15-0.4 Hz) in AP (mmHg^2/Hz)—No Significant effects						
AB	3.5 ± 0.6	3.1 ± 0.6	3.5 ± 0.5	4.3 ± 0.4	4.2 ± 0.4	3 ± 0.6
Paraplegic	6.1 ± 2.7	2.6 ± 0.8	7.3 ± 3.4	5.3 ± 2.3	3.5 ± 0.9	7.4 ± 4.9
Tetraplegic	3.3 ± 1.3	1.5 ± 0.7	1.2 ± 0.4	1.5 ± 0.4	1.3 ± 0.2	2.3 ± 0.6

Table 4.3: Heart Rate (HR) Group Results (Mean ± SEM)						
HR (beats/min, bpm)—HUT (p<0.0001), Group x HUT (p<0.05) effects						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	65.4 ± 4	67 ± 5♦	75 ± 5♦	86 ± 5♦	91.7 ± 6.5	63.9 ± 4.4
Paraplegic	79 ± 3	81± 2♣∗♦	87 ± 2♦	96 ± 3♦	104.5 ± 3.2	83 ± 4♣∗
Tetraplegic	62.7 ± 3	67 ± 6♦	71 ± 9♦	79 ± 10♦	83.2 ± 11	52 ± 3♣
VLF (0.01-0.4 Hz) in HR (bpm^2/Hz)—Group effect (p<0.011)						
AB	124 ± 25	125.5 ± 29	199.6 ± 35	195.7 ± 31	240.1 ± 60	115.5 ± 23
Paraplegic♣	92.2 ± 41	56.7 ± 31	123.9 ± 42	83.9 ± 19	29.3 ± 6	76.3 ± 14
Tetraplegic♣	56 ± 15	93.7 ± 60	50.3 ± 19	51.9 ± 8	19.6 ± 11	79.8 ± 7
LF (0.04-0.15 Hz) in HR (bpm^2/Hz)—Group effect (p<0.036)						
AB	41.5 ± 9.5	37.4 ± 9.7	59.8 ± 12.4	71.7 ± 17.8	75.5 ± 17.4	36.9 ± 5.1
Paraplegic♣	23.1 ± 10.5	12.6 ± 4.4	16.7 ± 4.5	19.8 ± 9.8	4.6 ± 1	12.9 ± 2.2
Tetraplegic♣	31 ± 14	31.1 ± 23.2	18 ± 13.5	11.7 ± 2.1	3.2 ± 1.5	15.7 ± 3.9
HF (0.15-0.4 Hz) in HR (bpm^2/Hz)—No Significant effects						
AB	12.1 ± 2.2	8.3 ± 1.2	5.6 ± 0.9	4.9 ± 1.4	4.7 ± 1.5	10.9 ± 2.4
Paraplegic	1.8 ± 0.8	0.57 ± 0.17	1.2 ± 0.4	0.8 ± 0.2	0.1 ± 0.02	1.1 ± 0.6
Tetraplegic	19.6 ± 11.9	5.7 ± 4.3	3.8 ± 2.6	1.1 ± 0.1	0.6 ± 0.2	7.7 ± 4

Table 4.4: Upper Body (Forearm) Skin Perfusion (SP1) Results (Mean ± SEM)						
SP1 (Perfusion Units, PU)—HUT (p<0.03), Group x HUT (p<0.025) effects						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	10.6 ± 2	11.5 ± 1.9	11.3 ± 2	10 ± 2♦	9.3 ± 1.8	11.3 ± 2♦
Paraplegic	18.3 ± 5♣	17.3 ± 4.7	14.1 ± 2.9	12.3 ± 2♦	10.5 ± 1.9	12.6 ± 3♦
Tetraplegic	11 ± 1.8	10.4 ± 2	8.9 ± 2	7.1 ± 2♦	5.4 ± 1.7	9.8 ± 2♦
VLF (0.01-0.04 Hz) in SP1 (PU^2/Hz)—No Significant effects						
AB	11.2 ± 4	18 ± 9	33.4 ± 14	20.2 ± 5	18.7 ± 7	20 ± 6
Paraplegic	95 ± 60	21.8 ± 5	22.2 ± 4	19.1 ± 7	19 ± 9	38.2 ± 24
Tetraplegic	4.8 ± 3	5 ± 4	1.9 ± .3	2.8 ± 1	1 ± .3	3.8 ± 1
LF (0.04-0.15 Hz) in SP1 (PU^2/Hz)—No Significant effects						
AB	5.4 ± 1.2	10.7 ± 4.9	10.9 ± 3.7	9.4 ± 2.4	8.5 ± 2.5	7.5 ± 2.1
Paraplegic	17.8 ± 9.2	8.3 ± 1.4	7 ± 3.4	8.6 ± 5.9	5.7 ± 2.5	11.2 ± 6.6
Tetraplegic	1.6 ± 0.6	1.1 ± 0.4	1.3 ± 0.9	1 ± 0.2	0.5 ± 0.1	1.7 ± 0.9
HF (0.15-0.4 Hz) in SP1 (PU^2/Hz)—No Significant effects						
AB	0.4 ± 0.1	0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.3	0.8 ± 0.4
Paraplegic	1.9 ± 0.9	1 ± 0.5	1.2 ± 0.7	2.5 ± 1.8	1 ± 0.5	3.6 ± 2.9
Tetraplegic	0.4 ± 0.1	0.4 ± 0.2	0.2 ± 0.04	0.3 ± 0.1	0.2 ± 0.1	0.6 ± 0.3

Table 4.5: Lower Body (Shin) Skin Perfusion (SP2) Group Results (Mean ± SEM)						
SP2 (Perfusion Units, PU)—HUT effect (p<0.001)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	8.1 ± 1	5.5 ± 0.4♦	4.8 ± 0.3♦	4.6 ± 0.3♦	4.6 ± 0.4	7.8 ± 0.9♦
Paraplegic	7.5 ± 1	5.6 ± 1♦	5.2 ± 1♦	4.7 ± 1♦	4.7 ± 0.9	6.3 ± 1♦
Tetraplegic	6.9 ± 1	4.8 ± 1♦	4.5 ± 1♦	4.2 ± 1♦	4.3 ± 1	5.4 ± 1♦
VLF (0.01-0.04 Hz) in SP2 (PU^2/Hz)—Group effect (p<0.016)						
AB	5.4 ± 1	5 ± 1	6.6 ± 2	5.3 ± 2	4 ± 1	13 ± 6
Paraplegic♣	7 ± 4	1 ± .7	1 ± .4	1 ± .6	0.4 ± .2	1.4 ± .6
Tetraplegic♣	1 ± .2	1.2 ± 1	1 ± .8	0.3 ± .2	0.2 ± .1	1 ± .7
LF (0.04-0.15 Hz) in SP2 (PU^2/Hz)—HUT (p<0.007), Group (p<0.004) effects						
AB	1.7 ± 0.2	1.2 ± 0.2♦	1 ± 0.3♦	1 ± 0.3♦	0.7 ± 0.2	1.6 ± 0.4
Paraplegic♣	1.5 ± 1	0.4 ± 0.2♦	0.3 ± 0.1♦	0.3 ± 0.2♦	0.1 ± 0.03	0.4 ± 0.3
Tetraplegic♣	0.5 ± 0.2	0.1 ± 0.1♦	0.1 ± .05♦	0.1 ± .01♦	0.1 ± 0.06	0.3 ± 0.1
HF (0.15-0.4 Hz) in SP2 (PU^2/Hz)—HUT effect (p<0.022)						
AB	0.2 ± 0.05	0.3 ± 0.06	0.1 ± .04♦	0.2 ± 0.07	0.1 ± 0.02	0.2 ± 0.06
Paraplegic	0.3 ± 0.2	0.4 ± 0.1	0.1 ± .05♦	0.2 ± 0.1	0.2 ± 0.06	0.1 ± 0.1
Tetraplegic	0.1 ± 0.08	0.03 ± 0.01	.01 ± .01♦	0.03 ± 0.01	0.05 ± 0.04	0.04 ± 0.01

Table 4.6: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Heart Rate & Arterial Pressure (Mean ± SEM)						
LF Negative Magnitudes—Group effect (p<0.001)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.4 ± .03	-0.4 ± .02	-0.5 ± .06	-0.5 ± .06	-0.5 ± .07	-0.4 ± .03
Paraplegic♣	-0.2 ± .05	-0.2 ± .05	-0.3 ± .07	-0.4 ± .09	-0.2 ± .13	-0.2 ± .06
Tetraplegic♣	-0.2 ± .1	-0.1 ± .09	-0.2 ± .1	-0.07 ± .1	-0.03 ± .04	-0.09 ± .08
LF Negative Lag Times (sec)—No Significant effects						
AB	-2.2 ± .02	-2.1 ± .05	-2.1 ± .03	-2.2 ± .01	-2.12 ± .03	-2.05 ± .09
Paraplegic	-2.2	-2.2	-2.2	-2.2 ± .04	-2.12 ± .08	-2.2
Tetraplegic	-1.8 ± .3	-1.8 ± .3	-1.8 ± .3	-1.3 ± .4	-1.8 ± .4	-1.8 ± .3
LF Positive Magnitudes—Group effect (p<0.0001)						
AB	0.5 ± .04	0.4 ± .03	0.4 ± .03	0.4 ± .04	0.4 ± .05	0.5 ± .04
Paraplegic*	0.5 ± .09	0.5 ± .05	0.4 ± .07	0.4 ± .07	0.4 ± .03	0.4 ± .07
Tetraplegic♣	0.6 ± .1	0.4 ± .1	0.4 ± .1	0.2 ± .1	0.03 ± .1	0.5 ± .1
LF Positive Lag Times (sec)—HUT (p<0.003), Group x HUT (p<0.036), Group (p<0.003) effects						
AB	1.7 ± .03	1.8	1.8	1.8	1.8 ± .05	1.8
Paraplegic*	1.6 ± .1	1.6 ± .1♣	1.8 ± .04	1.8	1.4 ± .4	1.6 ± .2
Tetraplegic♣	1.3 ± .3♣	1.2 ± .3♣	1.3 ± .3♣	0.7 ± .4♣	0.2 ± .2	1 ± .3♣

Table 4.7: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Arterial Pressure & Upper Body Skin Perfusion (Mean ± SEM)						
LF Negative Magnitudes—Group effect (p<0.002)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.4 ± .03	-0.4 ± .03	-0.4 ± .03	-0.4 ± .05	-0.3 ± .05	-0.4 ± .03
Paraplegic♣	-0.3 ± .1	-0.4 ± .05	-0.3 ± .04	-0.2 ± .05	-0.1 ± .02	-0.3 ± .1
Tetraplegic♣	-0.2 ± .04	-0.2 ± .05	-0.3 ± .03	-0.2 ± .02	-0.2 ± .1	-0.1 ± .04
LF Negative Lag Times (sec)—Group effect (p<0.006)						
AB	4.3 ± .2	3.9 ± .2	4 ± .3	3.7 ± .4	3.9 ± .5	3.4 ± .4
Paraplegic♣	5.7 ± .8	4.8 ± .6	5.5 ± 1.1	5.6 ± .9	5.2 ± 2	4 ± .7
Tetraplegic♣	6.6 ± 1.1	7.2 ± 1	4.9 ± .9	5.3 ± 1.2	5.9 ± 1.1	4.1 ± .9
LF Positive Magnitudes—No Significant effects						
AB	0.3 ± .03	0.4 ± .04	0.4 ± .04	0.4 ± .05	0.3 ± .05	0.3 ± .03
Paraplegic	0.4 ± .1	0.4 ± .05	0.3 ± .03	0.3 ± .05	0.2 ± .02	0.3 ± .1
Tetraplegic	0.3 ± .06	0.4 ± .09	0.3 ± .05	0.3 ± .05	0.2 ± .04	0.3 ± .07
LF Positive Lag Times (sec)—No Significant effects						
AB	-0.2 ± 1	-1.4 ± .3	1.7 ± 1.4	-1.1 ± 1.3	0.2 ± 1.2	1.5 ± 2
Paraplegic	-0.3 ± 1	-1.1 ± .6	-0.9 ± .6	-0.5 ± .9	0.6 ± 1	-0.2 ± 3.1
Tetraplegic	-0.03 ± .2	-0.6 ± .7	-0.4 ± .7	0.1 ± 1.4	2.9 ± 2.1	2.1 ± 1.5

Table 4.8: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Heart Rate & Upper Body Skin Perfusion (Mean ± SEM)						
LF Negative Magnitudes—HUT (p<0.03), Group (p<0.013) effects						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.3 ± .03	-0.3 ± .02	-0.3 ± .03	-0.2 ± .04♦	-0.2 ± .03	-0.3 ± .02
Paraplegic♣	-0.3 ± .03	-0.2 ± .05	-0.2 ± .07	-0.2 ± .05♦	-0.2 ± .04	-0.2 ± .07
Tetraplegic♣	-0.2 ± .04	-0.2 ± .05	-0.2 ± .04	-0.1 ± .04♦	-0.06 ± .03	-0.1 ± .02
LF Negative Lag Times (sec)—HUT (p<0.002), Group x HUT (p<0.006) effects						
AB	7 ± .2	6.7 ± .2	6 ± .7	5.7 ± .9	4.7 ± 1.1	6.5 ± .3♦
Paraplegic	6.9 ± .7	6.2 ± .4*	5.3 ± 1.4	4.4 ± 1.4	2.9 ± 1.9	5.5 ± .7♦
Tetraplegic	6.1 ± .9	8.2 ± .7♣	5.5 ± 1	6.3 ± 1.2	6.2 ± 1.6	3.8 ± 1♣♦
LF Positive Magnitudes—HUT (p<0.023), Group (p<0.013) effects						
AB	0.4 ± .04	0.4 ± .03	0.4 ± .05	0.4 ± .05♦	0.3 ± .04	0.3 ± .03♦
Paraplegic♣	0.4 ± .04	0.3 ± .02	0.3 ± .03	0.2 ± .04♦	0.2 ± .03	0.1 ± .03♦
Tetraplegic♣	0.4 ± .06	0.3 ± .07	0.3 ± .05	0.2 ± .02♦	0.1 ± .02	0.2 ± .05♦
LF Positive Lag Times (sec)—No Significant effects						
AB	1.5 ± .2	1.4 ± .2	-0.1 ± .9	-0.4 ± 1.2	1.9 ± .8	0.4 ± .8
Paraplegic	0.4 ± .4	2.4 ± 1.9	-1.2 ± 1.6	2.4 ± 1.8	2.6 ± 3.8	-3.9 ± 3.7
Tetraplegic	2.3 ± .9	-0.7 ± 1.3	0.6 ± .9	-0.3 ± .9	1.5 ± 2.5	2.2 ± 1.7

Table 4.9: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Arterial Pressure & Lower Body Skin Perfusion (Mean ± SEM)						
LF Negative Magnitudes—Group effect (p<0.004)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.3 ± .04	-0.3 ± .03	-0.3 ± .04	-0.3 ± .04	-0.3 ± .04	-0.3 ± .04
Paraplegic	-0.2 ± .06	-0.2 ± .04	-0.1 ± .06	-0.3 ± .06	-0.2 ± .04	-0.2 ± .06
Tetraplegic♣	-0.1 ± .04	-0.2 ± .03	-0.2 ± .04	-0.1 ± .03	-0.2 ± .04	-0.1 ± .02
LF Negative Lag Times (sec)—No Significant effects						
AB	5.1 ± .2	4.8 ± .3	5.4 ± .6	5 ± .3	4.9 ± .6	5.7 ± .6
Paraplegic	5.4 ± 1.5	5.6 ± 1.5	6.5 ± .9	6.3 ± 1	4.3 ± 1.4	4.9 ± 2
Tetraplegic	4.6 ± 1.4	5.6 ± 1.4	4.4 ± 1	4.7 ± .9	5.9 ± 1.3	6.1 ± 1.8
LF Positive Magnitudes—No Significant effects						
AB	0.3 ± .04	0.3 ± .04	0.3 ± .03	0.4 ± .05	0.4 ± .05	0.4 ± .05
Paraplegic	0.4 ± .1	0.3 ± .1	0.3 ± .05	0.4 ± .1	0.2 ± .02	0.3 ± .1
Tetraplegic	0.3 ± .1	0.2 ± .05	0.3 ± .04	0.2 ± .02	0.2 ± .1	0.2 ± .03
LF Positive Lag Times (sec—No Significant effects)						
AB	-0.4 ± 1.1	1 ± 1.2	0.5 ± 1	-0.8 ± .3	-1.1 ± .3	1.3 ± 1.2
Paraplegic	1.6 ± 1.7	-3.4 ± 2.3	0.4 ± .6	0.1 ± .7	-3 ± 2.4	-0.2 ± 2.4
Tetraplegic	-0.6 ± 1.4	1.6 ± .8	2 ± 2.1	-1.3 ± .9	-1.8 ± 1	-1.6 ± 1.8

Table 4.10: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Heart Rate & Lower Body Skin Perfusion (Mean ± SEM)						
LF Negative Magnitudes—No Significant effects						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.2 ± .02	-0.2 ± .03	-0.2 ± .04	-0.3 ± .05	-0.3 ± .03	-0.2 ± .04
Paraplegic	-0.1 ± .03	-0.2 ± .05	-0.2 ± .05	-0.2 ± .03	-0.1 ± .04	-0.2 ± .06
Tetraplegic	-0.2 ± .04	-0.1 ± .03	-0.1 ± .03	-0.1 ± .02	-0.1 ± .03	-0.2 ± .03
LF Negative Lag Times (sec)—Group effect (p<0.001)						
AB	-4.5 ± .5	-3.2 ± .4	-4 ± .8	-3.2 ± .6	-4.7 ± 1.1	-3 ± .7
Paraplegic✱	-6.2 ± 1.2	-2.4 ± .7	-4.2 ± 1.3	-2.8 ± .8	-4.3 ± 1.6	-2.6 ± 1
Tetraplegic♣	-4.9 ± 1.1	-7.2 ± .9	-6 ± 1.5	-5.6 ± 1.3	-6.8 ± 1	-6.4 ± 1.4
LF Positive Magnitudes— Group effect (p<0.035)						
AB	0.4 ± .04	0.3 ± .03	0.3 ± .04	0.3 ± .04	0.3 ± .02	0.3 ± .04
Paraplegic✱	0.3 ± .06	0.2 ± .1	0.2 ± .1	0.3 ± .06	0.1 ± .02	0.3 ± .04
Tetraplegic	0.3 ± .1	0.2 ± .06	0.3 ± .04	0.2 ± .04	0.1 ± .02	0.2 ± .04
LF Positive Lag Times (sec)—No Significant effects						
AB	2 ± .2	1.7 ± 1.4	0.1 ± 1.2	1.8 ± .9	1.5 ± .8	1.9 ± 1
Paraplegic	2 ± .4	-1.1 ± 2.5	-1 ± 1.6	-0.9 ± 3	-0.3 ± 2.4	-0.4 ± 2
Tetraplegic	2.7 ± 1.5	3.1 ± 1	0.9 ± 1	1.8 ± .6	-0.4 ± 1.6	-0.8 ± 1.6

Table 4.11: Low Frequency (0.04-0.15 Hz) Cross Correlation Between Upper (Forearm) & Lower (Shin) Body Skin Perfusion Group Results (Mean ± SEM)						
LF Negative Magnitudes—Group effect (p<0.0001)						
	Control	**20°**	**40°**	**60°**	**80°**	**Recovery**
AB	-0.3 ± .03	-0.2 ± .04	-0.3 ± .03	-0.3 ± .03	-0.3 ± .03	-0.3 ± .02
Paraplegic♣	-0.2 ± .05	-0.2 ± .04	-0.2 ± .02	-0.1 ± .02	-0.1 ± .02	-0.2 ± .1
Tetraplegic♣	-0.1 ± .02	-0.1 ± .03	-0.2 ± .04	-0.2 ± .02	-0.1 ± .02	-0.1 ± .03
LF Negative Lag Times (sec)—HUT effect (p<0.013)						
AB	-5.5 ± .6	-5.2 ± .5	-5 ± .7♦	-5.2 ± .4	-5.1 ± .8	-4.1 ± .5
Paraplegic	-6 ± 1.6	-4.1 ± 1.1	-4 ± .9♦	-7.4 ± .8	-5.7 ± 1.6	-4.4 ± 1.8
Tetraplegic	-6.9 ± 1.1	-5.9 ± 1.5	-3.8 ± 1♦	-5.8 ± .6	-7.5 ± 1.1	-4.7 ± 1.1
LF Positive Magnitudes—Group effect (p<0.0001)						
AB	0.4 ± .03	0.4 ± .05	0.4 ± .05	0.4 ± .06	0.3 ± .06	0.5 ± .04
Paraplegic♣	0.3 ± .1	0.2 ± .05	0.2 ± .04	0.2 ± .04	0.2 ± .04	0.2 ± .04
Tetraplegic♣	0.2 ± .03	0.2 ± .06	0.2 ± .04	0.3 ± .01	0.2 ± .06	0.2 ± .03
LF Positive Lag Times (sec)—Group x HUT effect (p<0.042)						
AB	0.5 ± .4	-0.2 ± .9	1.2 ± .5	0.5 ± 1.2	-1.8 ± 1.6	2.1 ± .5
Paraplegic	-0.7 ± 1.1	0.5 ± 1.4	1.7 ± .9✱	1.1 ± 2.2	1.4 ± 1.1	2.1 ± 1.5✱
Tetraplegic	0.2 ± 1.7	1.6 ± 1.5	-2.9 ± 1.8♣	0.8 ± 1.3	-0.2 ± 2.9	-3.7 ± 2.5♣

Figure 4.1: Hemodynamic responses to HUT for one AB and one Tetraplegic subject

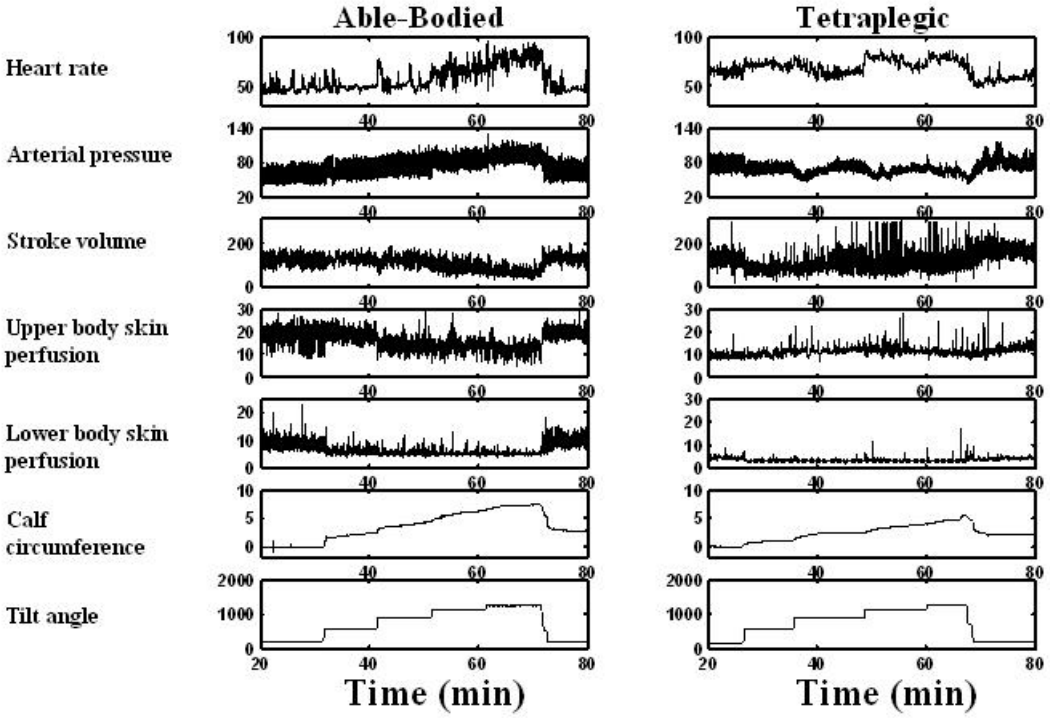


Figure 4.1a: Arterial pressure from five min of supine control, 20°, 40°, 60° and 80° HUT and recovery in AB, Paraplegic and Tetraplegic groups

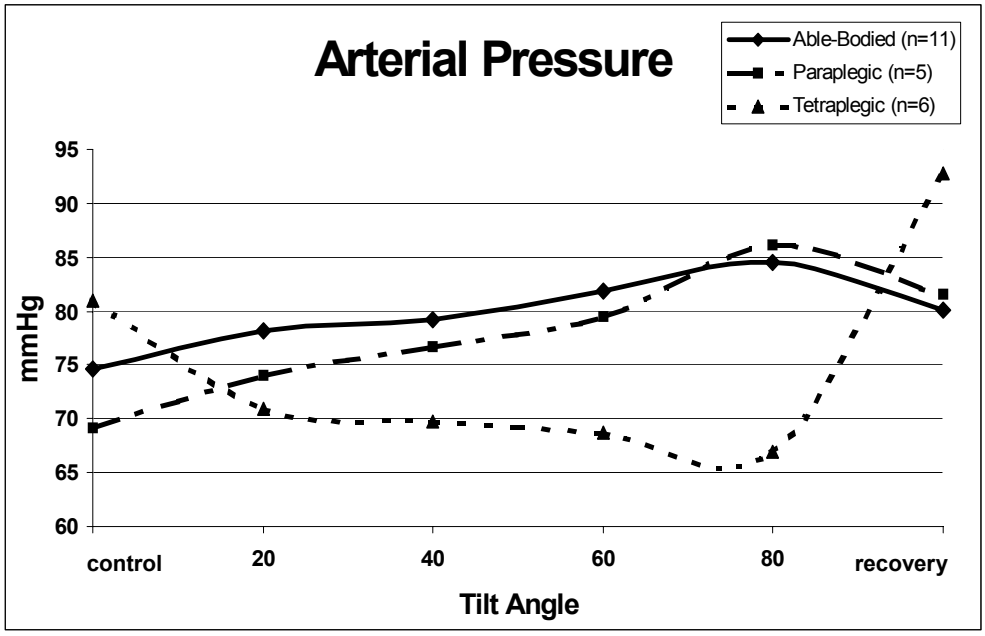


Figure 4.1b: Orthostatic hypotension in response to head-up-tilt, characterized by a gradual decline in arterial pressure (bottom trace) and declines in heart rate (top trace) during the last minute of tilt in one Tetraplegic.

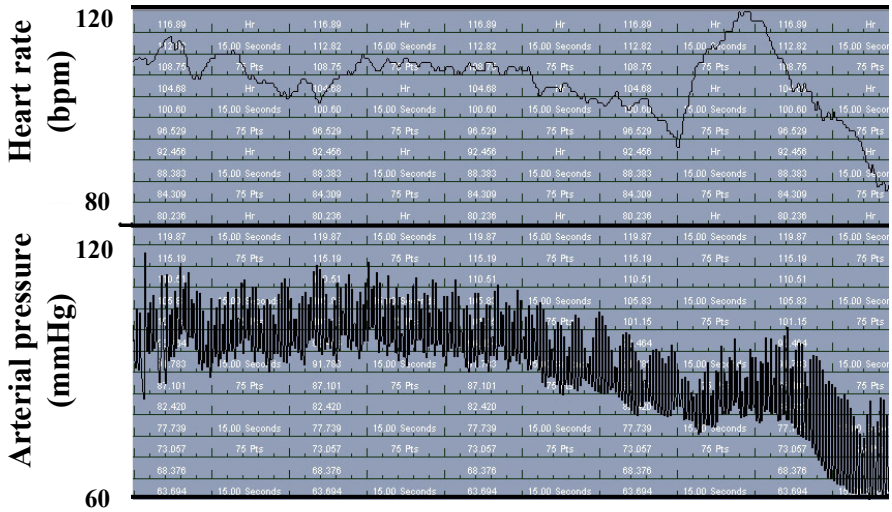


Figure 4.2: Arterial pressure raw data and spectral power (top right insert) from five min supine control in one AB subject

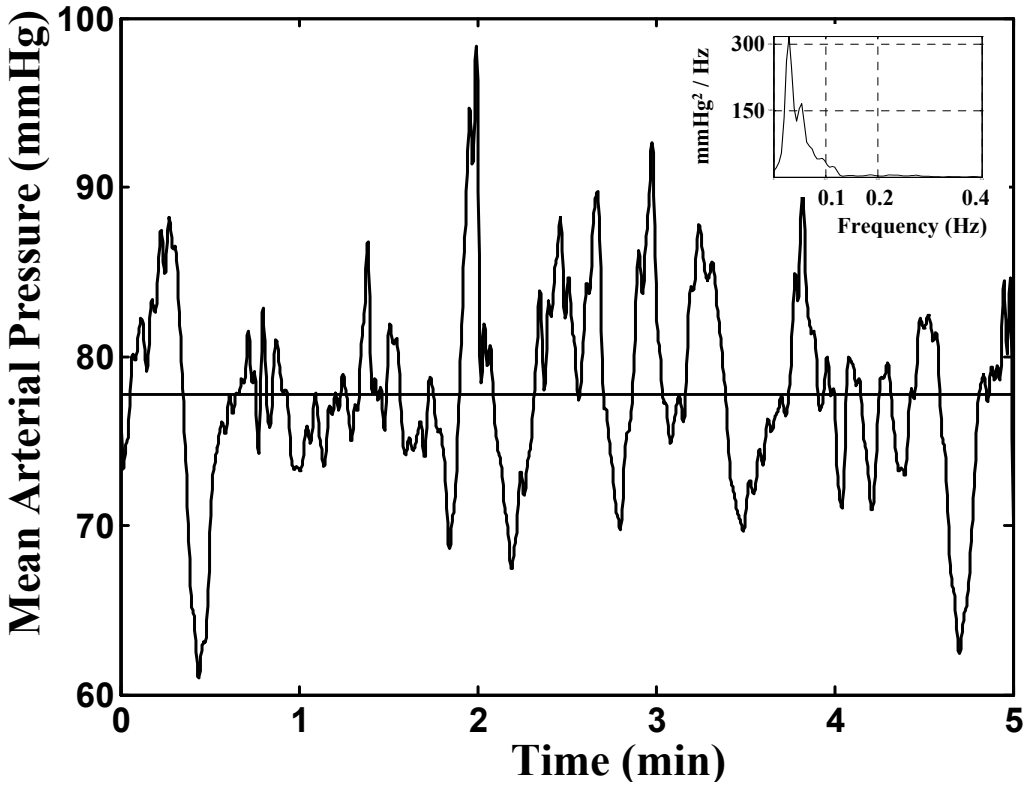


Figure 4.2a: Mean (top left), VLF (top right), LF (bottom left) and HF (bottom right) arterial pressure in AB, Paraplegic and Tetraplegic groups

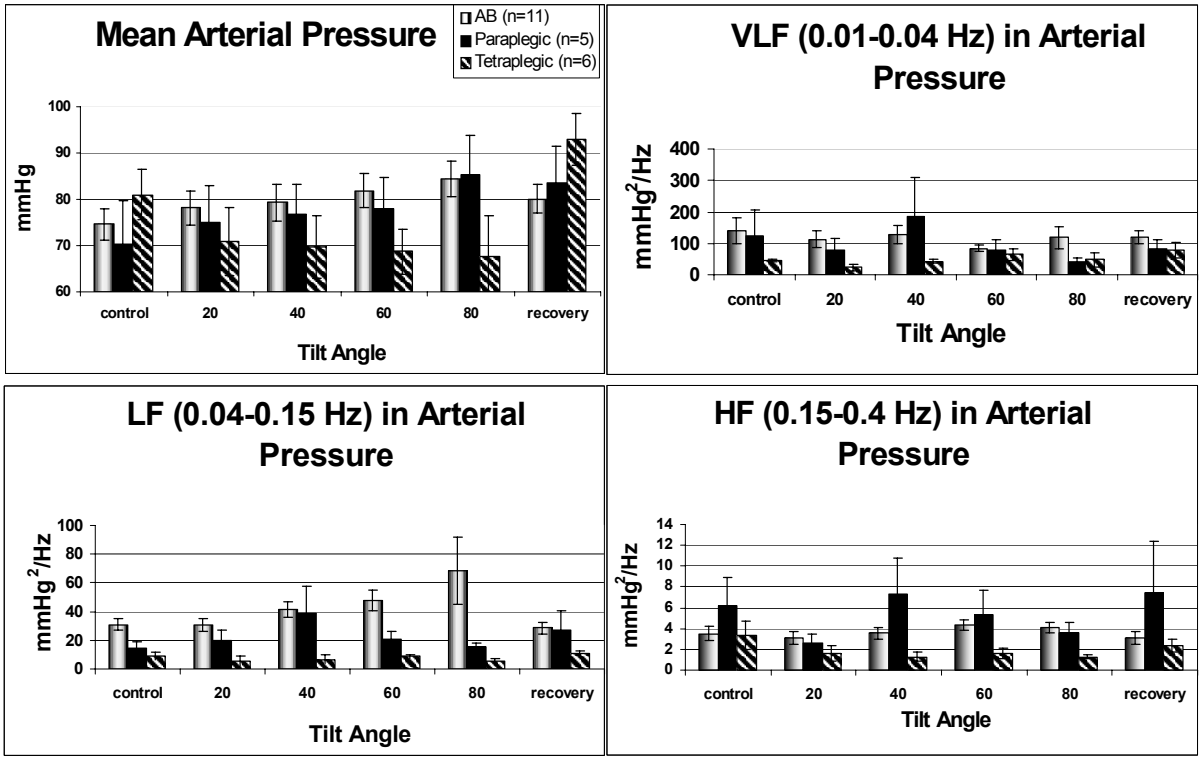


Figure 4.3: Heart rate raw data and spectral power (top insert) from five min supine control in one AB subject

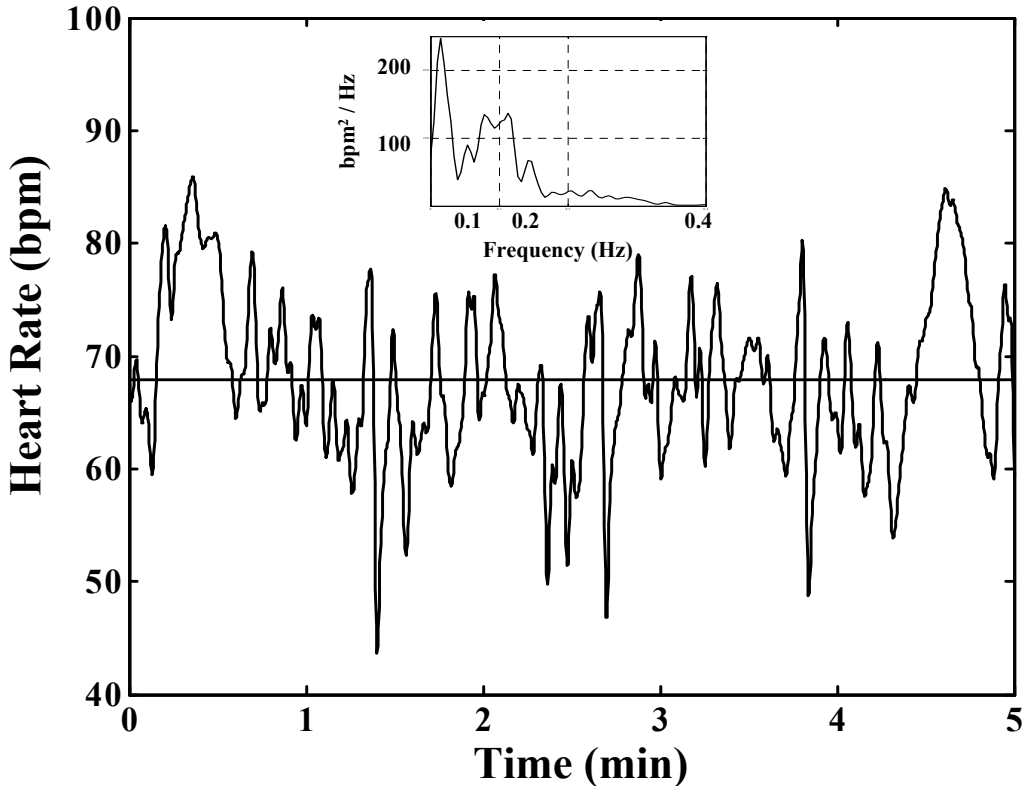


Figure 4.3a: Mean (top left), VLF (top right), LF (bottom left), and HF (bottom right) heart rate in AB, Paraplegic and Tetraplegic groups

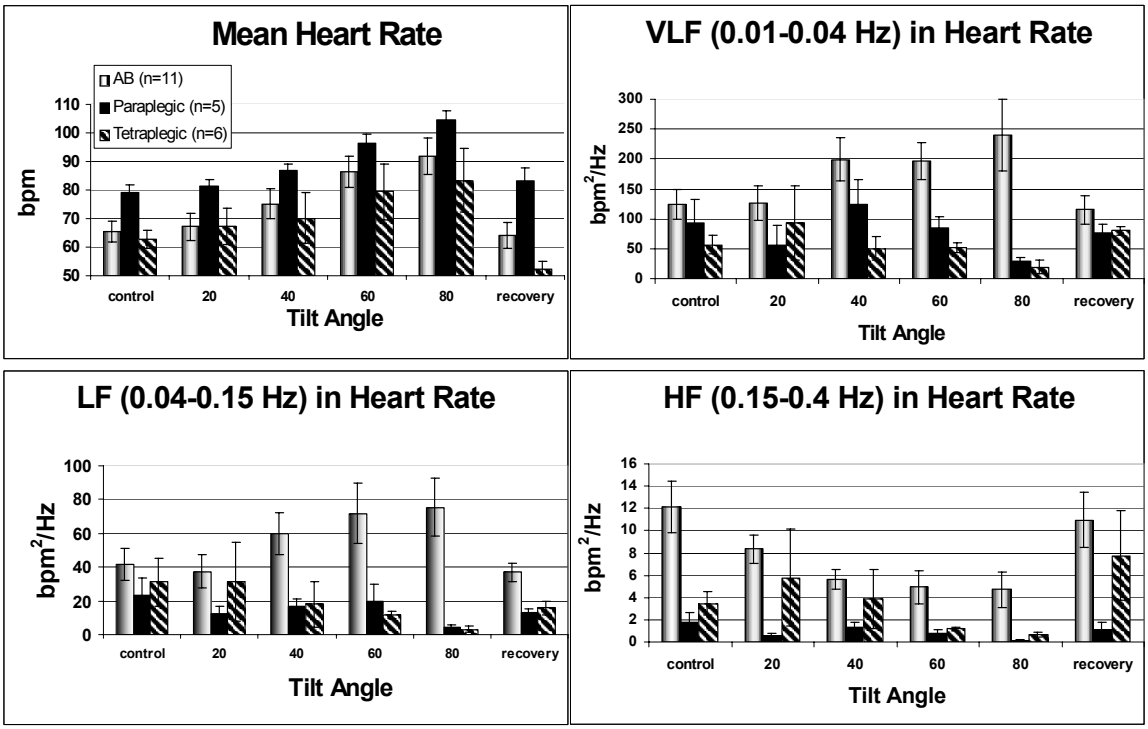


Figure 4.4: Upper body skin perfusion raw data and spectral power (top right insert) from five min supine control for one AB subject

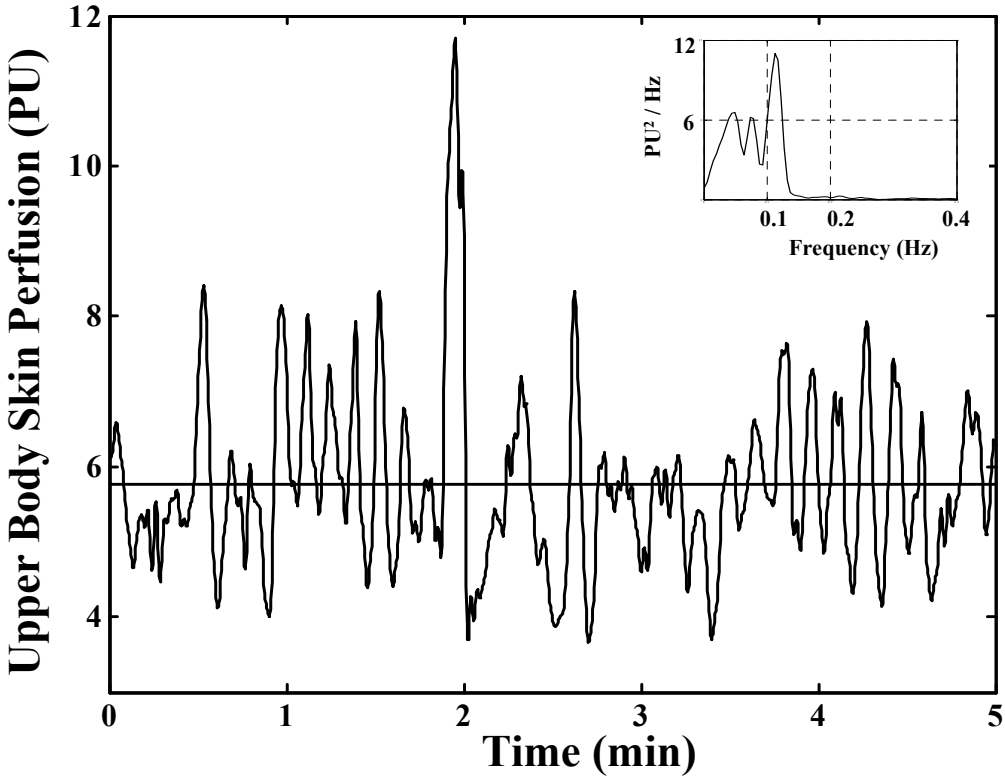


Figure 4.4a: Mean (top left), VLF (top right), LF (bottom left), and HF (bottom right) upper body skin perfusion in AB, Paraplegic and Tetraplegic groups

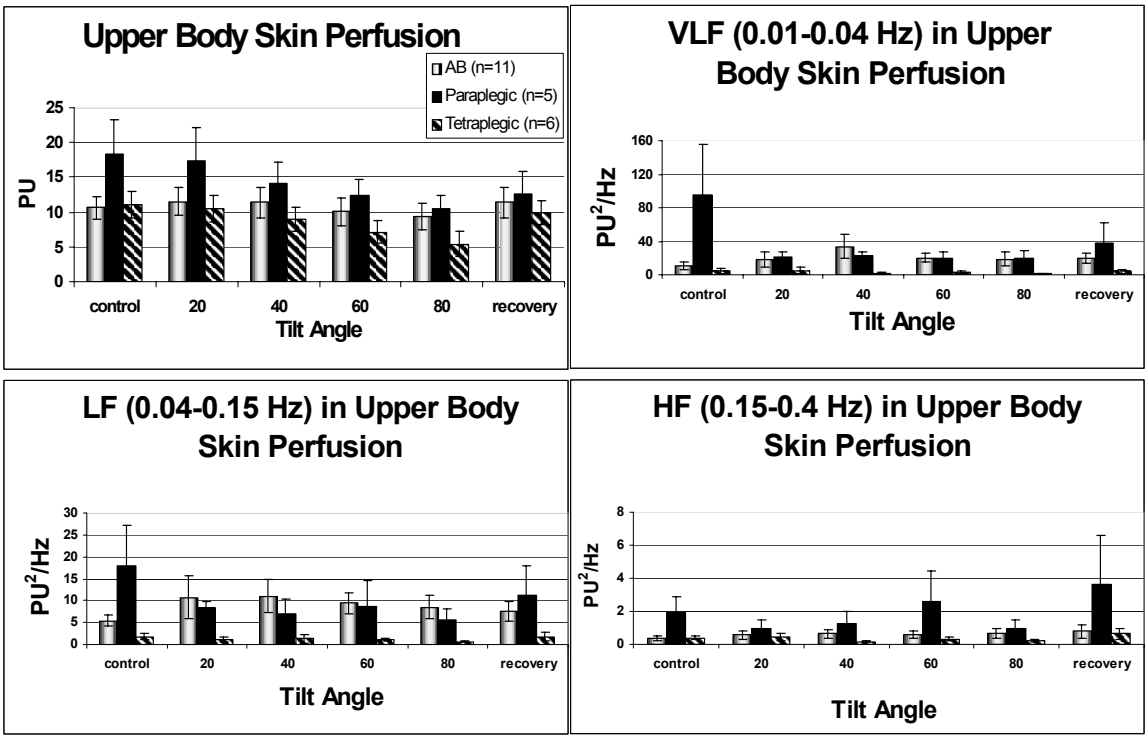


Figure 4.5: Lower body skin perfusion raw data and spectral power (top right insert) from five min supine control in one AB subject

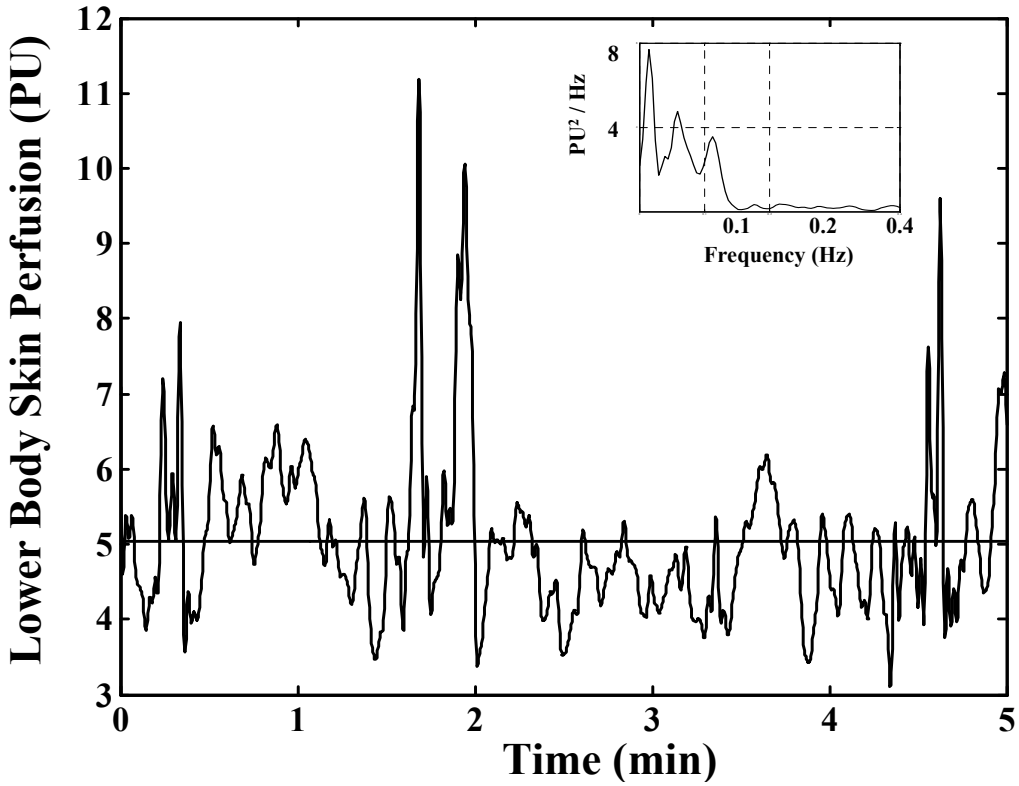


Figure 4.5a: Mean (top left), VLF (top right), LF (bottom left), and HF (bottom right) lower body skin perfusion in AB, Paraplegic and Tetraplegic groups

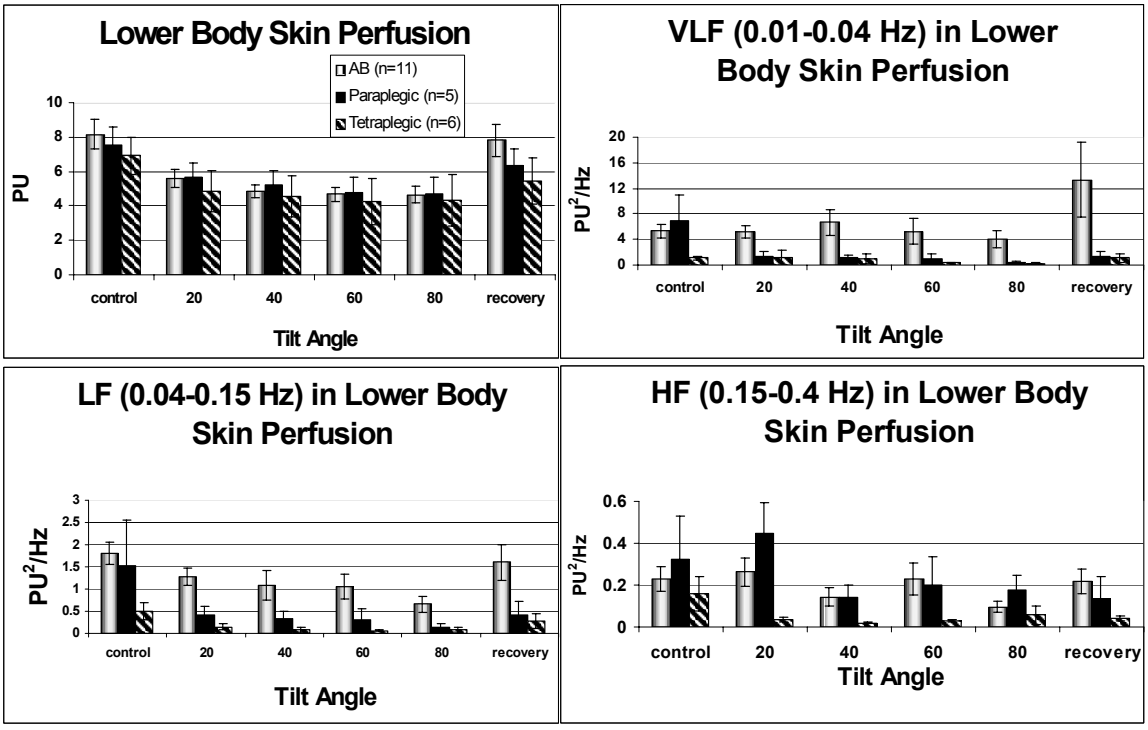


Figure 4.6 : Heart rate and arterial pressure raw data with mean subtracted from two min of control, shown for illustrative purposes (right) and the cross correlation of five min of heart rate and arterial pressure in one AB subject (left).

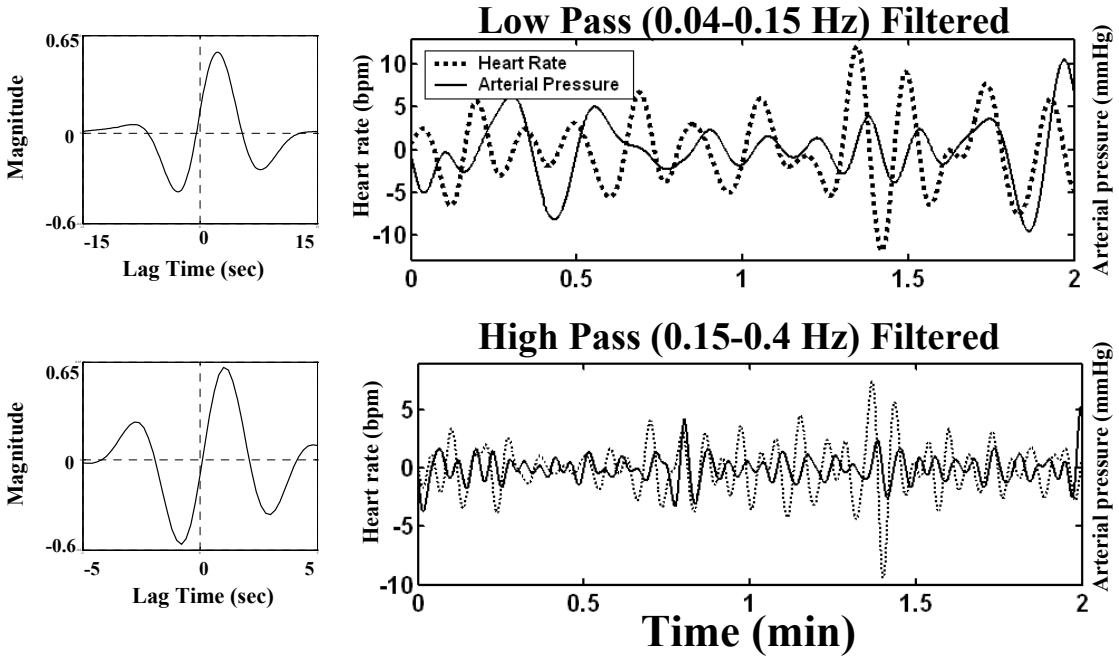


Figure 4.6a: Cross correlation of heart rate (HR) and arterial pressure (AP) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

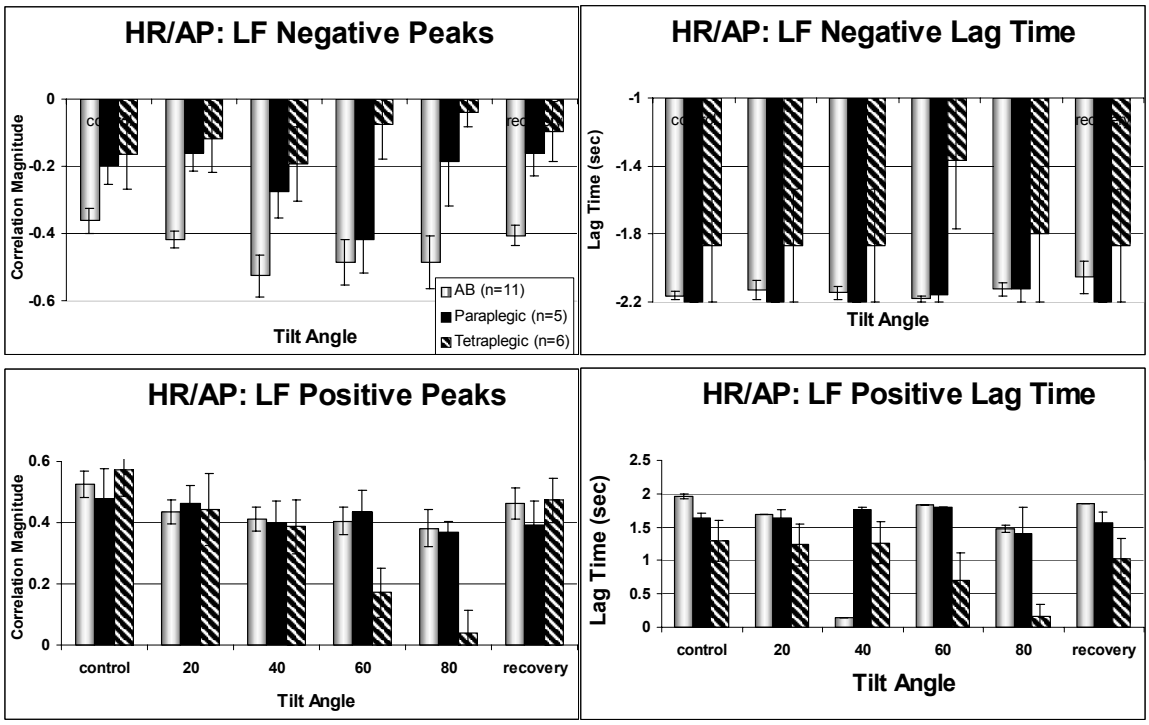


Figure 4.7: Arterial pressure and upper body skin perfusion raw data with mean subtracted from two min of control, shown for illustrative purposes (right) and the cross correlation of five min of arterial pressure and upper body skin perfusion in one AB subject (left).

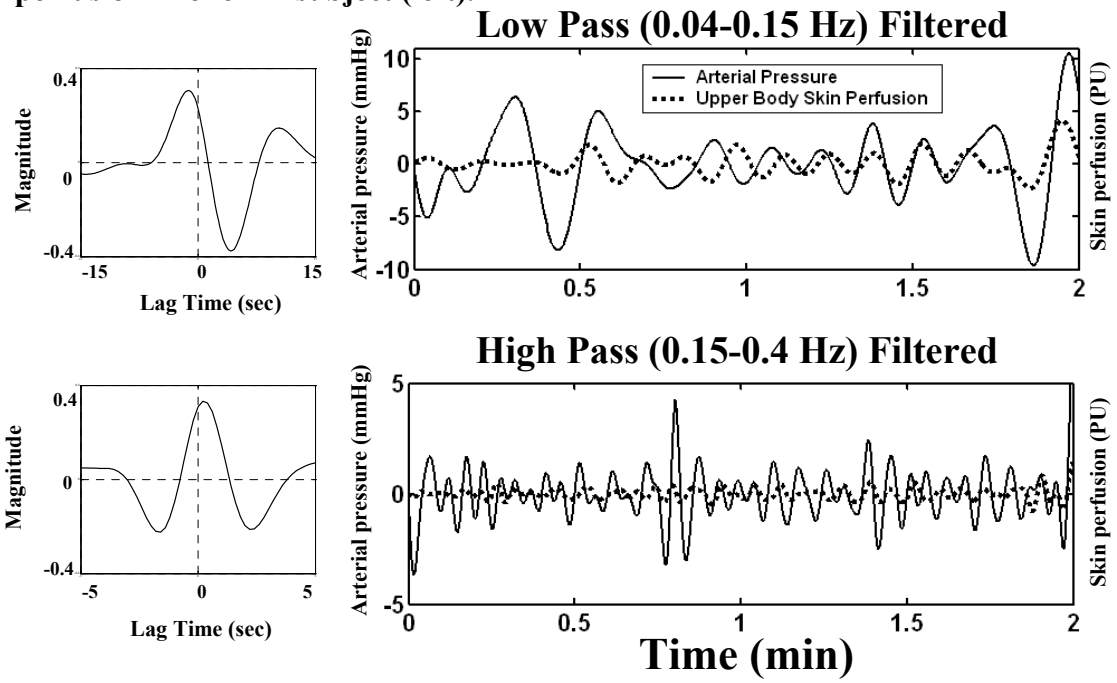


Figure 4.7a: Cross correlation of arterial pressure (AP) and upper body skin perfusion (SP1) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

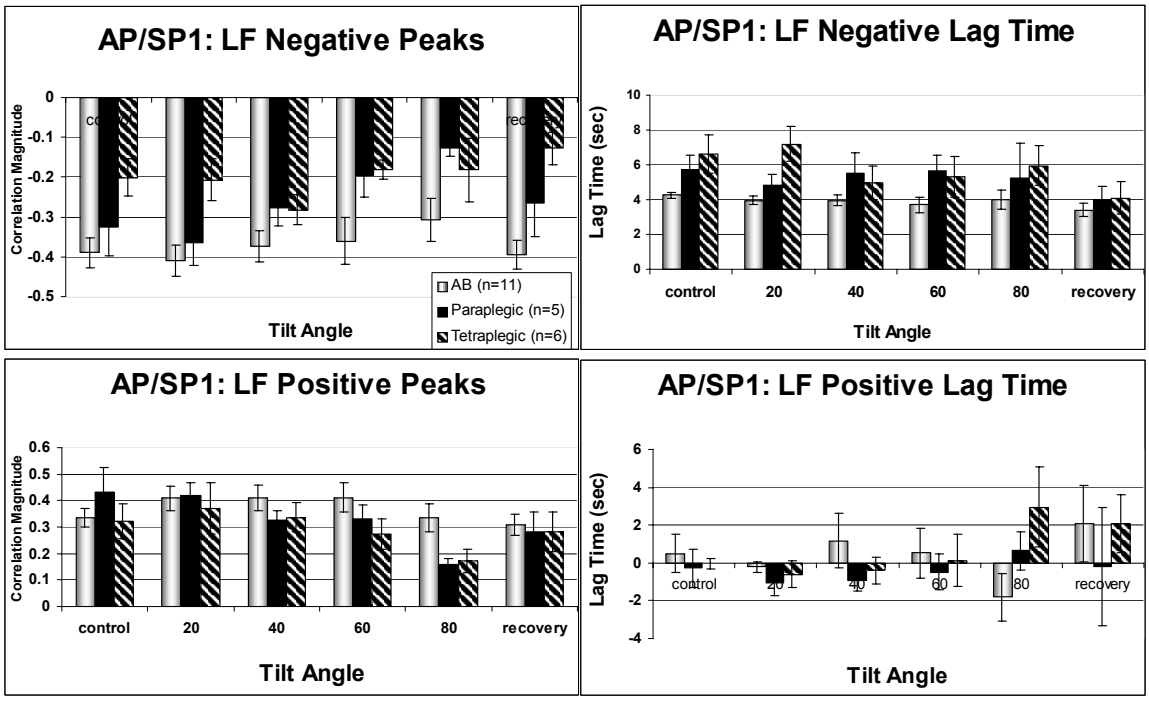


Figure 4.8: Heart rate and upper body skin perfusion raw data with mean subtracted from two min of control, shown for illustrative purposes (right) and the cross correlation of five min of heart rate and upper body skin perfusion in one AB subject (left).

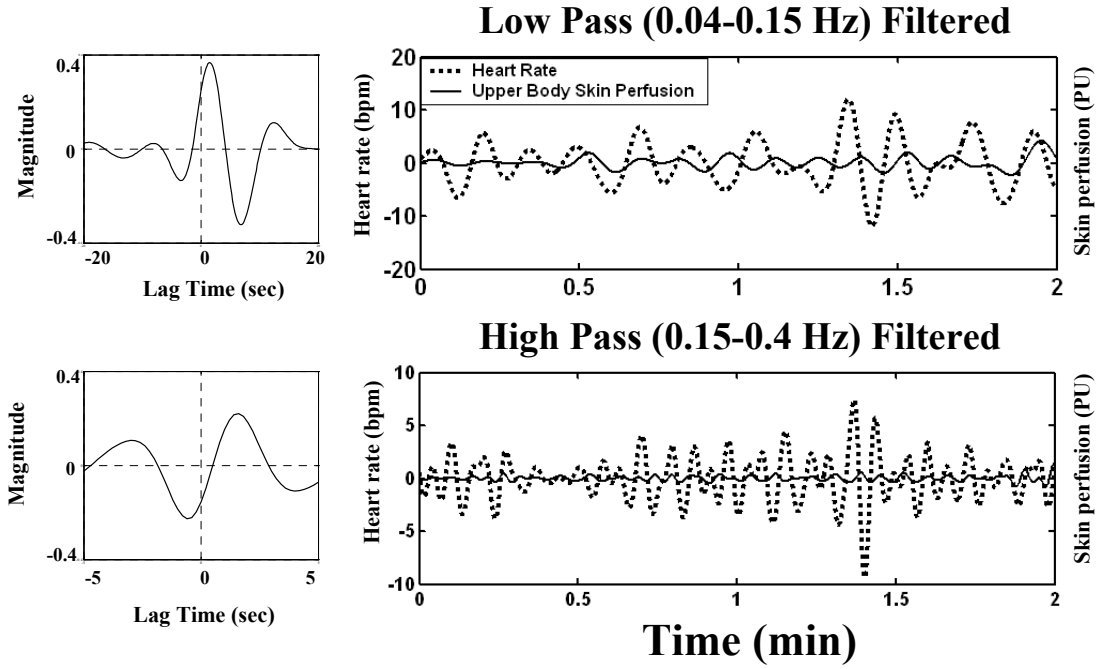


Figure 4.8a: Cross correlation of heart rate (HR) and upper body skin perfusion (SP1) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

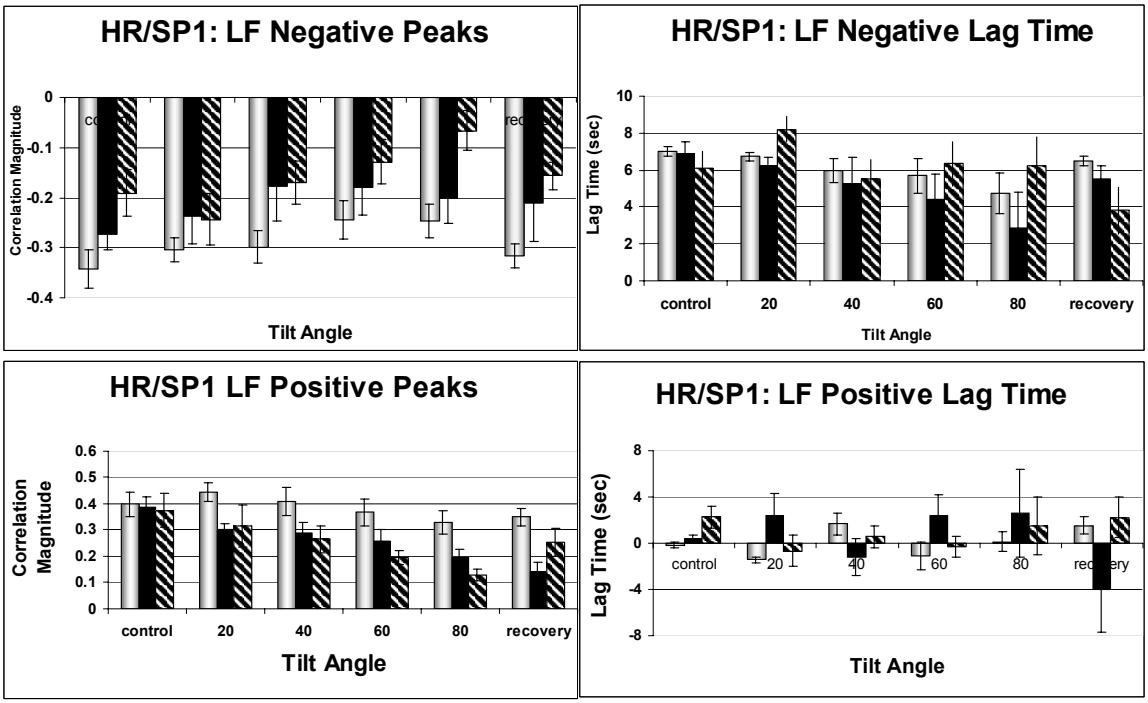


Figure 4.9: Arterial pressure and lower body skin perfusion raw data with mean subtracted (right) from two min of control and the cross correlation (left) of five min of arterial pressure and lower body skin perfusion in one AB subject.

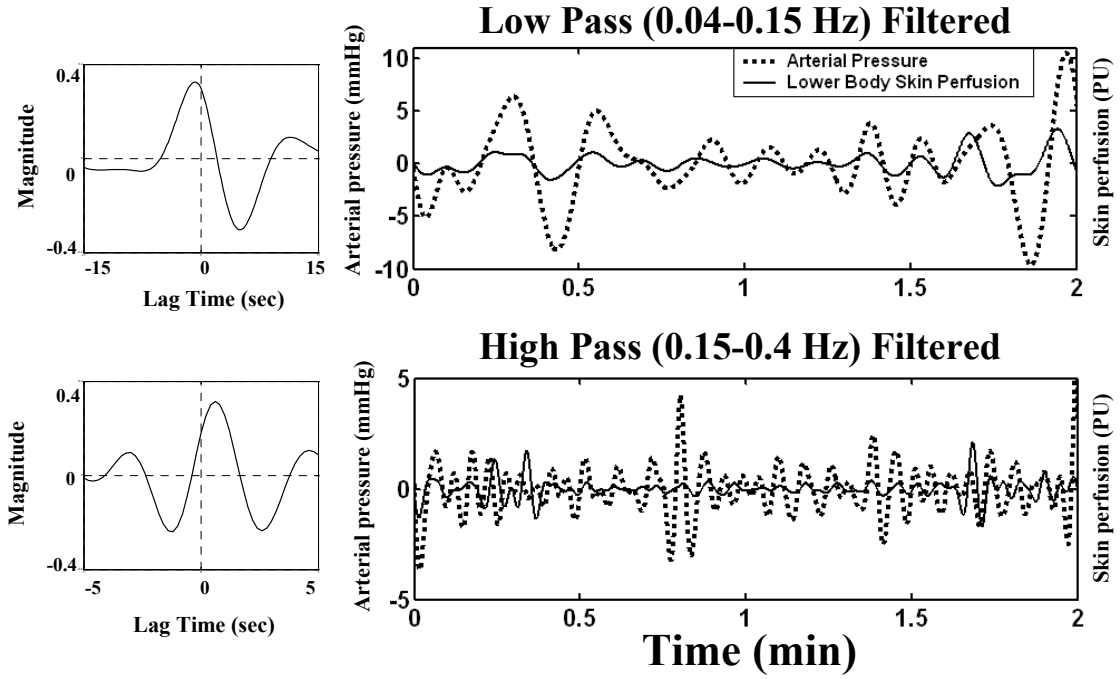


Figure 4.9a: Cross correlation of arterial pressure (AP) and lower body skin perfusion (SP2) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

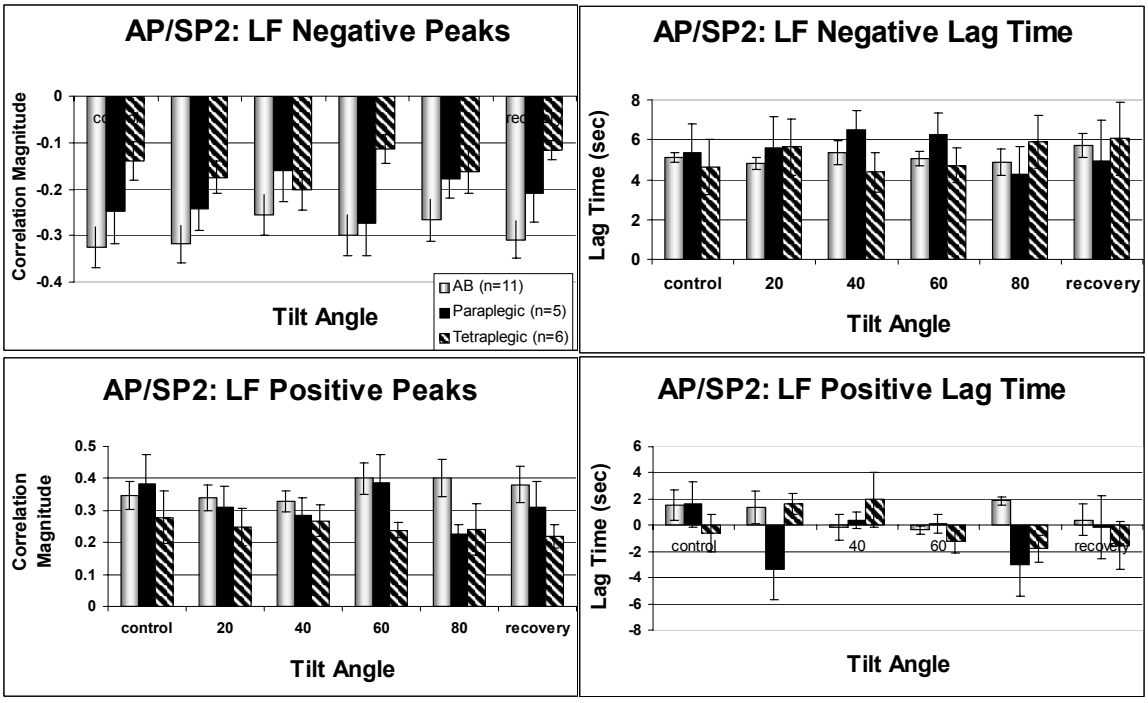


Figure 4.10: Heart rate and lower body skin perfusion raw data with mean subtracted from two min of control, shown for illustrative purposes (right) and the cross correlation of five min of heart rate and lower body skin perfusion in one AB subject (left).

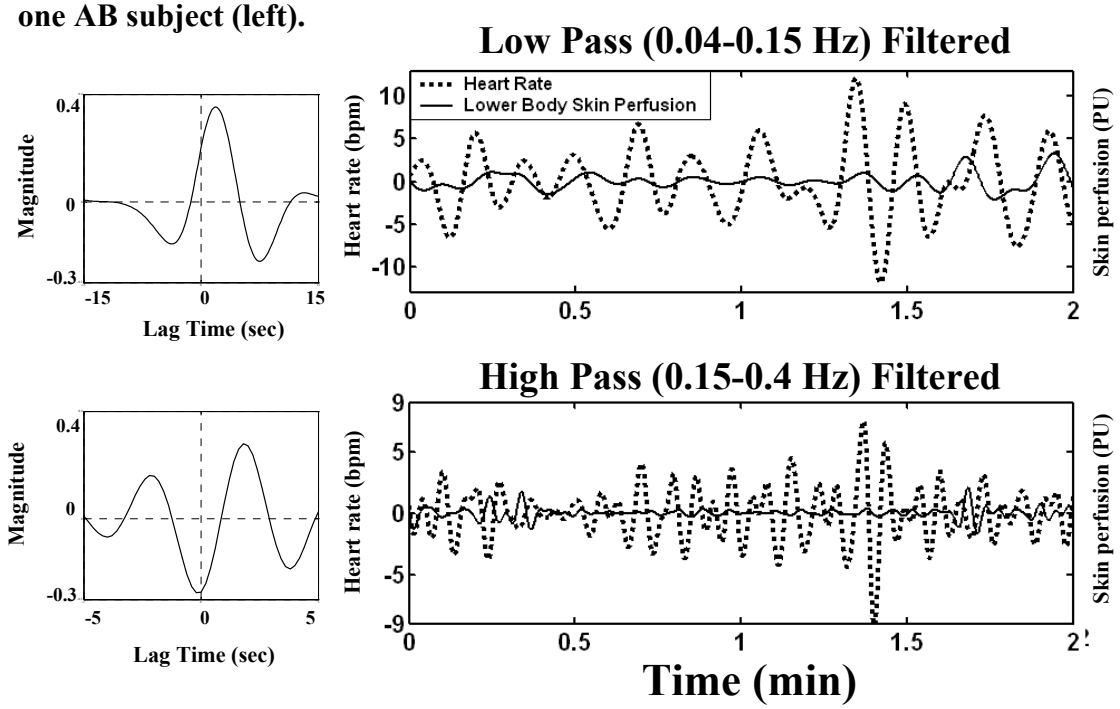


Figure 4.10a: Cross correlation of heart rate (HR) and lower body skin perfusion (SP2) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

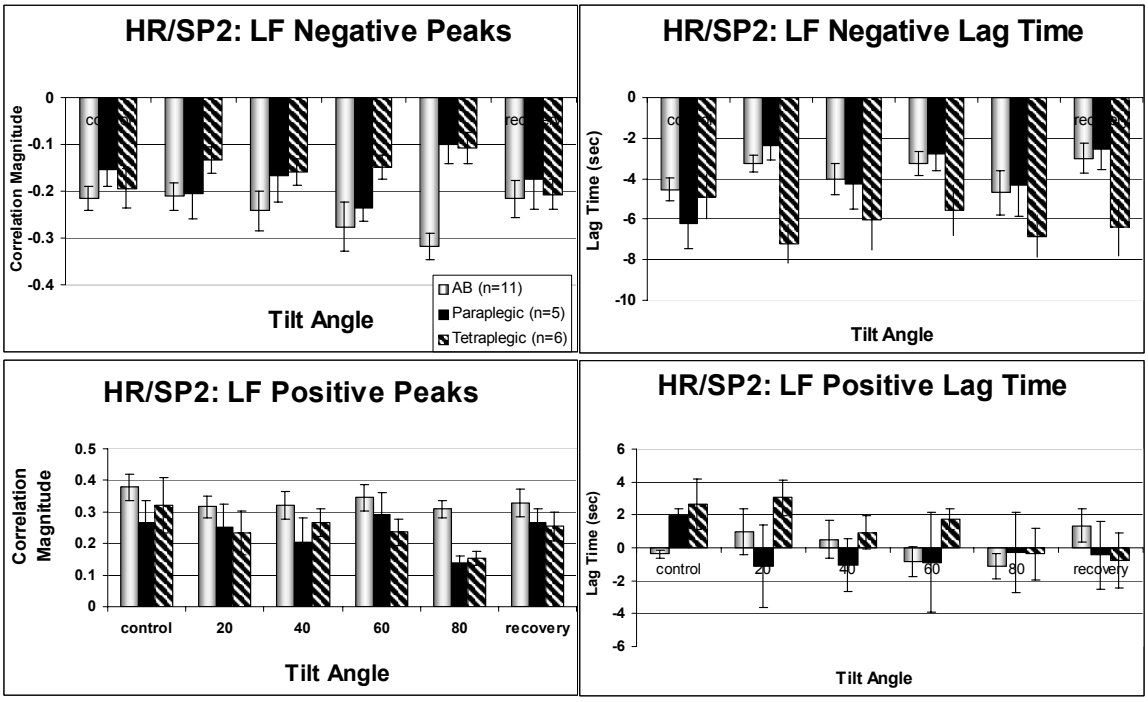


Figure 4.11: Upper and lower body skin perfusion raw data with mean subtracted from two min of control, shown for illustrative purposes (right) and the cross correlation of five min of upper and lower body skin perfusion in one AB subject (left).

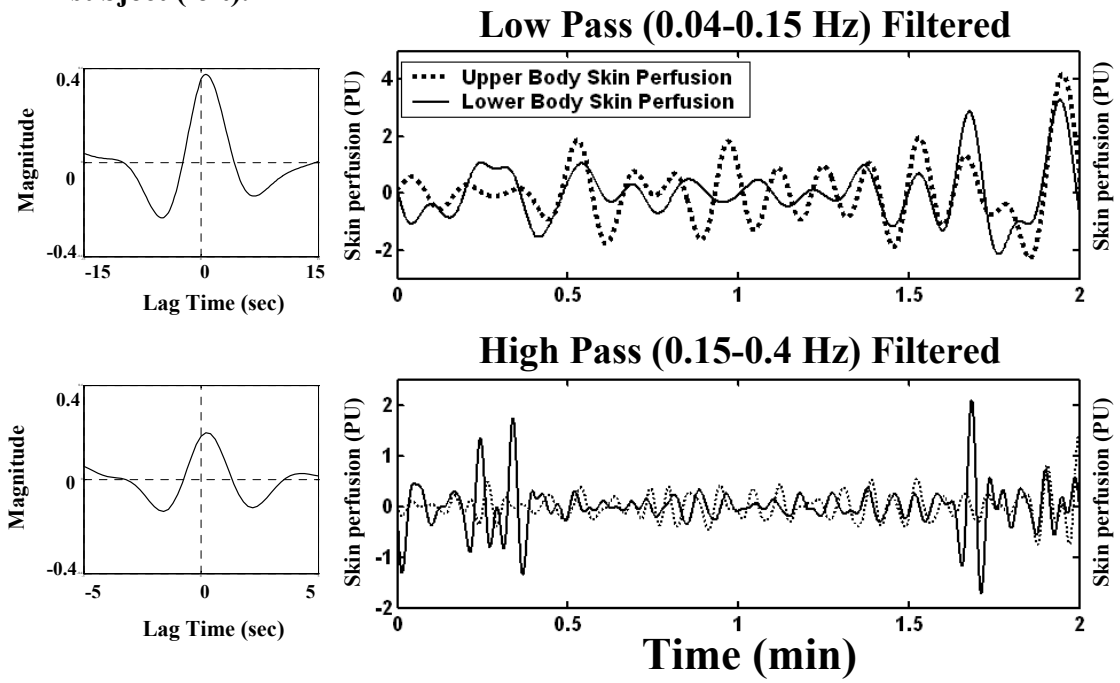


Figure 4.11a: Cross correlation of upper (SP1) and lower body skin perfusion (SP2) LF negative peaks (top left) and lag times (top right) and LF positive peaks (bottom left) and lag times (bottom right) for AB, paraplegic and tetraplegic groups.

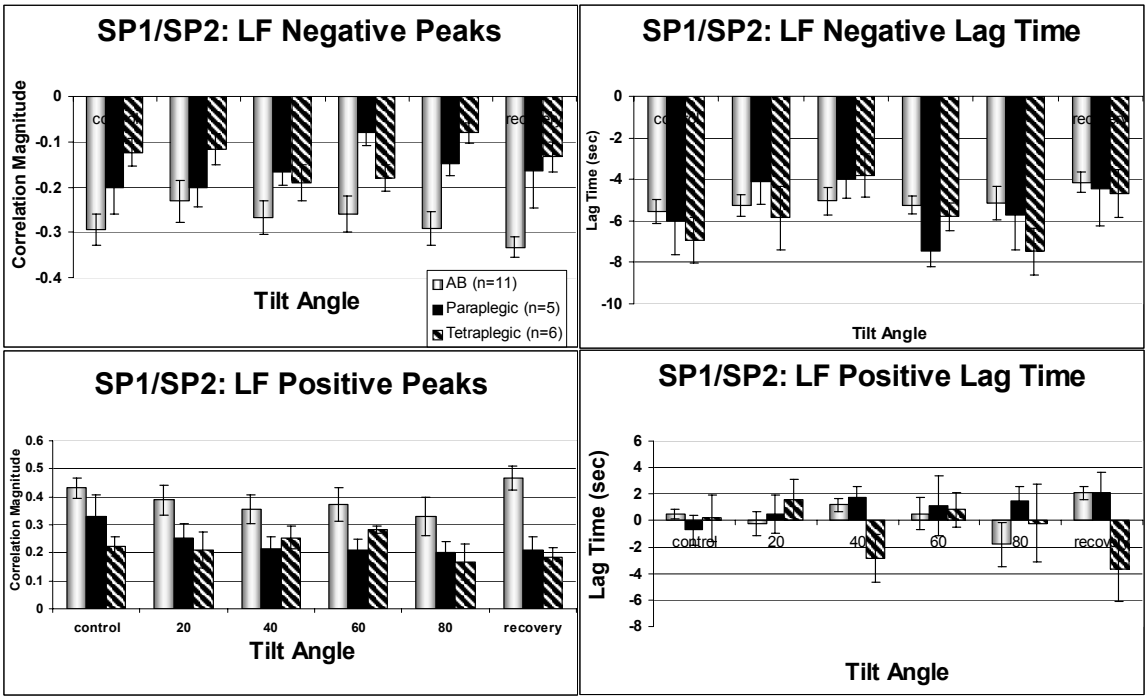


Fig 4.12: Tilt-Induced Rate of Change in Plasma Volume

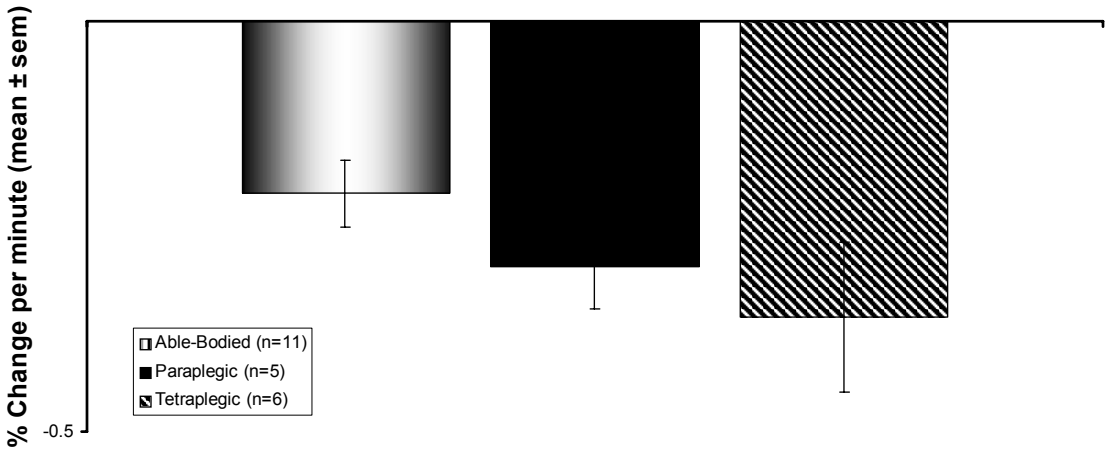


Figure 4.13: Index of fluid volume regulation (plasma renin activity) for AB (top) and SCI (bottom) subjects [*.*-- truncated at 25 for resolution purposes]

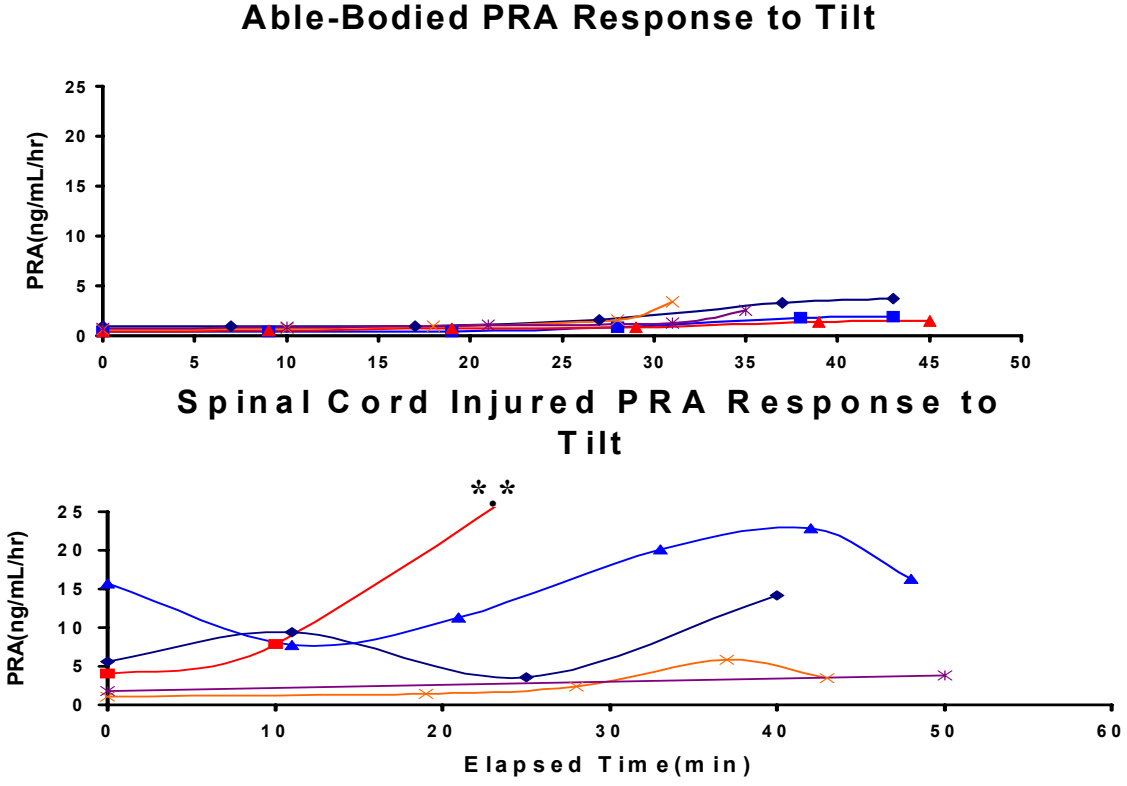


Figure 4.14: Epinephrine as an index of sympathetic activity for AB (top) and SCI (bottom) subjects

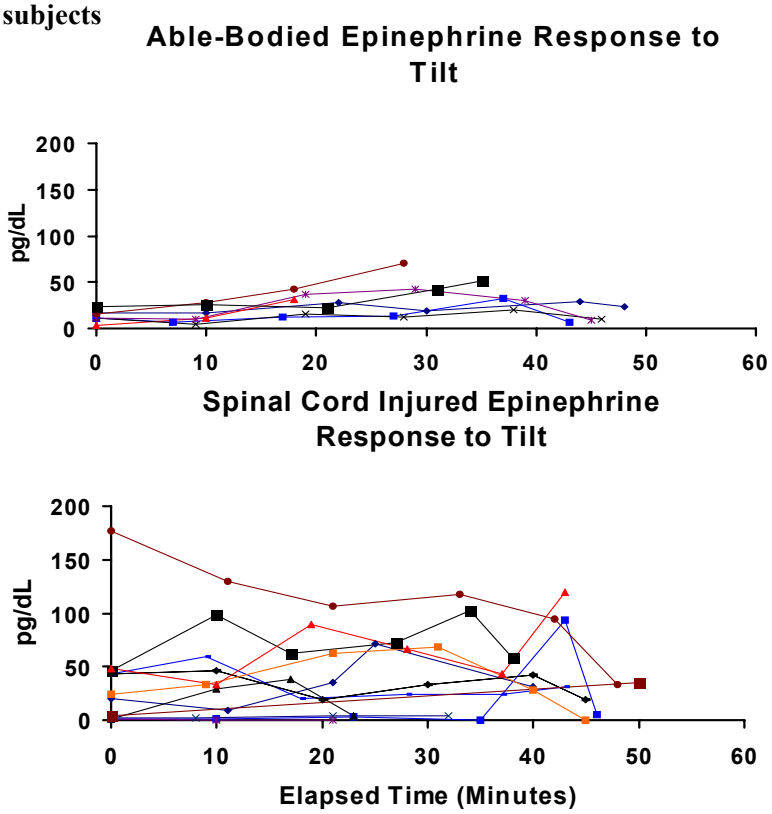
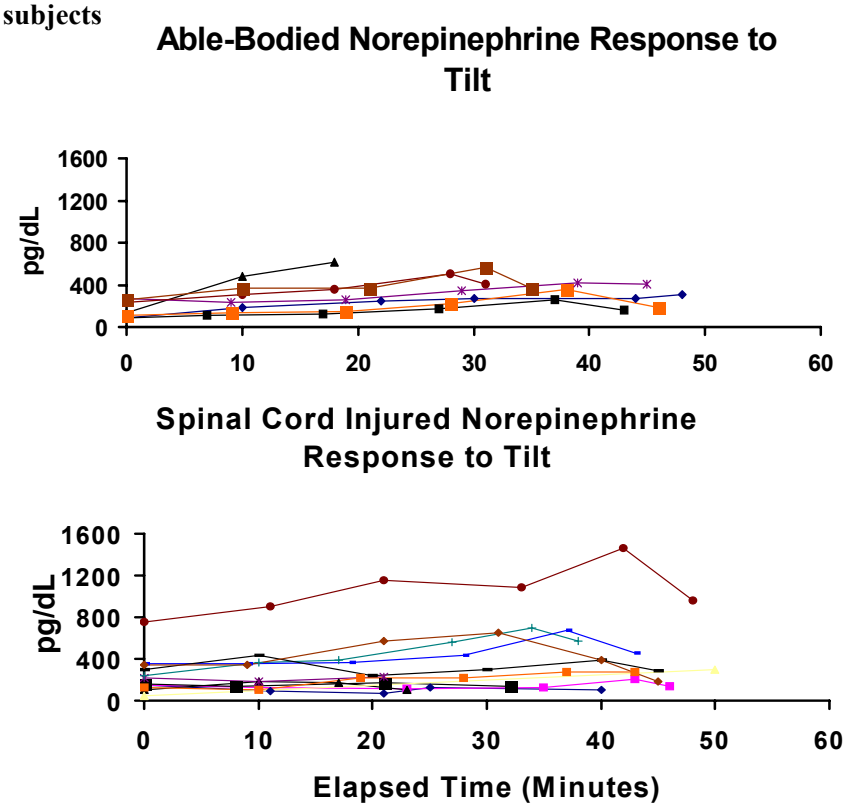


Figure 4.15: Norepinephrine as an index of sympathetic activity for AB (top) and SCI (bottom) subjects



Chapter Five

Discussion

The foundation of the discussion section focuses on whether or not the present research provides some useful information that helps to answer the central questions of our larger SCI research program: "Have we enhanced our knowledge and improved our understanding of cardiovascular function following SCI, mainly in the peripheral vasculature, so that classifications of autonomic function can be made in rehabilitation protocols and drug therapies to expedite post-SCI recovery? I have focused on a few variables that lend the most promise towards achieving these goals.

Mean value analysis in the time domain of arterial blood pressure, heart rate, cardiac output, stroke volume, total peripheral resistance, upper and lower body skin perfusion during control and HUT did not provide any significant discriminators among AB, paraplegic and tetraplegic groups. However, trends within and between groups were apparent in these variables, especially in arterial blood pressure during HUT. Analysis of these variables in the frequency domain via spectral power analysis was a step in the right direction as the differences among the three groups were more apparent. First of all, patients with tetraplegia and paraplegia failed to show increased SNS activity, based on arterial pressure and heart rate variability spectral analysis, during head-up-tilt (HUT), in contrast to able-bodied subjects. For example, spectral power of arterial blood pressure in the LF region was greatly reduced in paraplegic and tetraplegic subjects during supine control, all levels of HUT and recovery (figure 4.2a, table 4.2, Appendix E). Arterial pressure oscillations in the 0.1 Hz frequency region (also known as the LF region) are indicative of sympathetic control. This paves the way for the application of relating 0.1 Hz oscillations in arterial pressure to sympathetic activity and autonomic function in AB subjects and more importantly subjects who have sustained SCI. Results from spectral analysis lead me to believe that these oscillations in arterial pressure are a good precursor to determine level of SCI and degree of autonomic function (figure 5.1) [More paraplegic and tetraplegic subjects will be required to further separate the three groups]. The increase in LF spectral power of arterial pressure, with increasing levels of HUT, in AB subjects was expected due to sympathetic mediated vasoconstriction to the peripheral vasculature. I also expected to see paraplegic subjects maintain some sympathetic induced vasoconstriction (this was observed during control, 20^{o} and 40^{o} low levels of HUT, but not the higher levels of HUT and recovery)

due to the nature of their injury. In tetraplegic subjects I observed little to no sympathetic activity due to the lack of sympathetic innervation to the heart and peripheral vasculature (in tetraplegic subjects, sympathetic activity, marked by 0.1 oscillations, started very low during supine control and decreased with increasing levels of HUT). In studies by others in which SNS was assessed by spectral analysis of blood pressure (Houtman 2000, Pagani 1986, de Boer 1987) or heart rate variability (Houtman 2000, Malliani 1991, Bootsma 1994, Yamamoto 1991) SNS activity assessed in this way during supine rest was reported to be lower in patients with tetraplegia and paraplegia than in able-bodied (AB) subjects. The observations from the present study are consistent with these arterial pressure and heart rate variability findings of others. In the present study, SNS activity increased in AB subjects, but decreased in paraplegic and tetraplegic subjects with increasing levels of HUT which is consistent with the work of other researchers (Figoni 1984).

Secondly, spectral power of lower body skin perfusion analyzed in the LF region is an additional way to discriminate among the three groups. I have found a reduction of 0.1 Hz skin perfusion fluctuations during control and HUT below the level of injury (lower body) in paraplegic and tetraplegic subjects when compared to AB subjects. Skin perfusion fluctuations in the 0.1 Hz frequency region (also known as the LF region) are due to the activity of the sympathetic nervous system (Bernardi 1997). Reduction of skin blood flow oscillations below the level of injury are indicative of a loss of sympathetic control of the arteriolar tone and peripheral vasculature. Paraplegic and tetraplegic subjects exhibit significant decreases (when compared to AB) of skin perfusion oscillations in the LF region for supine control, all levels of HUT and recovery. Thus an important question to ask is: Are these LF oscillations in lower body skin perfusion a good way to separate AB, paraplegic and tetraplegic groups (in order to classify autonomic function)? In fact, lower body skin blood flow appears to be at least as good of an approach as arterial pressure to investigate level of sympathetic activity, autonomic function and level of SCI (figure 5.2). However, caution must be exercised because of the limited number of paraplegic and tetraplegic subjects studied. Nonetheless, I expected AB subjects to have higher LF spectral power in skin blood flow in the lower body than the paraplegic and tetraplegic subjects during supine control, all levels of HUT and recovery. All three groups exhibit decreased spectral power of lower body skin blood flow with increasing levels of HUT. A few possible reasons could exist for this phenomenon: lower body skin perfusion must

decrease to maintain consciousness and venous pooling could lower the pressure gradient thus decreasing blood flow and it's accompanying 0.1 Hz oscillations in the lower body. Muscle metabolic needs in SCI subjects have decreased in the lower body, thus creating an environment that doesn't require a great deal of nutrient, oxygen, and blood flow supply, however these decreased muscle demands do not have an effect the skin. Decreased oscillations in the lower body of SCI individuals could be attributed to the cut in the sympathetic chain, the chain that innervates skin arterioles causing them to vasoconstrict. AB subjects, however, still need a large amount of skin blood flow because the tissue requires a nutrient and oxygen supply. Another topic worthy of discussion is the mechanical nature of the vasculature. Vessel walls have parameters equivalent to an electrical RLC circuit (consists of resistance, inductance and capacitance). These parameters can change at any time due to local, neural and hormonal influences and can have a direct effect on arteriolar tone, thus affecting capillary skin blood flow and skin perfusion at the forearm and shin. Different parts of the skin have different capacitances, resistances and inductances.

Cross correlation analysis in the low frequency region of heart rate/upper body skin perfusion, arterial pressure/upper body skin perfusion, arterial pressure/lower body skin perfusion and upper/lower body skin perfusion provided additional discriminates among the three groups, while showing the coordination or lack of coordination between cardiac and peripheral vascular function. The negative cross correlation peak of heart rate and upper body skin perfusion during control is a significant ($p<0.05$) discriminator between the three groups: AB (-0.35) > paraplegic (-0.25) > tetraplegic (-0.18). The negative cross correlation peak of arterial pressure and upper body skin perfusion during control is a significant ($p<0.05$) discriminator between the three groups: AB (-0.4) > paraplegic (-0.32) > tetraplegic (-0.2). The negative cross correlation peak of arterial pressure and lower body skin perfusion during control is significant ($p<0.05$) discriminator between the three groups: AB (-0.35) > paraplegic (-0.25) > tetraplegic (-0.15). The negative and positive cross correlation peaks of upper and lower body skin perfusion during control are significant ($p<0.05$) discriminators between the three groups. All of the above cross correlation negative peaks are indicative of negative feedback and in paraplegic and tetraplegic subjects there is diminished control (compared to AB) of blood vessels in the upper (tetraplegic) and lower (paraplegic and tetraplegic) body. The above cross correlation results demonstrate a lack of central or neural control in paraplegic and tetrapleigc

subjects. It is possible that heart rate and arterial blood pressure changes can occur without those same changes taking place in skin blood flow (i.e. the predominantly centrally controlled system in AB oscillates together, whereas the predominantly locally controlled system in paraplegic and tetraplegic doesn't oscillate together).

Possible mechanical and neural regulatory control mechanisms have been covered, but what is the effect of catecholamines and hormones on heart rate, arterial pressure and skin blood flow? Indexes of sympathetic activity, epinephrine and norepinephrine, have increased circulating levels in SCI subjects, compared to AB, during supine control. This could be attributed to a possible end organ spillover or many receptor sites are saturated or less sensitive to the circulating hormones. Erratic behavior of epinephrine and norepinephrine with increasing levels of HUT is indicative of a receptor site issue because there is a large concentration level but no response (i.e. no vasoconstriction). Epinephrine levels could also increase due to inhibition of release at the adrenal medulla, whereas norepinephrine levels could increase due to organ spillover Other researchers, Rowell et al, believe that plasma norepinehrine and epinephrine levels do not increase during HUT unless sympathetic nerves are activated by local spinal sympathetic reflexes caused by skeletal muscle spasms or urinary bladder contractions (Rowell 1993). Our data support the Rowell hypothesis in that our SCI subjects do not exhibit increased levels of epinephrine during orthostatic stress. In addition, SCI subjects demonstrated significantly elevated concentrations of epinephrine during control and HUT when compared to AB subjects. Norepinephrine levels in SCI subjects were higher during control, when compared to AB, however SCI subjects did exhibit a tendency to control release of norepinephrine in response to HUT.

Other potential invasive measures of level of injury could lie in hormonal analysis, however these measures would not be as direct of a technique as the ones stated above. As observed by other researchers, supine tetraplegics have low tonic sympathetic activity, however PRA tends to be above normal (Rowell 1993). PRA is an attempt to regulate fluid volume and increased circulating levels indicate that fluid has been lost or shifted out of the vasculature and the body goes into "conserve" mode. With increasing levels of HUT, paraplegic and tetraplegic subjects filter more plasma volume out of the vasculature (than do AB subjects) indicating "leaky pipes". Compensation for these leaky pipes is an increase in the release of PRA as the body makes an attempt to retain as much fluid as possible. The large variability in all hormonal

analysis in SCI subjects indicate that more subjects will be required in the paraplegic and tetraplegic groups in order to achieve statistical significance with these variables.

To summarize, low frequency spectral analysis of arterial pressure and lower body skin perfusion are equally important discriminators between the three groups, followed by cross correlation analysis of arterial pressure/upper and lower body skin perfusion, upper/lower body skin perfusion and heart rate/upper body skin perfusion. Hormonal analysis of epinephrine, norepinephrine, measures of fluid volume shifts (hematocrit and total proteins) and measures of fluid volume regulation (PRA) are invasive methods that discriminate among the three groups.

Limitations of Study: Medications that subjects were taking (Appendix G), motion artifacts and the thermal environment in which the study was conducted are additional topics worthy of discussion because they could affect data collection. Many subjects were taking medications to treat hypotension, bradycardia, hypertension, tachycardia and muscle spasms. These medications are necessary for the health of the subject and could possibly have an affect on data collection. Skin perfusion acquired via the Perimed is susceptible to motion artifacts caused by movement of the fiber optic probe, displacement of probe from the skin and movement of the subject. These anomalies were removed to the best of abilities, but there is some chance that a motion artifact could have gone unnoticed. Skin is also known to have a thermal regulatory component that acts in the very low frequency region in the range of 0.01-0.03 Hz. Because of this thermal component, our protocol, at times, is vulnerable. For the most part, the environment in which the study is conducted is thermally neutral and this does not have a great effect on data collection, however it is worthy of mention.

The microcirculatory network of the skin, like other body tissues, continuously exhibits rhythmic changes in diameter and flow (Bernardi 1997). The fundamental mechanism of these fluctuations is not yet clarified, particularly for the skin microvessels. Some researchers hypothesized that skin blood flow is exclusively under local control, whereas others have suggested both general and baroreflex induced changes. Skin blood flow decrease induced by HUT is a good index of arterioloar tone, which is regulated by sympathetic nerve traffic (Bernardi 1989). However, other mechanisms mediate changes in skin blood flow, such as local autoregulatory mechanisms, local temperature, the status of arteriovenular shunts and venous reflexes (Bernari 1989). There is evidence of both, local (Rowell 1993) and central (Rowell 1993) control of skin blood flow. Although, there is evidence of neural and local control of skin

blood flow, the present study has proven that a lack of sympathetic innervation to skin arterioles is a factor in the decreased amount of 0.1 Hz oscillations which lends a good way to separate AB, paraplegic and tetraplegic subjects.

Figure 5.1: Assessing level of injury and degree of autonomic function using low frequency spectral analysis of arterial blood pressure as a determinant during supine control and 80° HUT.

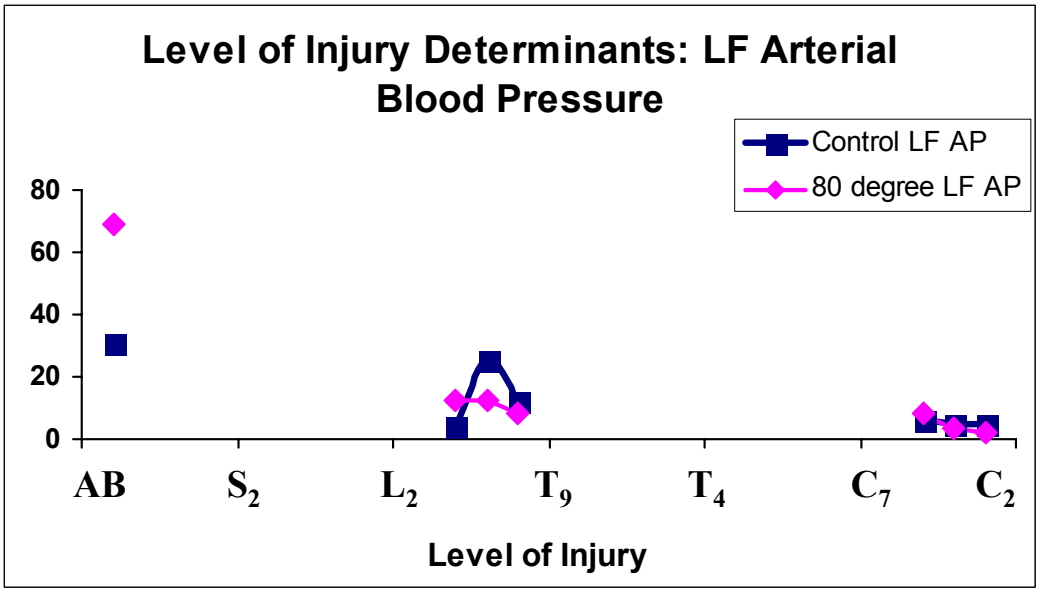
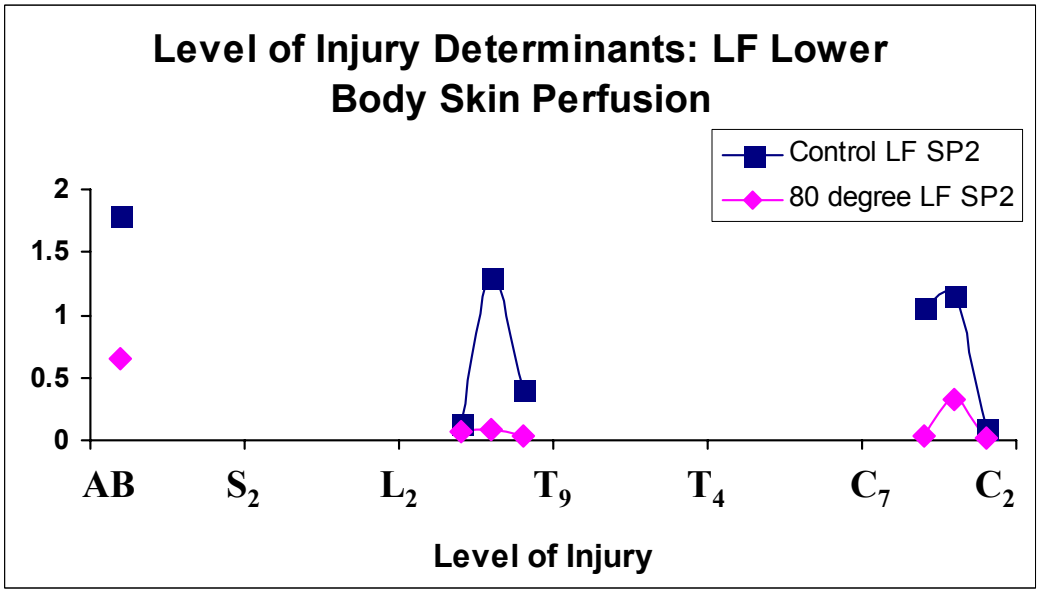


Figure 5.2: Assessing level of injury and degree of autonomic function using low frequency spectral analysis of lower body skin perfusion as a determinant during supine control and 80° HUT.



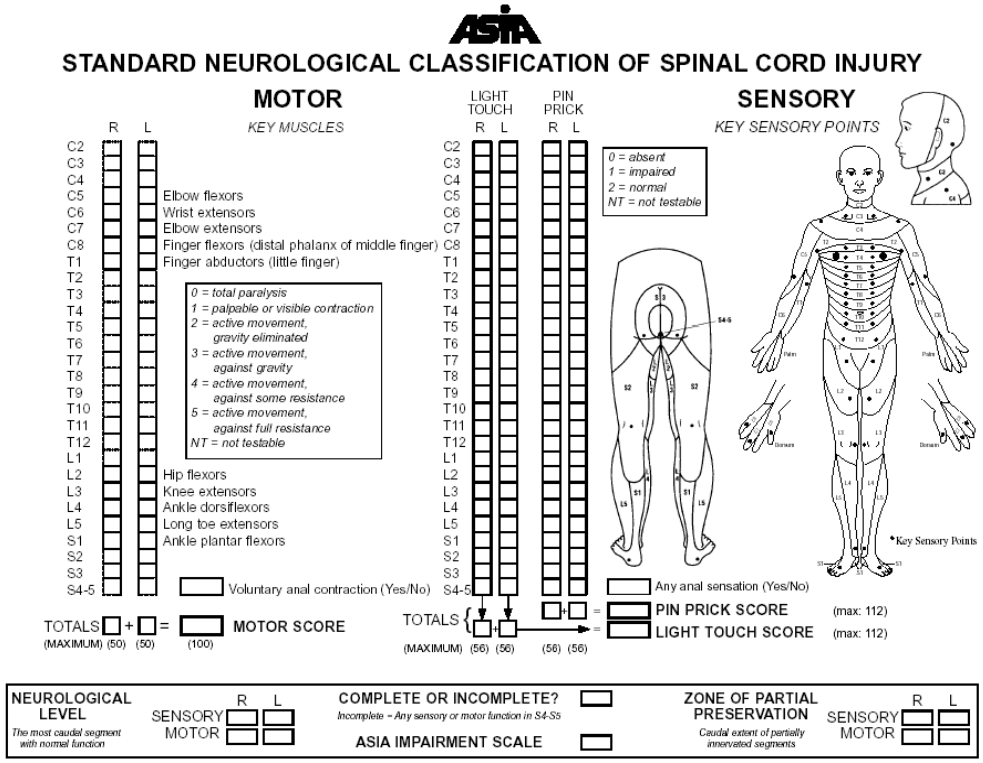
Chapter Six

Conclusion

The present study primarily utilized noninvasively acquired, easily accessible variables that may have promise as indicators of autonomic activity for assessing the level of autonomic injury and recovery of visceral control following SCI. Peripheral vascular function was analyzed using power spectral density estimates of upper and lower body skin blood flow. Low frequency (0.1 Hz) oscillations in lower body skin blood flow proved to be a good discriminator between the three groups as our findings indicate a high occurrence of sympathetic impairment of skin vascular control in paraplegic and tetraplegic subjects. Arterial blood pressure analyzed in the low frequency range also proved to be a good discriminator between the three groups, since our results show decreased 0.1 Hz oscillations in arterial pressure in paraplegic and tetraplegic subjects. These two variables are very good potential candidates to use in a clinical setting in order to assess level of autonomic function in persons with spinal cord injury. Unfortunately, more subjects will be required to produce sufficient significance, however I have provided substantial evidence that low frequency spectral analysis of arterial blood pressure and lower body skin perfusion are promising indicators of autonomic function and level of spinal cord injury.

Additional potential invasive measures of vascular function, with the possibility to determine the level of SCI, lie within hormonal analysis. Paraplegic and tetraplegic subjects filtered more fluid volume out of the vasculature than did AB subjects during HUT (shown by increases in hematocrit and total proteins with HUT). Paraplegic and tetraplegic subjects had increased circulating PRA levels compared to AB during control and HUT.

Appendix A: ASIA scale used to assess motor and sensory function



Appendix C: Additional Instrumentation Background

Portapres and Penaz Principle

The portrapres uses the volume-clamp method, originally described by the Czech physiologist Jan Penaz, to measure blood pressure in the finger. In this method the diameter of an artery under a cuff wrapped around the finger is kept constant (clamped), in spite of the changes in arterial pressure during each heartbeat. Changes in arterial diameter are detected by means of an infrared photo-plethysmograph and opposed by a fast pressure servo controller that changes pressure in an inflatable air bladder, both of which are built into the finger cuff. The system is used to define and maintain the correct diameter at which the finger artery is clamped.

The main components of the finger cuff (figure C1) are an inflatable air bladder and a plethysmograph consisting of a light source and a light detector. The light source is a light emitting diode (LED) emitting infrared light and the light detector in the finger cuff is an infrared photodiode. The air bladder is connected to the Portapres frontend unit via an air hose and both components of the infrared plethysmograph via a cuff cable (figure C2). A blood pressure waveform is created from a signal coming from a finger infrared plethysmograph when the pressure in the finger cuff is kept constant. A sudden rise in finger intra-arterial pressure during systole causes an increase in arterial diameter, which is detected as an increase in light absorption and thus as a decrease in the signal detected by the plethysmograph. During the diastolic phase of a heartbeat, when blood pressure declines gradually, the blood is expelled from the artery and consequently the amount of light detected by the photodiode will increase again (Portapres Model-2 User's Guide).

The relationship between changes in arterial diameter and changes in intra-arterial pressure depends on the mechanical properties of the artery. When the artery is very compliant (low rigidity) diameter changes are relatively large, whereas diameter changes in stiff arteries are small. It is a well-known fact that arterial compliance depends on the transmural pressure, the pressure difference between the pressure inside the artery and the pressure of the surrounding tissue. At high transmural pressures, when cuff pressure is low, the arterial diameter is relatively large. Therefore, the artery is distended and becomes stiff causing small diameter changes. When transmural pressure is low, when cuff pressure is high with respect to mean blood pressure, the artery is almost collapsed and diameter changes will be small. At zero transmural

pressure, when the pressure inside the artery equals the pressure in the finger cuff, diameter changes are largest Portapres Model-2 User's Guide).

To compensate for the hydrostatic head caused by the distance from the instrumented finger to the heart, the built-in Portapres height-correction adjustment feature was used. Keeping the transducer ending and reference ending of the height correction unit at the same level and pressing the "height" key performed the height nulling procedure. After doing this the reference ending was placed at heart level and the transducer ending was placed on the finger cuff.

Thoracic Electrical Bioimpedance Cardiac Output

TEBCO uses four pairs of TEB electrodes and leads (two black and white pairs for the neck and two red and green pairs for the thorax). Before placing any TEB leads, the skin area is to be prepared with alcohol to remove skin oils and to assure good adhesion and proper electrical performance of the electrodes. In TEB, a patient's thorax is utilized as the impedance transducer and the eight electrodes (four electrode pairs with 5 cm, 2", nipple-to-nipple distance) used with EXT-TEBCO's application, provide the electrical connections to the transducer.

The sensing electrodes (white and red pair) should always be placed on the patient first. The white electrode pair, located at the intersection of frontal plane and the line of the root of the neck (the plane of the root of the neck is sloping down, toward the sternum) on each side of the neck (figure C3). The red electrode pair, located at each midaxillary line at the xiphoid process level (figure C3). The black and green electrodes are positioned above and below each corresponding sensing electrode. These electrodes are the source and sink of the TEB measurement current and must meet TEB requirements for the skin-to-electrode impedance. The spacing between each sensing and measurement current electrode is critical and must be maintained at 5 cm, 2", nipple-to-nipple.

In TEB, the thorax is utilized as an impedance transducer. A high frequency measurement current of a constant magnitude is introduced between the black and green pairs of electrodes and flows through the thorax approximately in a direction parallel with the spine. A HF voltage, which develops across the impedance of the thorax, is differentially sensed between the white and red electrode pairs. This voltage is directly proportional to the impedance of the thorax (EXT-TEBCO Operator's Manual).

Perimed and Laser Doppler Flowmetry

Quantitative measurement of skin blood flow continues to be a problem. Presently, there is no way to determine total skin blood flow. Measurements of flow, regardless of the organ, are indirect (except timed collection of volume in a calibrated container: beaker and stopwatch), being derived from variables that are related to flow. Some measurements provide estimates of absolute flow, whereas others can only provide information about relative changes in flow. However, none give quantitative measurements of skin blood flow in absolute units. Changes in regional skin blood flow have been assessed from changes in skin temperature, thermal conductivity, rates of heat loss by calorimetry, absorption of light by red cells and transilluminated skin, light-scattering techniques, and rates of isotope clearance. Laser-Doppler flowmetry has become especially useful because it provides reasonable estimates of flow changes in any cutaneous region (Johnson 1984).

Laser Doppler technique is a simple method for monitoring microvascular perfusion. A narrow beam of laser-generated monochromatic light is applied to the surface of the tissue being studied via a fiber optic probe. Back-scattered light (caused by moving blood cells which undergo a slight change in wavelength [Doppler shift]) is picked up by sensitive photodetectors via a separate fiber in the probe (Figure C4). The magnitude & frequency distribution of the shifted light is related to the number & velocity of moving cells, no matter what their direction of movement (Perimed PF2 Operator's Manual):

Skin perfusion (PU) = Concentration of moving cells (CU) * Velocity of moving cells (VU)

Skin perfusion is defined by the above equation in arbitrary perfusion units, which is the product of the concentration of moving cells in arbitrary concentration units and the velocity of those moving cells in arbitrary velocity units.

Appendix D: Matlab Functions (MATLAB 6.5 Help Menu)

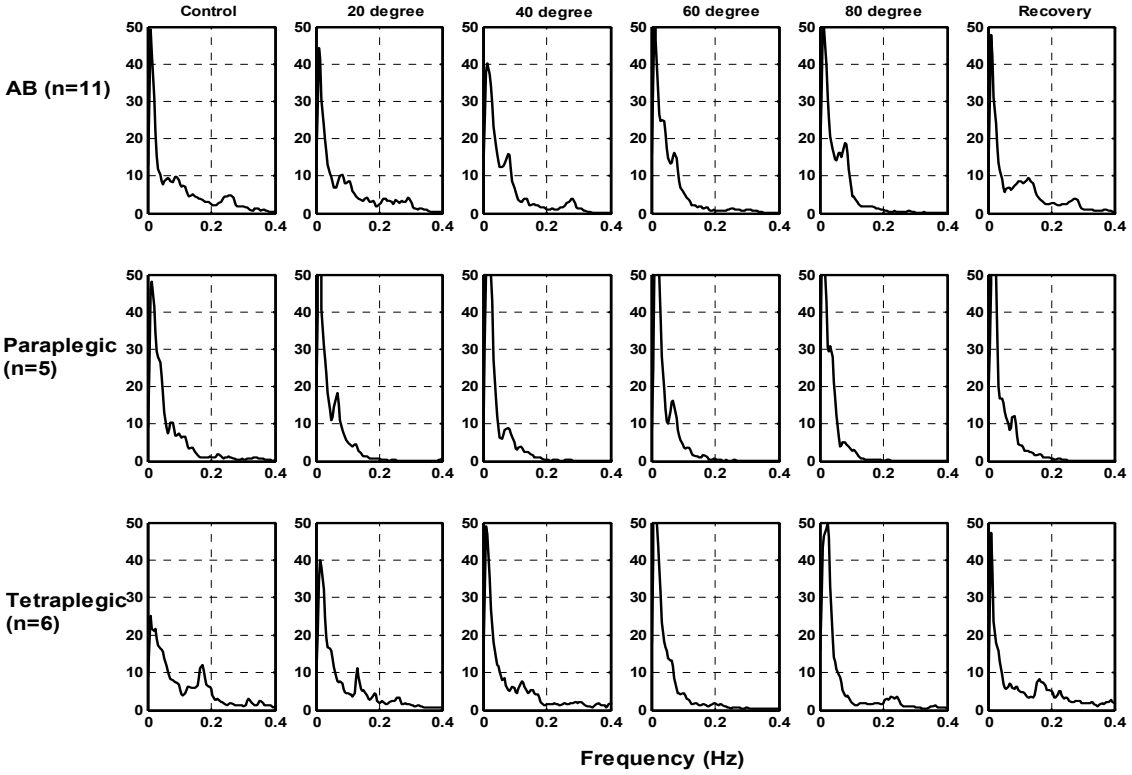
FIR1 filter design using the window method.
B = FIR1(N,Wn) designs an N'th order lowpass FIR digital filter
and returns the filter coefficients in length N+1 vector B.
The cut-off frequency Wn must be between 0 < Wn < 1.0, with 1.0
corresponding to half the sample rate (MATLAB 6.5 Help Menu)
-Applied fir1 as: b=fir1(100,[(2*0.5)/5]); Initializing a 100th order LPF and setting the LPF coefficient to 0.5Hz

FILTFILT Zero-phase forward and reverse digital filtering.
Y = FILTFILT(B, A, X) filters the data in vector X with the filter described
by vectors A and B to create the filtered data Y. The filter is described
by the difference equation:

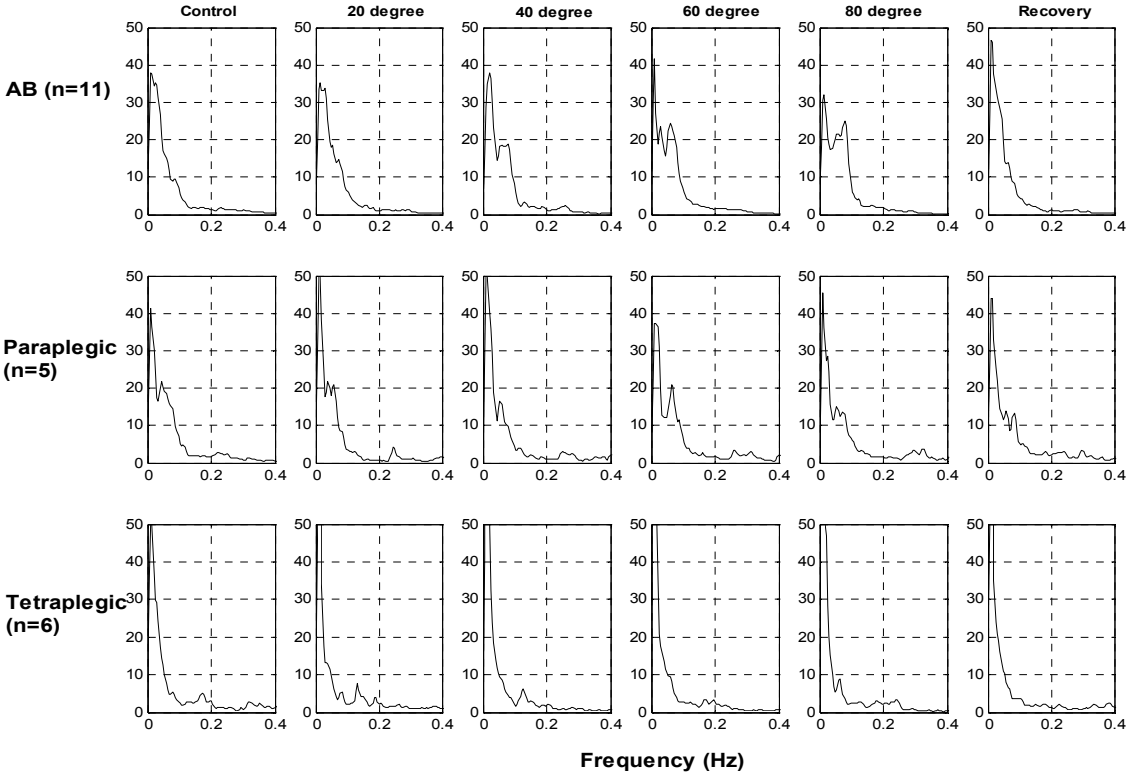
y(n) = b(1)*x(n) + b(2)*x(n-1) + ... + b(nb+1)*x(n-nb)
- a(2)*y(n-1) - ... - a(na+1)*y(n-na)

After filtering in the forward direction, the filtered sequence is then
reversed and run back through the filter; Y is the time reverse of the
output of the second filtering operation. The result has precisely zero
phase distortion and magnitude modified by the square of the filter's
magnitude response. Care is taken to minimize startup and ending
transients by matching initial conditions (MATLAB 6.5 Help Menu).
Applied filtfilt as: y = filtfilt(b,1,signal); Low Pass Filtering the data using a LPF cutoff coefficient of 0.5

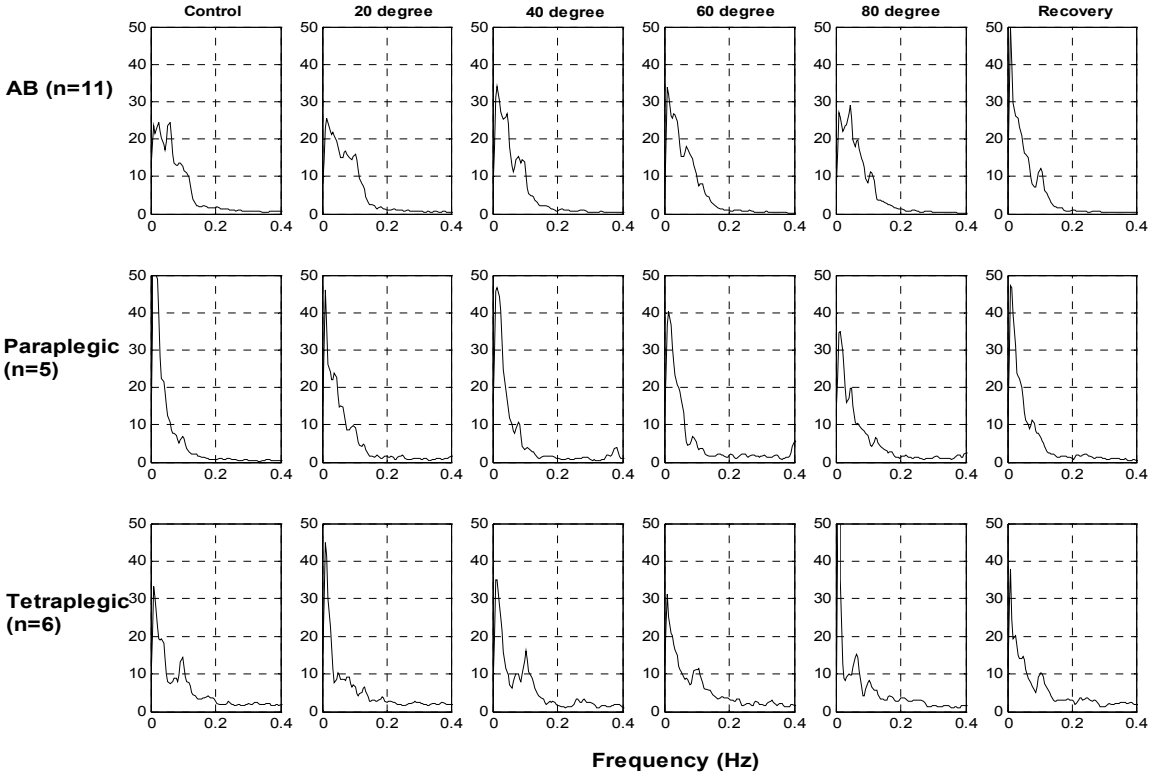
Appendix E: Heart rate averaged spectral power for AB, Paraplegic & Tetraplegic



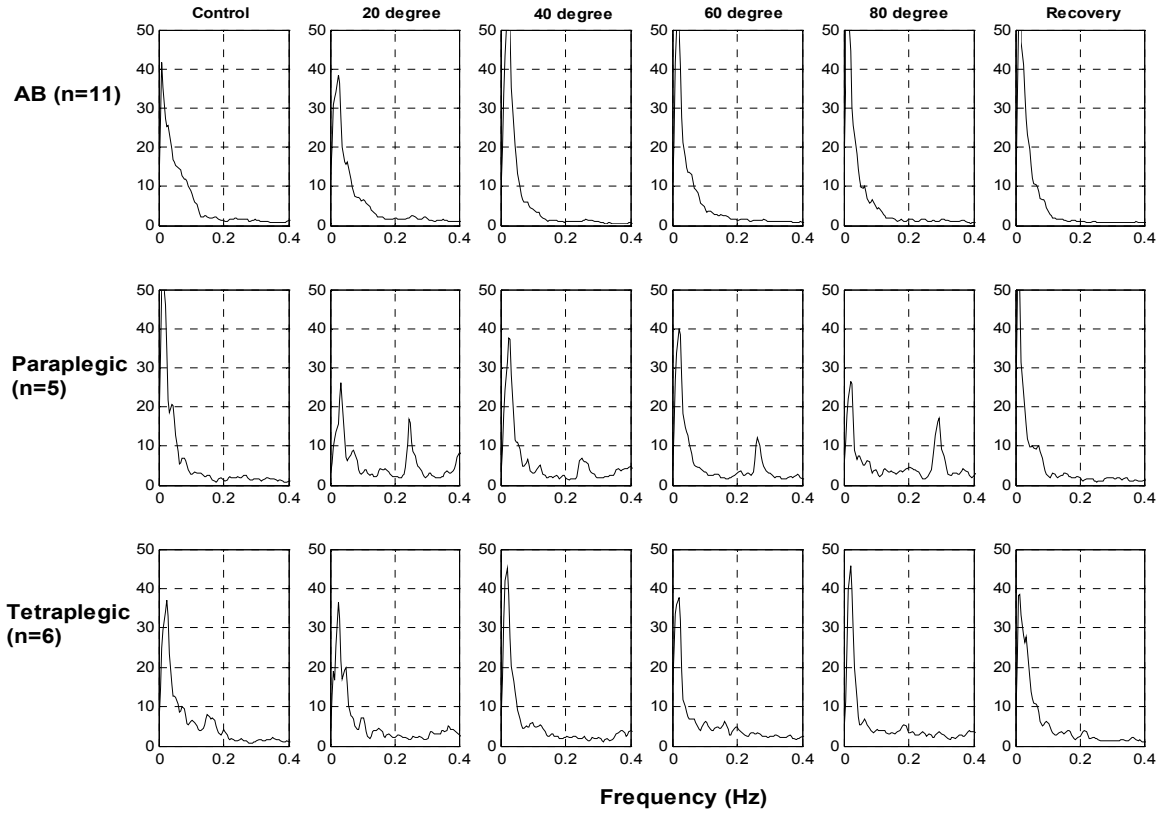
Appendix E: Arterial blood pressure averaged spectral power for AB, Paraplegic & Tetraplegic



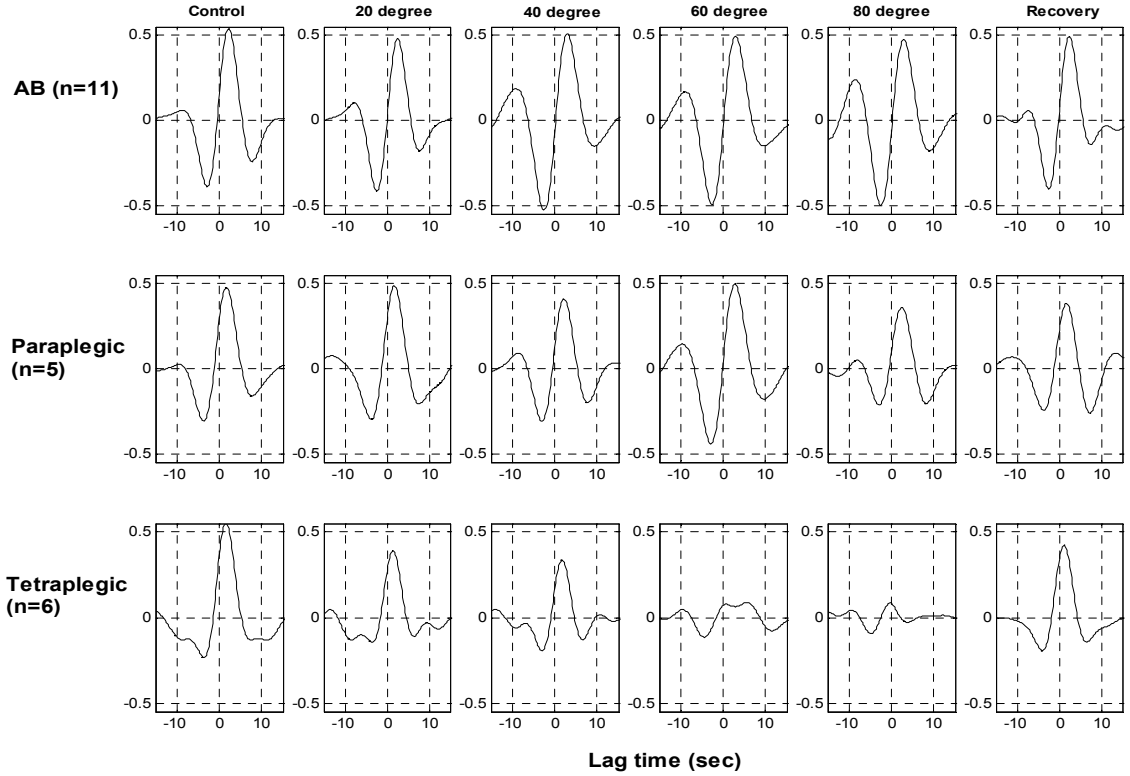
Appendix E: Upper body skin perfusion averaged spectral power for AB, Paraplegic & Tetraplegic



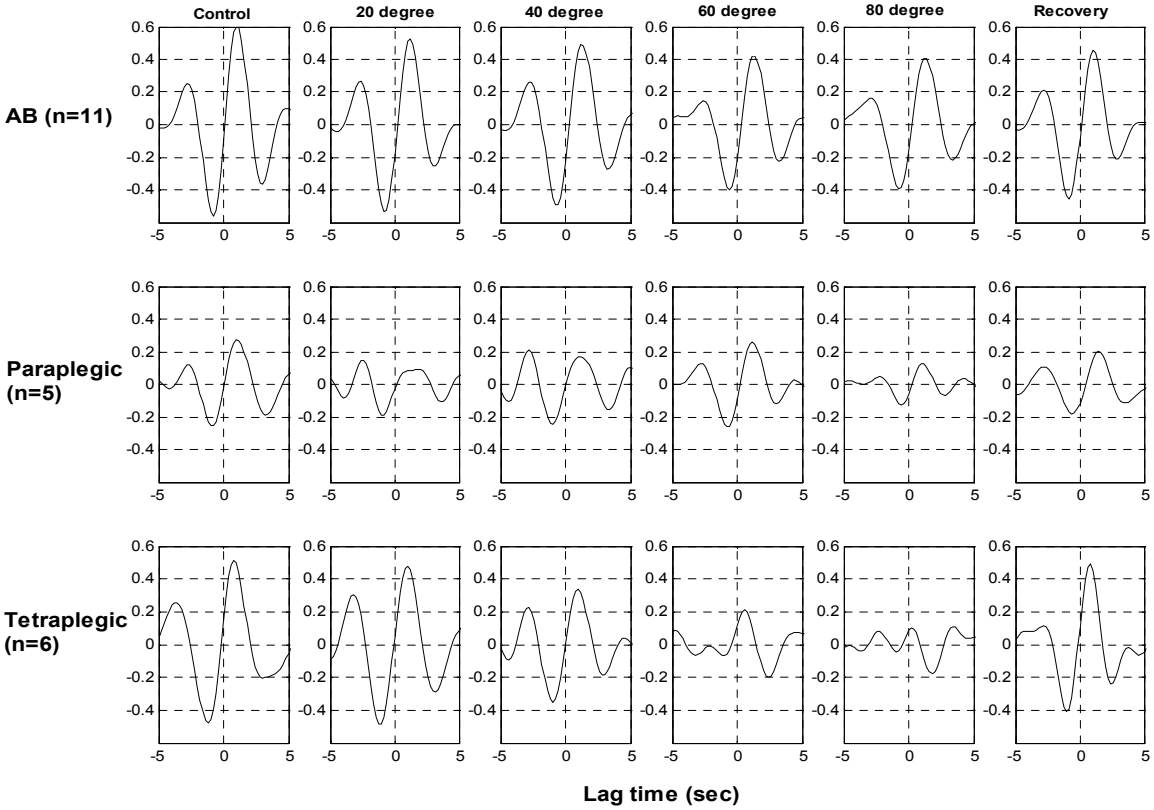
Appendix E: Lower body skin perfusion averaged spectral power for AB, Paraplegic & Tetraplegic



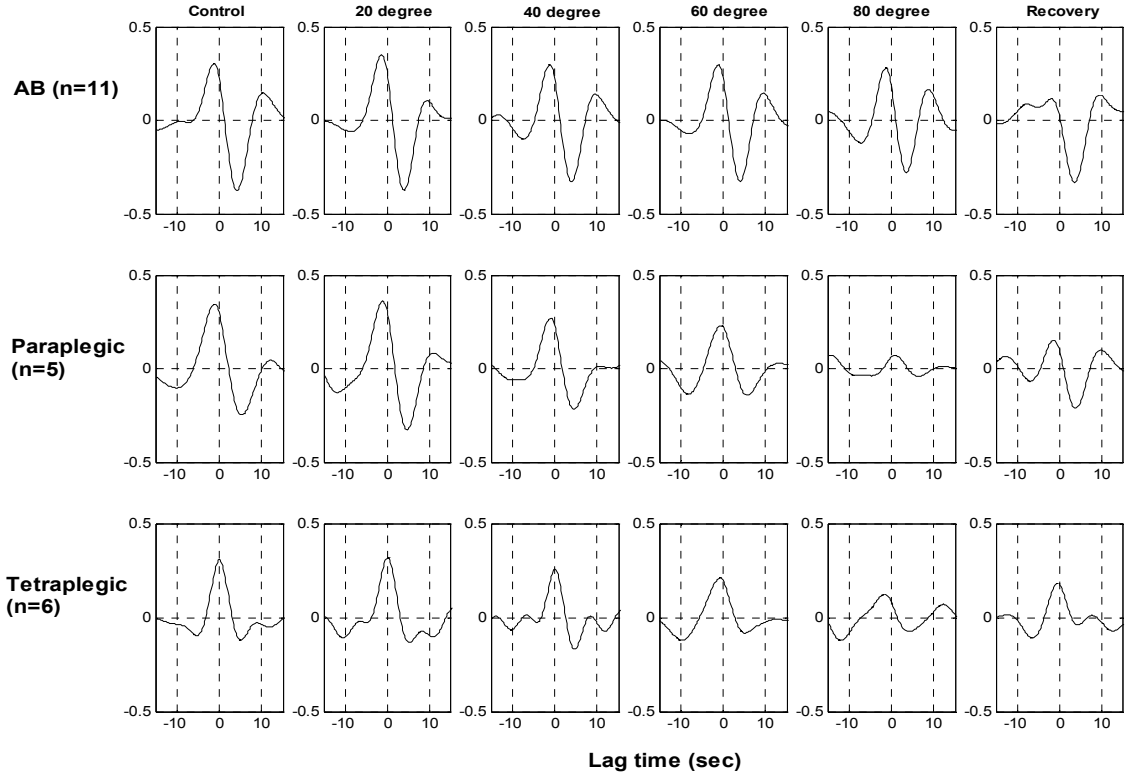
Appendix F: Heart rate & arterial pressure: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



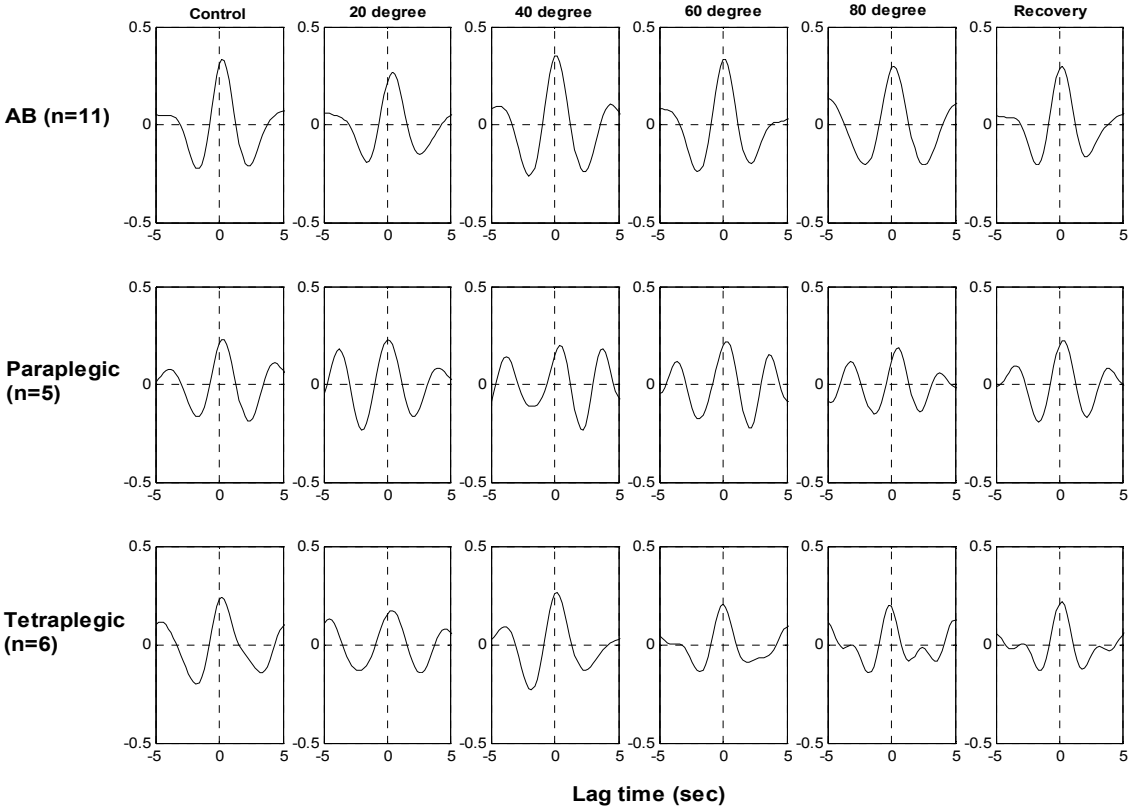
Appendix F: Heart rate & arterial pressure: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



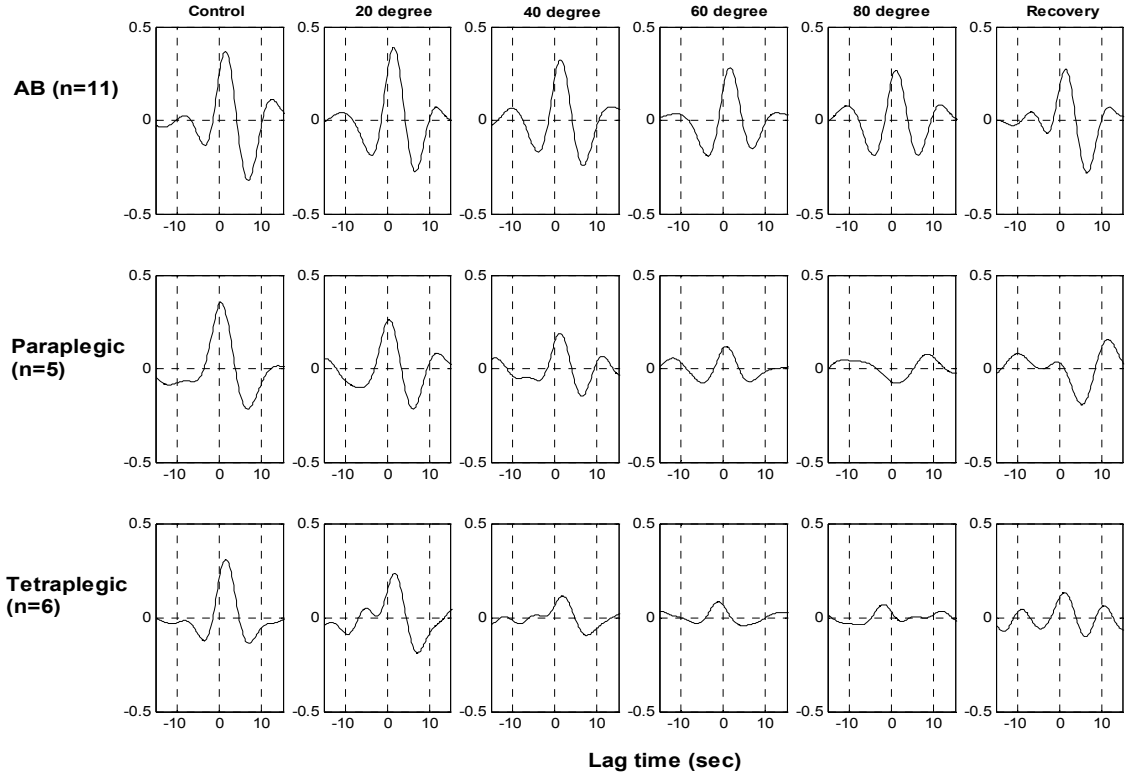
Appendix F: Arterial pressure & upper body skin perfusion: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



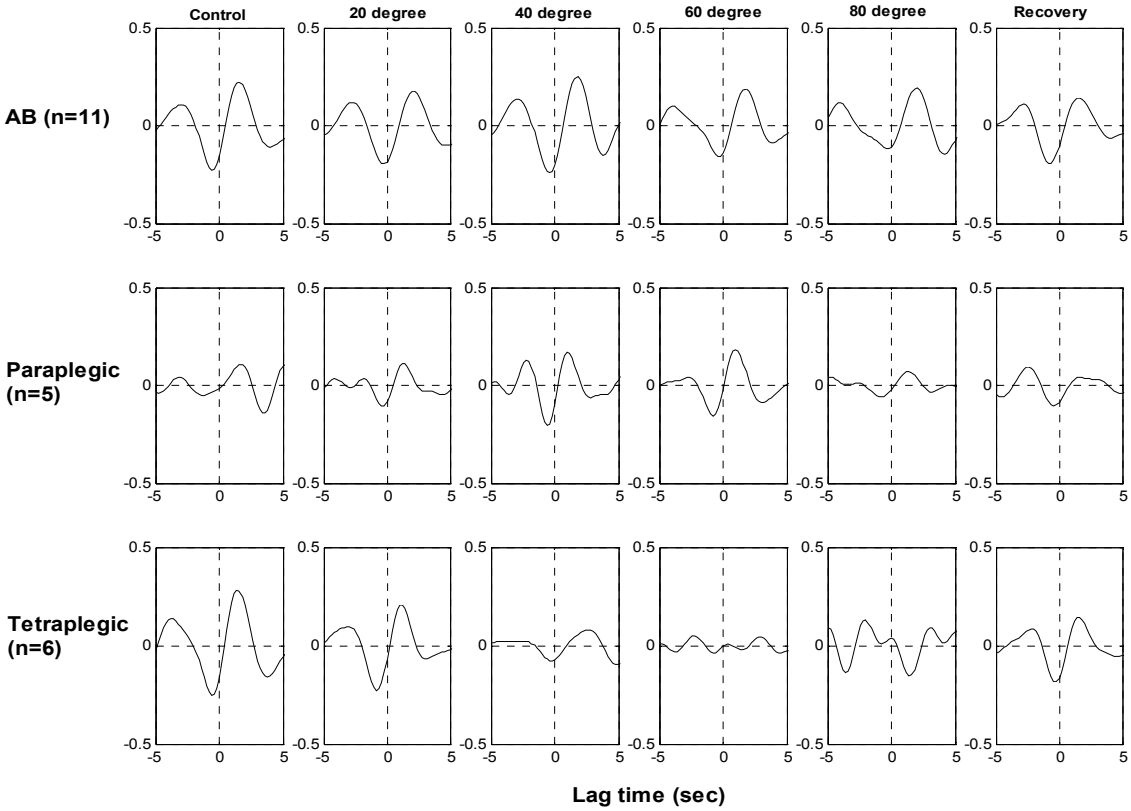
Appendix F: Arterial pressure & upper body skin perfusion: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



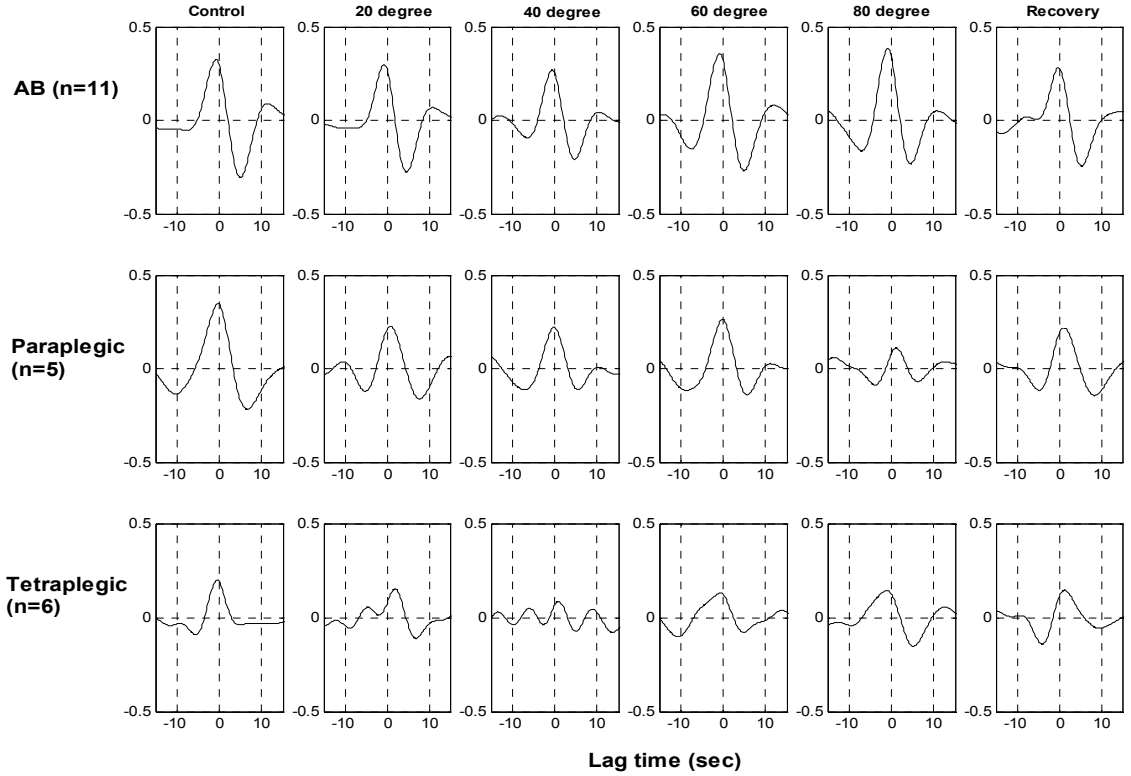
Appendix F: Heart rate & upper body skin perfusion: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



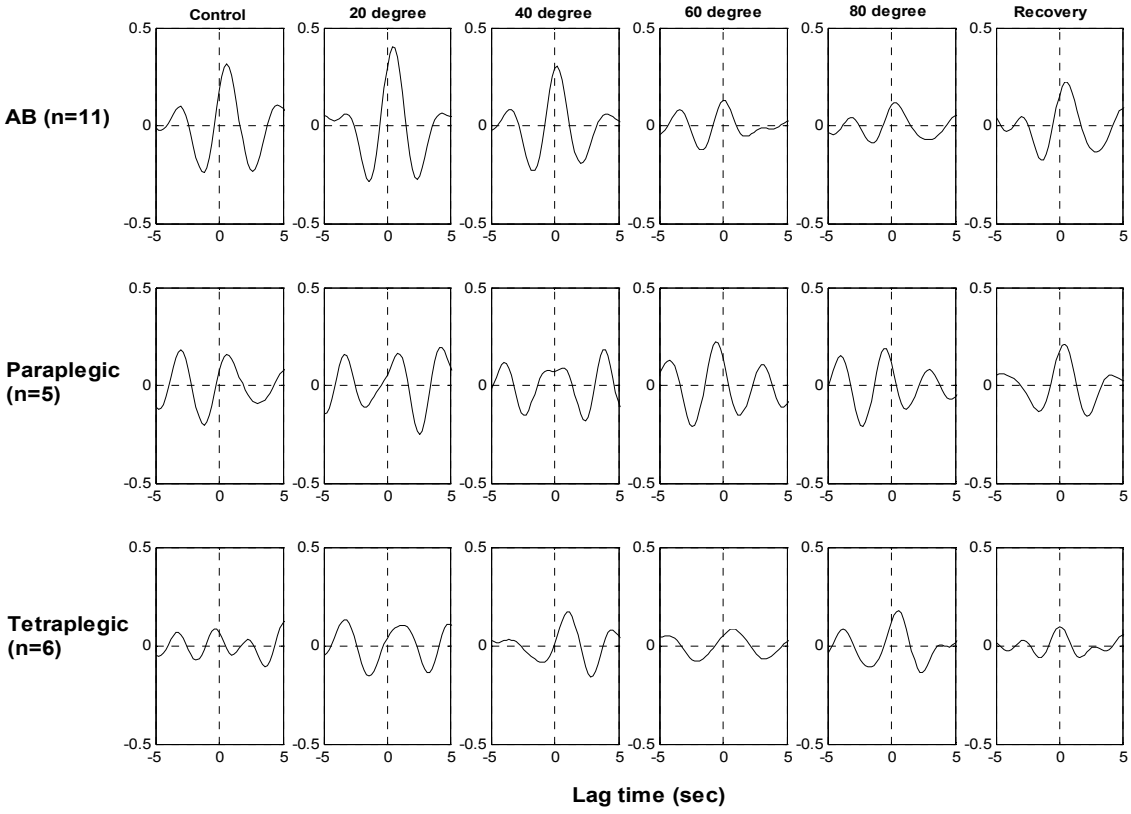
Appendix F: Heart rate & upper body skin perfusion: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



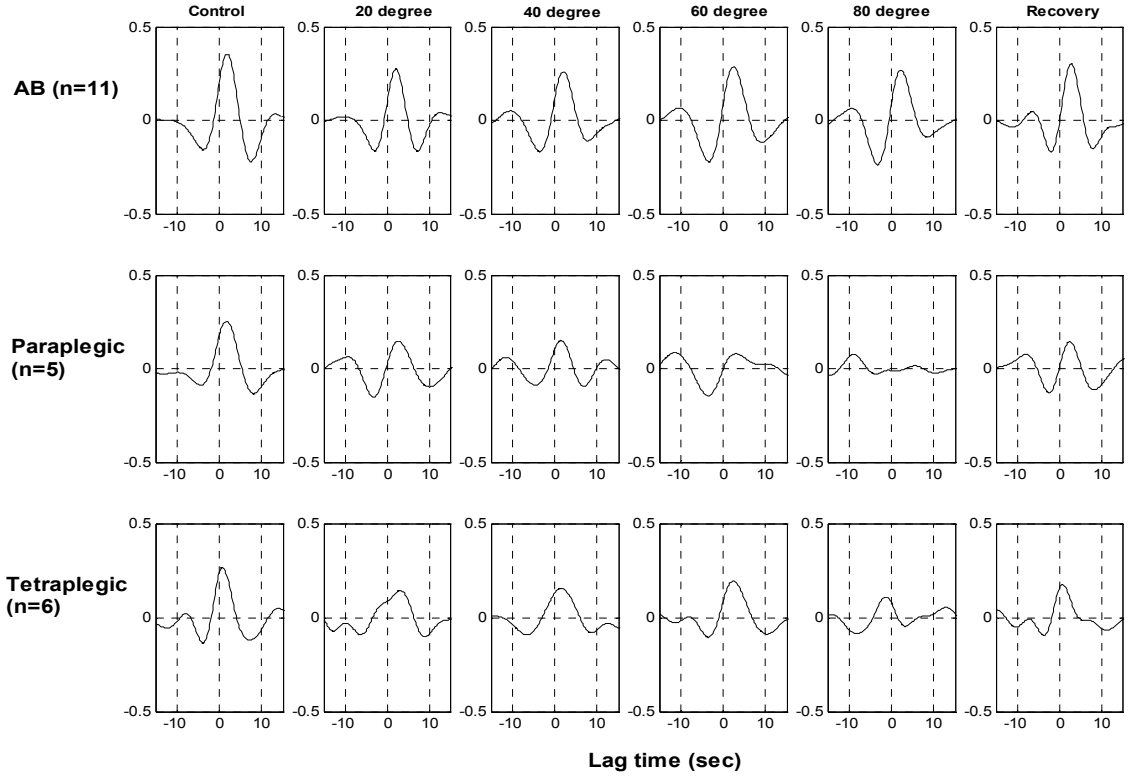
Appendix F: Arterial pressure & lower body skin perfusion: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



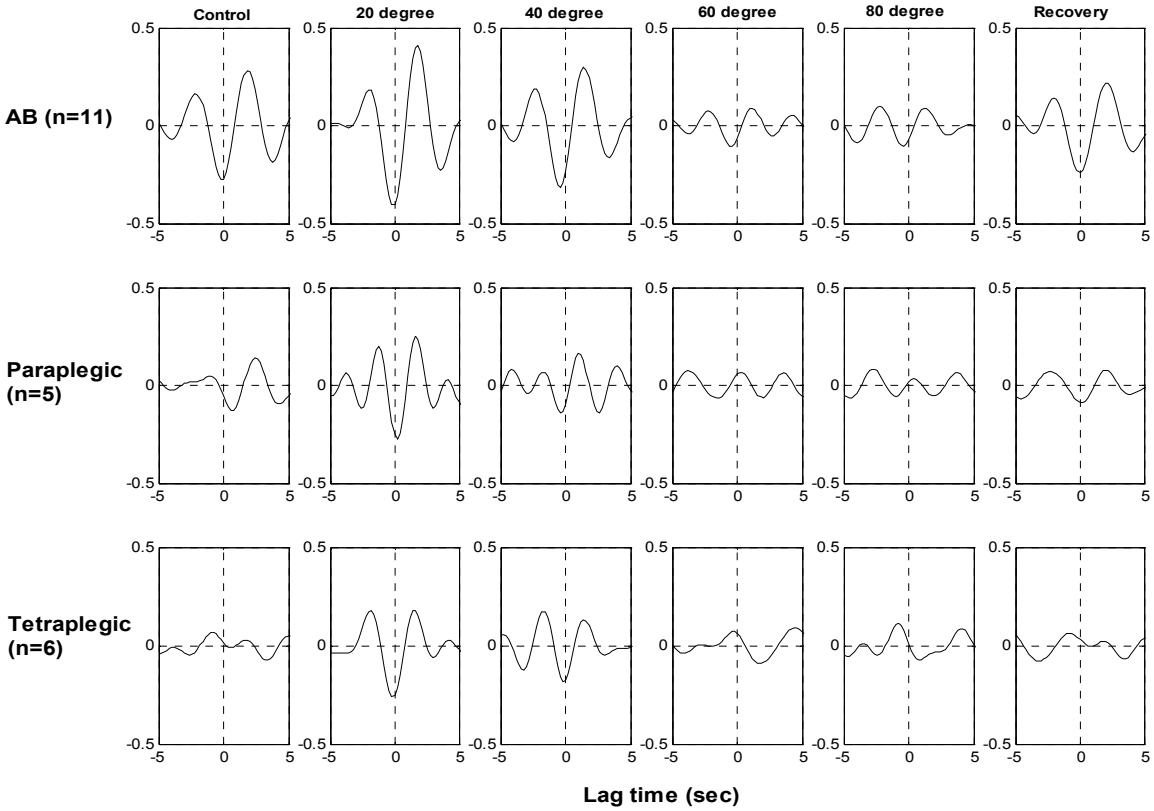
Appendix F: Arterial pressure & lower body skin perfusion: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



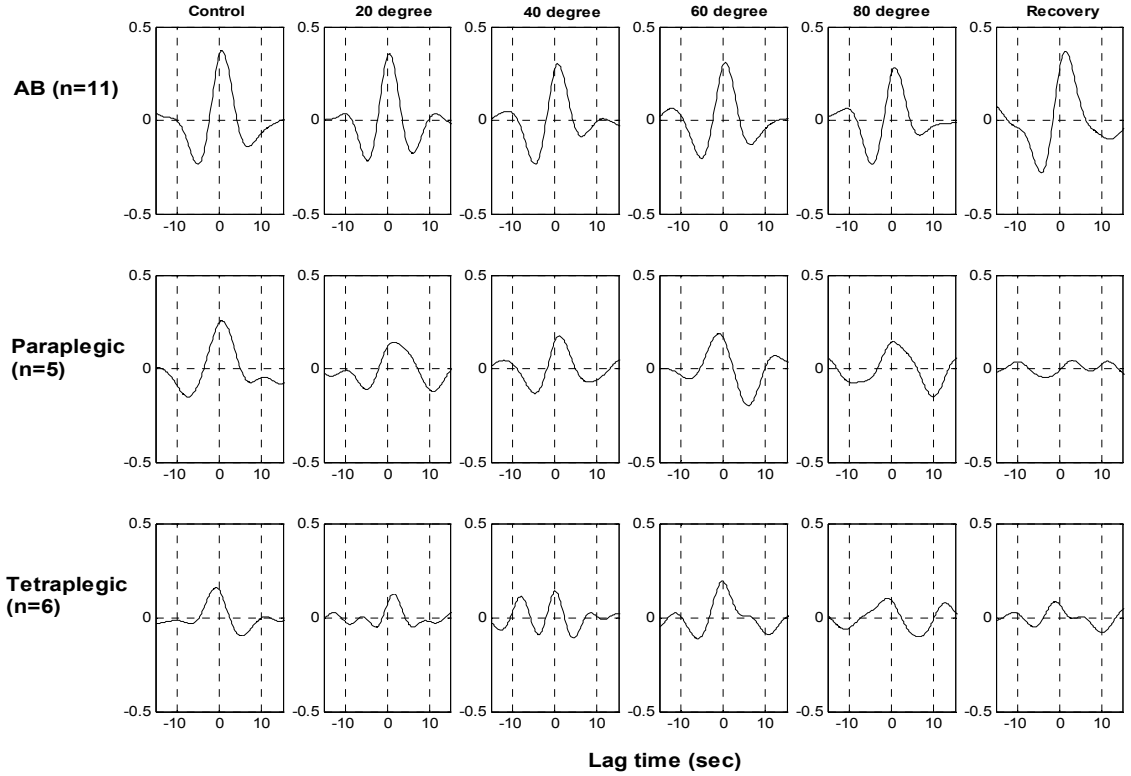
Appendix F: Heart rate & lower body skin perfusion: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



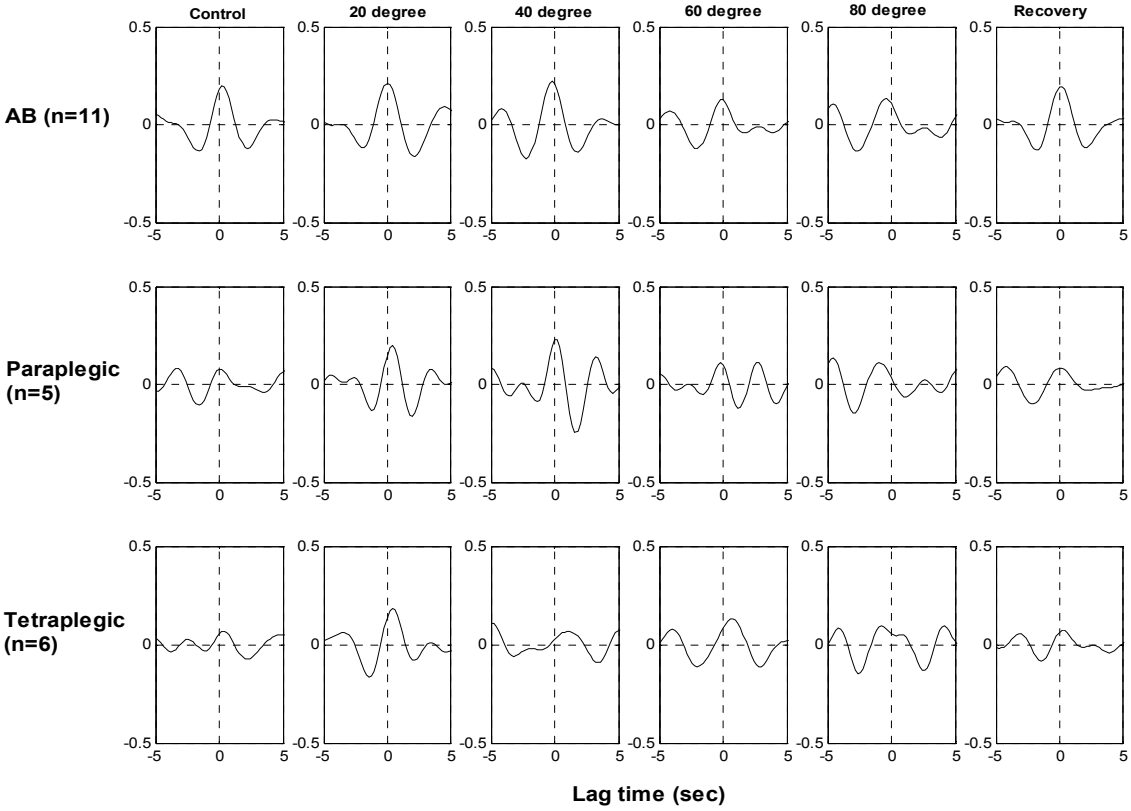
Appendix F: Heart rate & lower body skin perfusion: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



Appendix F: Upper & lower body skin perfusion: averaged cross correlation in LF for AB, Paraplegic & Tetraplegic



Appendix F: Upper & lower body skin perfusion: averaged cross correlation in HF for AB, Paraplegic & Tetraplegic



Appendix G: 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

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Impact Symposium, *Campus Relations*, Promoted University-wide symposiums by H. Norman Schwarzkopf and Thomas Von Essen, 2001-2002
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