

UNIVERSITY OF CALIFORNIA

Los Angeles

Baroreflex Sensitivity during Positional Changes in
Patients with Traumatic Brain Injury

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Nursing

by

Norma Dianne McNair

2012

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ABSTRACT OF THE DISSERTATION

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Professor Mary A. Woo, Chair

Background and Significance: Traumatic brain injury (TBI) affects 1.7 million Americans annually leading to significant morbidity and health care costs. An important cause of morbidity in TBI is secondary brain injury due to abnormal cerebrovascular autoregulation (CA). Standard measures of CA are not amenable to use outside of the intensive care unit (ICU) and patients continue to be at risk for secondary brain injury post- ICU. Baroreflex sensitivity (BRS) is a non-invasive assessment of autonomic tone that may be useful in evaluating CA. Evaluation of BRS and its relation to CA has not been examined in patients with TBI and predictors of CA are unknown. **Purpose:** The specific aims for this study were to 1) examine the association between BRS and CA in patients with TBI, 2) compare BRS and CA in TBI patients and age and gender matched healthy volunteers (HV) and 3) identify predictors of BRS and CA in TBI.

Methods: This study used a two group comparative design with 52 subjects (26 with moderate to severe TBI; 26 HV).

Measurement of variables: BRS was calculated as heart rate/mean arterial pressure; CA was calculated as cerebral blood flow velocity using transcranial Doppler; and cognition was assessed using the Galveston Orientation and Amnesia Test (GOAT). **Results:** There was no significant correlation between BRS and CA, however, BRS had high specificity (77%) for normal CA. BRS was not significantly different between TBI and HV subjects, those with normal or abnormal CA nor was BRS an independent predictor of CA. Forty six percent of TBI subjects had abnormal CA after their TBI (mean = 59.58 ± 36.54 days) and 34.6% of HV had abnormal CA. Predictors of abnormal CA were male gender, ACE-Inhibitors and GOAT. **Implications:** BRS can be used to identify normal CA. The GOAT has potential for routine assessment of CA status in non-ICU areas. Large proportions of TBI subjects long after a TBI event and HV had abnormal CA. Thus assessment of CA status is important in TBI subjects after ICU discharge and further research is needed on the impact of pre-existing CA abnormalities in HV.

The dissertation of Norma Dianne McNair is approved.

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DEDICATION

This work is dedicated to the patients, family members and healthy volunteers who so willingly participated in this research in the hopes that others would benefit from the results.

and

To the memory of my parents, Norman David McNair and Shirley Grady McNair, who whether they knew it or not, instilled in me a desire for life-long learning.

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Chapter 1

Introduction

Traumatic brain injury (TBI) is a significant problem that affects 1.7 million people in the United States each year. Of these, 52,000 die and 275,000 are hospitalized. Approximately 3.5-5.3 million people are living with long term disability as a result of their TBI. Direct medical costs and indirect costs related to lost productivity for survivors of TBI were estimated at \$60 billion in the United States in the year 2006 (Centers for Disease Control and Prevention, 2011). In addition, TBI in military personnel has increased from 10, 963 in the year 2000 to 30, 380 at the end of 2011 (Department of the Defense, 2012). While the majority of TBI in military personnel are classified as mild, there are still large numbers of men and women returning from theater who have sustained moderate to severe TBI (Department of the Defense, 2012). The majority of TBI affects both civilians and military personnel at the prime of their life, causing changes in cognition and ability to function in society (Franulic, Carbonell, Pinto, & Sepulveda, 2004; Jorge, 2005; Kim et al., 2007; Koskinen, 1998).

While the initial injury is significant, little can be done to affect damage to the brain at the time of injury. Secondary brain injury (that which occurs after the initial injury) can occur at any time along the continuum of hospitalization and may be caused by routine care that is provided to the patient through the course of recovery. There is increased morbidity and mortality associated with secondary brain injury resulting in long term sequelae such as difficulty with cognition, functional ability and return to work (Hammond et al., 2004; Jorge, 2005; Jorge et al., 2004; McCarthy et al., 2006). Most

secondary brain injuries are believed to be induced by abnormalities in cerebrovascular autoregulation ([CA], i.e., the ability to maintain constant blood flow to the brain despite changes in systemic blood pressure)(Rangel-Castilla, Gasco, Nauta, Okonkwo & Robertson, 2008). Moreover, while investigators have demonstrated that abnormal CA can be present at least 23 days after the initial injury (Sviri, Aaslid, Douville, Moore, & Newell, 2009), there is little information on the persistence of CA dysfunction after TBI. Unfortunately, the most common methods to assess secondary brain injury risk and CA are either invasive (intraventricular pressure monitoring – available for intensive care unit [ICU] use only) or not amenable at this time to routine clinical application (transcranial Doppler [TCD] which requires expensive equipment and high technician skill level).

Thus while it is agreed that secondary brain injury risk should be evaluated, there is a distinct lack of an instrument which the bedside nurse can utilize for this purpose. The ideal instrument for clinicians to evaluate secondary brain injury risk would be readily available at the bedside, repeatable, non-invasive, require minimal operator expertise, inexpensive, and have high correlation to standard measures of CA in TBI patients. Two possible alternatives for monitoring for secondary brain injury in TBI which meets these criteria are baroreflex sensitivity (BRS) and questionnaire evaluation of cognition (the Galveston Orientation and Amnesia Test [GOAT]).

Baroreflex sensitivity provides information regarding neural- and peripheral-vasculature interactions, and has been predictive of morbidity and mortality in persons with stroke and carotid disease (Matturri et al., 2005; Nasr, Traon, & Larrue, 2005). As there are similar pathophysiological changes in the autonomic nervous system and

cerebrovascular reactivity in persons with TBI or stroke, BRS may hold promise as a non-invasive method to assess CA in TBI patients outside of the ICU. A non-invasive method to assess CA, such as BRS, could allow clinicians to assess the impact of common nursing interventions on CA and to decrease secondary brain injury in TBI patients.

The GOAT provides an assessment of memory and cognitive status in patients who have sustained a TBI. The GOAT measures antegrade and retrograde amnesia and orientation (Levin, O'Donnell, & Grossman, 1979). This instrument is easy to use and readily available for the bedside clinician's daily assessment. Serial measurements using the GOAT may provide information about CA status due to shared pathways for memory, cognition and CA.

Background and Significance

Traumatic Brain Injury

Traumatic brain injury is defined as an “alteration in brain function manifested as confusion, altered level of consciousness, seizure, coma or focal sensory or motor neurologic deficit resulting from blunt or penetrating force to the head” (Bruns & Hauser, 2003, p. 2). The most common causes of TBI are related to firearms, motor vehicle crashes and falls (Centers for Disease Control and Prevention, 2011).

The primary brain injury occurs at the time of the initial injury and is the result of either a direct insult to the head or from rotational forces that move the brain within the skull. The result of these forces are shearing and tearing of white matter tracks, compression and contusion of brain tissue (Greve & Zink, 2009; Werner & Engelhard,

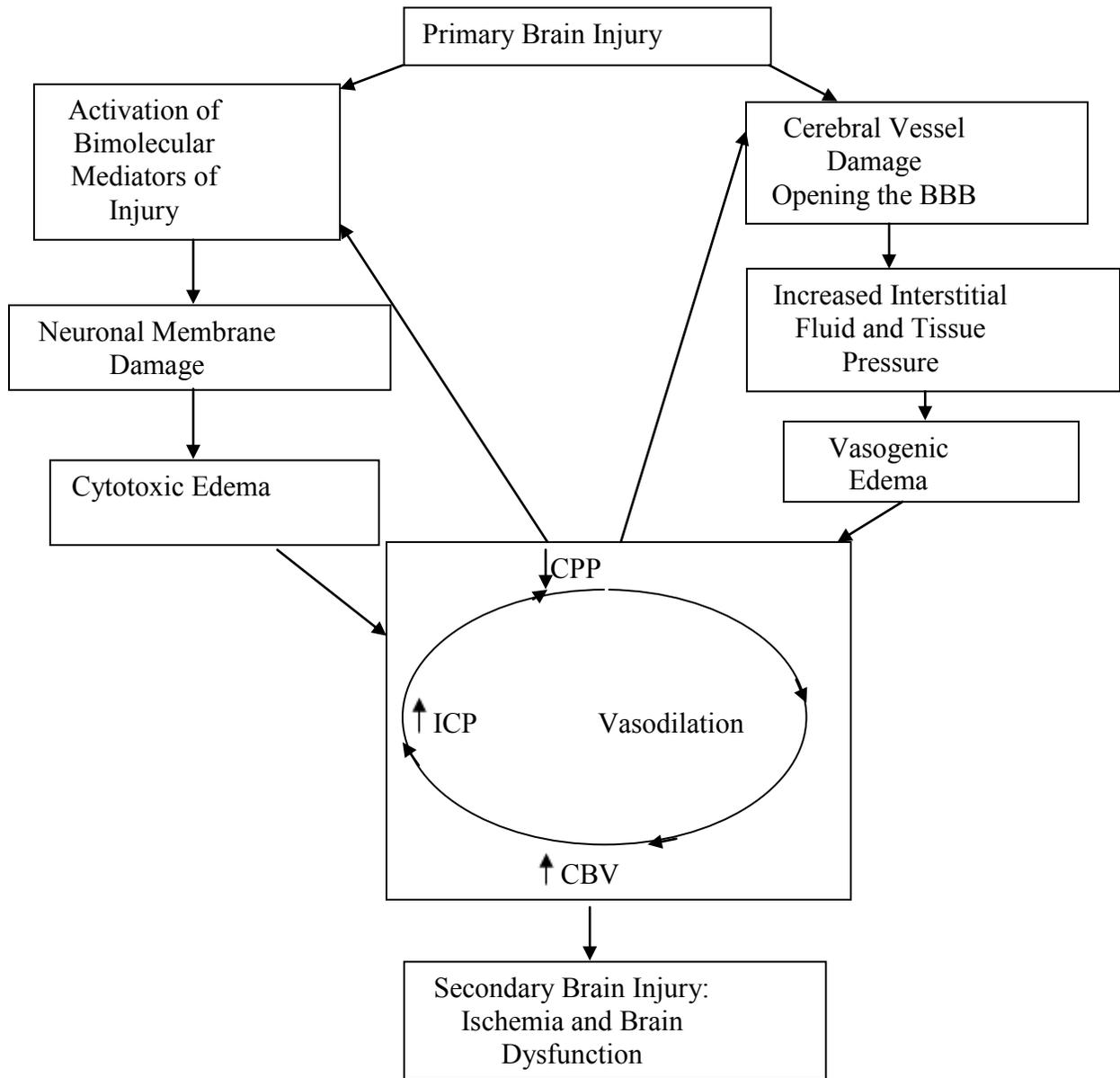
2007). After the primary injury, multiple derangements occur that lead to secondary brain injury including release of excitatory amino acids and oxygen free radicals (Greve & Zink, 2009; McAllister, 2011).

Secondary brain injury is often related to increased intracranial pressure (ICP) (Reilly, Graham, Adams, & Jennett, 1975), cerebral edema, poor oxygenation (Adams, 1951), poor cerebral perfusion and injury to neuronal tissue (Jennett, 1970) (Figure 1-1). Any or all of these injuries can affect long-term outcome. Secondary injury is a significant cause of morbidity and mortality in TBI patients (Chesnut et al., 1993; Manley et al., 2001; Miller, Sweet, Narayan, & Becker, 1978; Reilly, et al., 1975; Rose, Veltonen, & Bennett, 1977) and its impact can persist after ICU discharge (McHugh et al., 2007). Clinicians should assess risk for secondary brain injury, as many common therapies, such as re-positioning patients and ambulation, could place TBI patients at increased risk for this form of brain damage (Fan, 2004; Greve & Zink, 2009; Sullivan, 2000; Werner & Engelhard, 2007; Winkelman, 2000).

While secondary brain injury prevention is closely monitored for and managed in the ICU, patients who have moved out of the ICU are assumed to be at less risk for secondary brain injury and are monitored for oxygenation, glucose, electrolyte imbalances and gross changes in the neurological exam but not at the frequency of the same monitoring in the ICU (Littlejohns & Bader, 2005; Reed & Welsh, 2002; Verweij & Muizelaar, 1996). However, reports of continued neurological and cognitive deterioration in TBI patients after ICU discharge indicate that these persons remain at risk for secondary brain injury (Jeremitsky, Omert, Dunham, Protetch, & Rodriguez, 2003;

Manley, et al., 2001). The reasons for continued risk for secondary brain injury in TBI patients outside of the ICU are varied, and include autonomic nervous system (ANS) dysfunction and associated changes in cerebral blood flow (CBF) (Baguley et al., 2007; Baruley, Heriseanu, Felmingham, & Cameron, 2006). Injury to the brain can affect the function of the ANS due to disruption of white matter tracks that connect the central components of the ANS (Baguley, et al., 2007). The ANS is divided into two systems, the parasympathetic (PNS) and the sympathetic (SNS) nervous systems. Both of these systems regulate the heart and cerebral vasculature and injury to the areas of the brain that regulate the ANS may further exacerbate any injury to the brain related to poor cerebral perfusion because of changes in sympathetic stimulation (Baguley, et al., 2007; Keren et al., 2005; Rapenne et al., 2001). In addition, SNS stimulation and lack of PNS tone in patients with TBI are associated with poor outcome in patients with TBI and subarachnoid hemorrhage (Kawahara, Ikeda, Miyahara, & Kohno, 2003; Rapenne, et al., 2001). Evidence for alterations in ANS activity in TBI patients includes changes in heart rate variability (Keren, et al., 2005; Rapenne, et al., 2001) and “sympathetic storming” (tachycardia, diaphoresis, hypertension, hyperthermia and extensor posturing) (Blackman, Patrick, Buck, & Rust, 2004; Lemke, 2007; Srinivasan, Lim, & Thirugnanam, 2007).

Figure 1-1. Primary and Secondary Brain Injury Cycle



Legend: BBB: Blood Brain Barrier; CBV: Cerebral Blood Volume; CPP: Cerebral Perfusion Pressure; ICP: Intracranial Pressure

Adapted from: Greve, M. W., & Zink, B. J. (2009). Pathophysiology of traumatic brain injury. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*, 76(2), p. 102.

Cerebrovascular Autoregulation

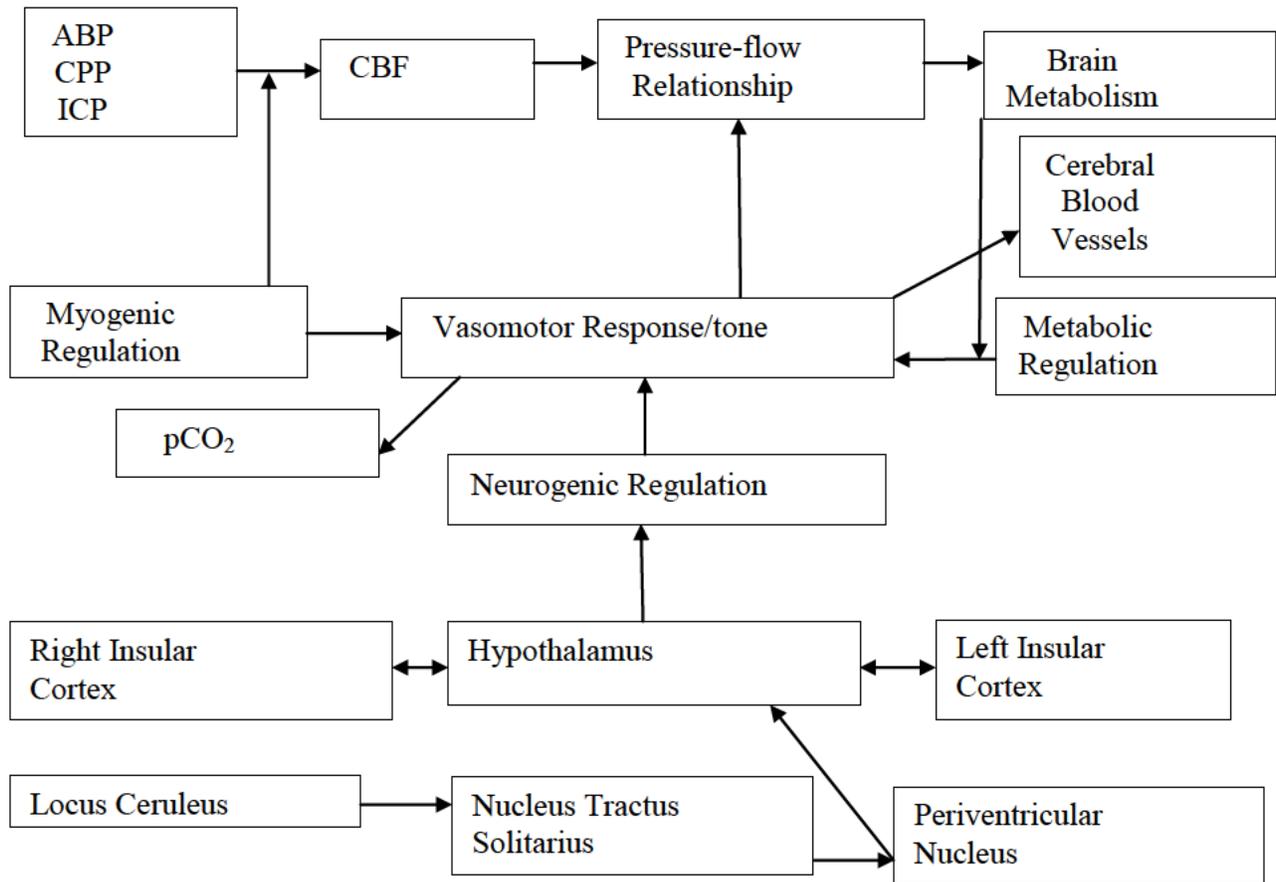
Under normal circumstances, the brain relies on cerebrovascular autoregulation to maintain blood flow. Cerebrovascular autoregulation is defined as the ability of the blood vessels of the brain to maintain a steady blood flow in the presence of a mean arterial blood pressure between 50 and 150 mmHg (Diehl, Linden, Lucke, & Berlit, 1998; Jaeger, Schuhmann, Soehle, & Meixensberger, 2006; Muller, Bianchi, Erulku, Stock, & Schwerdtfeger, 2003). Blood flow to the brain is maintained due to variations in cerebrovascular resistance in response to changes in blood pressure, and under normal circumstances is relatively independent from systemic blood pressure. Normal cerebral blood flow (CBF) averages 50 ml/100gm of brain tissue/minute. Irreversible neuronal injury occurs when CBF is below 10-15 ml/100gm/minute and reversible injury has been seen at 15-20 ml/100gm/minute (Astrup, Siesjo, & Symon, 1981). After TBI, CA is impaired and a drop in systemic blood pressure can lead to cerebral ischemia. If CA is absent, cerebral blood flow (CBF) is completely dependent on systemic blood pressure and there is even greater risk for secondary brain injury because of changes in blood pressure (high or low) which will alter CBF.

Impaired or absent CA after TBI is associated with a poorer outcome (Aaslid, Newell, Stooss, Sorteberg, & Lindegaard, 1991; Czosnyka, Smielewski, Kirkpatrick, Menon, & Pickard, 1996; Rangel-Castilla, Gasco, Nauta, , Okonkwo & Robertson, 2008; Zweifel et al., 2008). Cerebrovascular autoregulation becomes impaired within 24-48 hours of the injury and persists for an unknown period of time (Enevoldsen & Jensen, 1978). One study has indicated that CA remains impaired for at least 23 days post-TBI

(Sviri, et al., 2009) and an additional study indicated that CA gradually returned to normal about five days after acute trauma (Cold & Jensen, 1978). The neurological pathways that regulate CA adjust the caliber of the cerebral blood vessels without changes in perfusion pressure and are composed of two systems, intrinsic and extrinsic. The intrinsic system is made up of nerves that arise within the brain and pass through the substance of the brain to innervate the parenchymal vessels. The extrinsic system is the part of the ANS that influences CBF. In addition, influence from the trigeminal nerve (CN V) reflexively controls vasodilator effects in the cerebral circulation (Goadsby, 2004).

The ANS is also influenced by the hypothalamus, the amygdala and the insular cortices (Figures 1-2 and 1-3). The hypothalamus responds to input from the nucleus tractus solitarius (NTS) in the brainstem to release vasopressin which inhibits cardiac outflow; and affects the direct descending pathways (lateral tegmentum and lateral medullary formation) at the level of the intermediolateral column (IML) in the spinal cord which connects to the sympathetic chain and to the superior cervical ganglion.

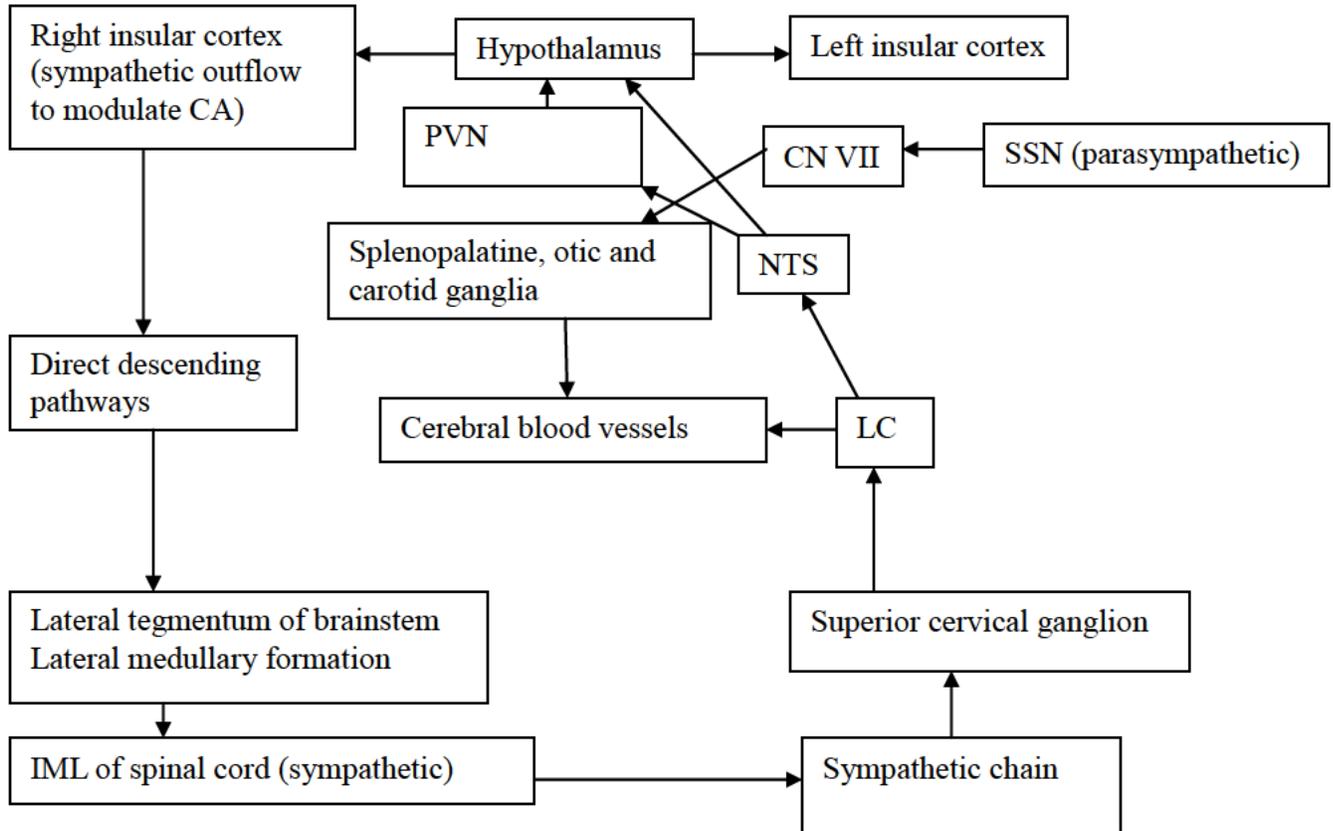
Figure 1-2. Cerebrovascular Autoregulation



Legend: ABP = Arterial Blood Pressure; CPP = Cerebral Perfusion Pressure; ICP = Intracranial Pressure; CBF = Cerebral Blood Flow; pCO₂ = partial pressure (saturation) of carbon dioxide

Adapted from: Aaslid, R (2006). Cerebrovascular autoregulation and vasomotor reactivity. *Frontiers in Neurology and Neuroscience* 21: 216-228.

Figure 1-3. Autonomic Nervous System and Cerebrovascular Autoregulation



Legend: CA = cerebrovascular autoregulation; LC = locus ceruleus; IML = intermediolateral column; CN VII = cranial nerve VII (facial nerve); NTS = nucleus tractus solitarii; SSN = superior salivatory nucleus; PVN = Periventricular nucleus

Sympathetic innervation of the cerebral blood vessels. The action of the SNS arises from the superior cervical ganglion. Fibers from the superior cervical ganglion form a network around blood vessels, primarily the large cerebral vessels and pial vessels. The intraparenchymal vessels are innervated, and receive their supply of noradrenaline, from the nucleus locus ceruleus in the pons. Sympathetic nerve fibers travel along the internal carotid artery to the Circle of Willis and the basilar artery. Cerebral blood vessels are innervated in the adventitia and the terminal effector neurons

are located on the medial layer of the vessel and the surface of the vascular smooth muscles (Franchini & Cowley, 2004).

Parasympathetic innervation of the cerebral blood vessels. The PNS regulates vasodilation of the cerebral vasculature. The PNS arises in the superior salivatory nucleus and leaves the CNS by way of the facial nerve (CN VII) and dilates the cerebral vessels. The fibers of the PNS travel through the geniculate ganglion to the greater petrosal nerve and then to the carotid plexus. From the carotid plexus, fibers travel to the carotid artery. After these fibers synapse, they travel along the ethmoidal nerve to innervate the cerebral vasculature (Goadsby, 2004). Stimulation of the facial nerve and the superior salivatory nucleus leads to an increase in total CBF from vasodilation without altering cerebral metabolic activity. While the parasympathetic nerves do not appear to have a direct role in CA, they are able to cause vasodilation in the cerebral vasculature and may be protective of the brain when brain metabolism goes awry (Goadsby, 2004).

Summary

While many studies have been conducted on modalities to measure CA (Czosnyka, et al., 1996; Jaeger, et al., 2006; Minassian et al., 2002; Panerai et al., 2002), little information is available that indicates when or if CA returns to normal after TBI (Cold & Jensen, 1978; Sviri, et al., 2009). Thus there is no evidence to support the common assumption that TBI patients are at low risk for secondary brain injury after ICU discharge.

The ability of the bedside clinician to determine if CA has returned to normal is an important component in the understanding of the effect of movement, positioning, and

other common nursing procedures on the TBI patient's blood pressure, heart rate, CA, and ultimately, cerebral perfusion. If a patient is repositioned and CA is not intact, a potentially deleterious outcome could occur because blood flow to the brain is now dependent on systemic blood pressure. A change in position (such as sitting upright) may cause a decrease in systemic blood pressure leading to decreased cerebral blood flow, central nervous system hypoxia, and secondary brain injury. In the ICU, presence or absence of CA can be determined using ICP monitoring devices or transcranial Doppler (TCD) ultrasound. Transcranial Doppler has been used frequently as a surrogate measure for CA both in and out of the ICU (Kirkness, 2005; Steiner & Czosnyka, 2002); however, measurement of CBFV using TCD does not meet the needs for frequent assessment of CA for most bedside clinicians.

Because of these difficulties in measuring CA using standard measures in patients with TBI, a bedside assessment technique that is easy to perform, can be used to assess the patient multiple times in a short period of time, and that provides immediate information on CA is necessary. Baroreflex sensitivity (BRS) and the GOAT may provide clinician-friendly methods to assess CA in TBI patients.

Baroreflex Sensitivity

Baroreflex sensitivity is reflective of ANS tone, and abnormalities in ANS function have been reported in moderate to severe TBI patients and associated with control of CA. Baroreflex sensitivity has been examined in patients with other neurological insults, such as stroke and carotid artery disease (Matturri, et al., 2005; Nasr, et al., 2005; Robinson, Dawson, Eames, Panerai, & Potter, 2003). Impaired BRS is

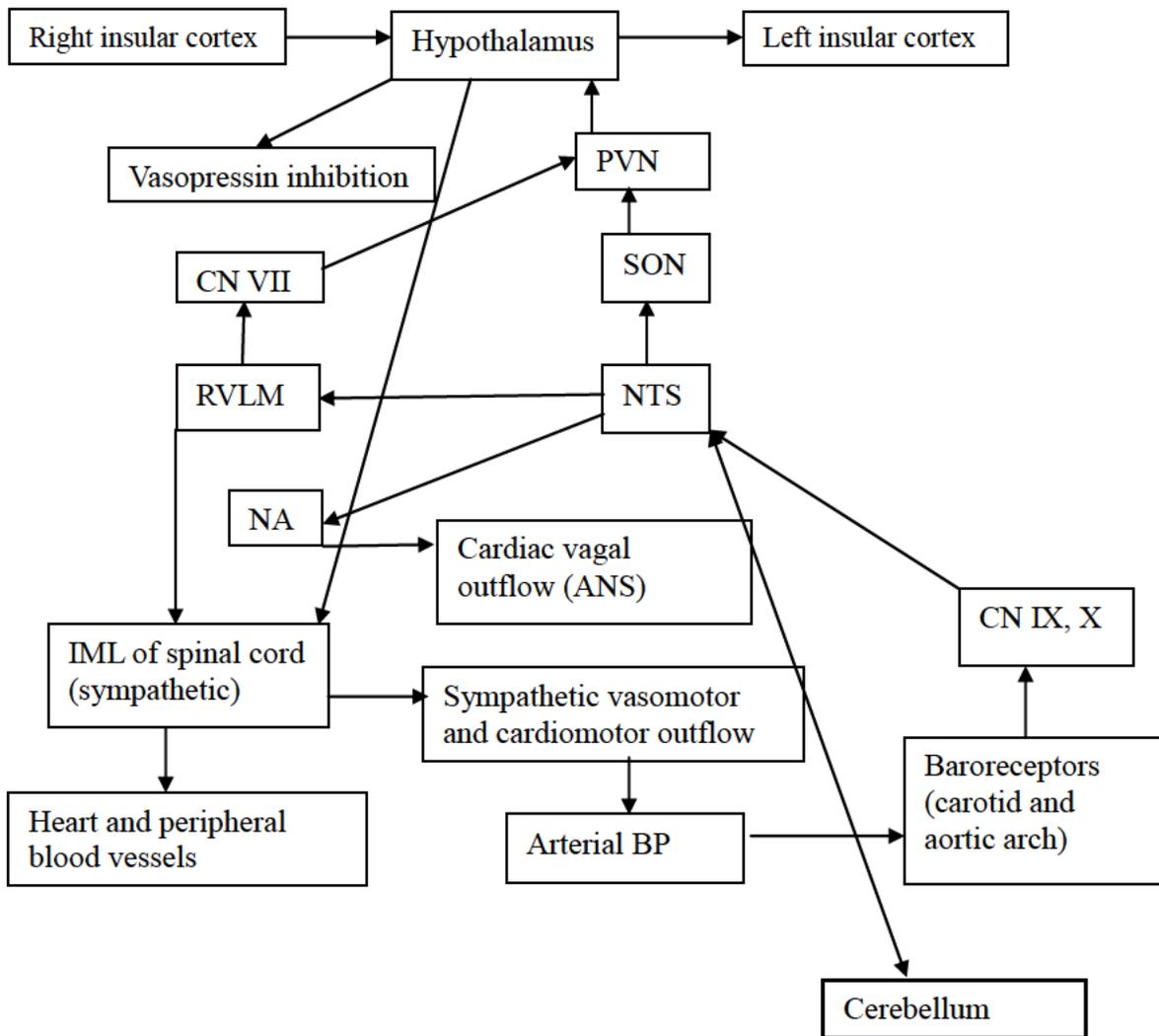
predictive of outcomes (morbidity and mortality) in these patients. The authors of these studies of non-TBI subjects have also determined that measuring BRS at the bedside is possible and relatively easy to accomplish. Given that non-TBI patients with abnormal BRS may have a poorer long-term prognosis (Nasr, et al., 2005; Robinson, et al., 2003), measurement of BRS in patients with TBI may provide information regarding the appropriate timing of common nursing procedures, such as positioning and movement out of bed. Baroreflex sensitivity may provide information about the return of CA in a manner that is easily measured by the bedside clinician by the calculation of heart rate (HR) and blood pressure (BP) measures.

Baroreflex Sensitivity - Physiology

Arterial baroreceptors are located in the adventitia of the carotid sinuses and the aortic arch (Eckberg, 2004) (Figures 1-4 and 1-5). They are stretch receptors that respond to increases or decreases in blood pressure (Weiling & Karemaker, 2002). Afferent impulses travel rapidly over myelinated nerve fibers and more slowly over unmyelinated fibers from the carotid sinus and aortic arch to the NTS in the medulla, which is the center for baroreflex integration. Information from the baroreceptors then goes to vagal motor neurons in the medulla and through the rostral ventrolateral medulla (RVLM) to the sympathetic motor neurons in the spinal cord (Eckberg, 2004). In addition, information travels from the NTS to the supraoptic nuclei, the paraventricular hypothalamic nucleus (PVN) and to the hypothalamus. Once the stimulus leaves the hypothalamus, it travels by way of direct descending pathways to the intermediolateral

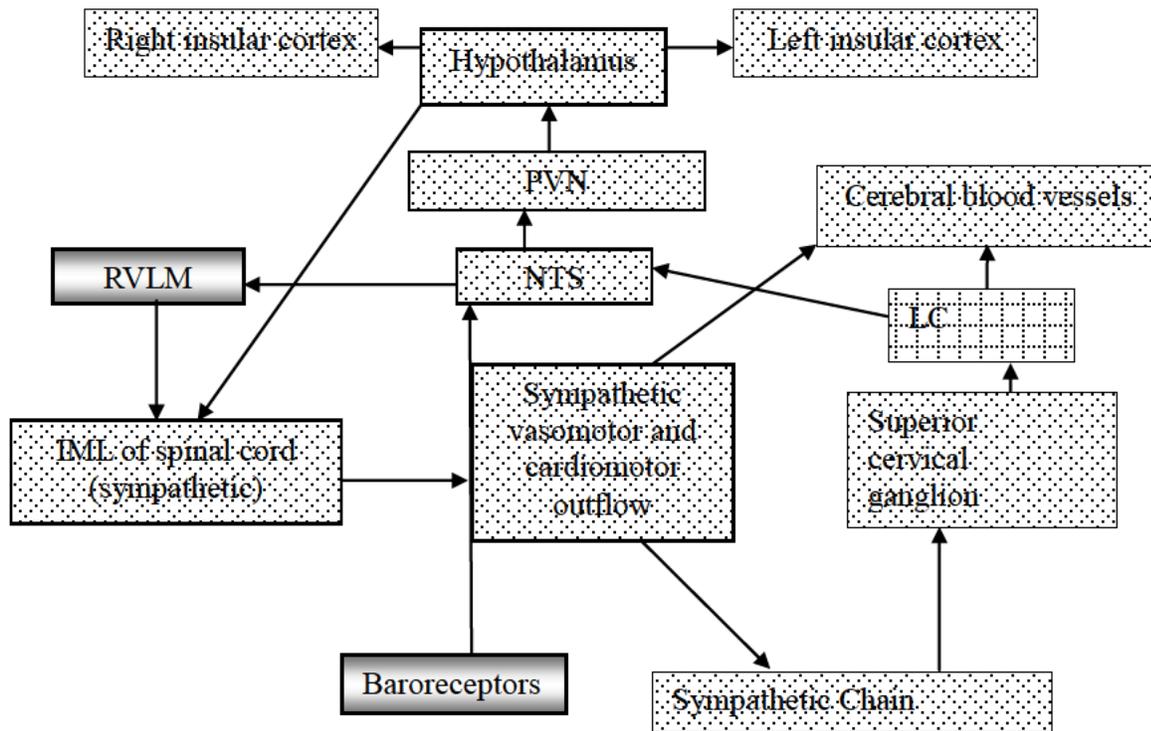
column (IML) of the spinal cord where sympathetic stimulation continues the cycle through the spinal cervical ganglion to the cerebral blood vessels.

Figure 1-4. Baroreflex Pathway



Legend: PVN = paraventricular hypothalamic nucleus; SON = supraoptic nuclei; CN VII = Cranial nerve VII (facial nerve); RVLM = rostral ventrolateral medulla; NTS = nucleus tractus solitarii; NA= nucleus ambiguus; ANS = autonomic nervous system; CN IX = Cranial nerve IX (glossopharyngeal nerve); CN X = Cranial nerve X (vagus nerve); IML = intermediolateral column; BP = Blood pressure

Figure 1-5. Major Common Cortical and Sub-cortical Pathways of Baroreflex Sensitivity and Cerebrovascular Autoregulation



Legend: RVLN = rostral ventrolateral medulla; NTS = nucleus tractus solitarii; IML = intermediolateral column; BRS pathways = ; CA pathways overlapping with BRS pathways = ; CA pathways = 

Other areas of the brain also influence neural control of BRS. The right insular cortex provides another source of sympathetic output to modulate CA. The left insular cortex regulates parasympathetic function and has been shown to affect cardiac rhythm in patients with stroke (Laowattana et al., 2006; Oppenheimer, Kedem, & Martin, 1996). The cerebellum influences the baroreflex by restraining its function to keep it from increasing or decreasing blood pressure too much or too little. Information from the

cerebellum travels through the inferior olives, the fastigial nucleus to the medulla, the reticular formation and to the RVLM.

Arterial baroreceptors cause excitation of the cardiac vagal centers and inhibition of the sympathetic vasomotor centers in the brainstem. This leads to a decrease in arterial blood pressure, because of decreased vagal excitation and sympathetic inhibition which causes an increase in heart rate, cardiac contractility and vasomotor tone in an effort to restore blood pressure to normal. In addition, if the baroreceptors are stimulated as a result of an increase in arterial pressure, adjustments occur to oppose that increase in blood pressure. Changes that occur as a result of baroreceptor activity occur quickly, often in less than two to three seconds (Weiling & Karemaker, 2002).

Baroreflex Sensitivity - Measurement

Direct quantification of BRS is difficult in humans due to the need for invasive monitoring and the inability to assess the entire vascular system. To increase its clinical utility, several non-invasive or less invasive methods to assess BRS have been proposed. Most of these non-direct BRS measurement techniques cause a rapid change in systemic blood pressure and allow observation of the change in HR and BP. These methods include administration of phenylephrine, measurement of levels of sympathetic activity such as norepinephrine, rapid postural changes, and Valsalva maneuver. Continuous measurement of BP and HR during these procedures provides indirect information regarding BRS status. Baroreflex sensitivity is calculated as heart rate in ms/mean arterial pressure in mmHg (Wieling & Karemaker, 2002).

Measurement of BRS can be conducted non-invasively using a monitoring device such as a Finapres[®] which provides information about changes in BP with postural change. Assessment of the subject's HR and BP during a position change challenge provides information regarding the integrity of the baroreceptors. Research on the integrity of BRS has been conducted in patients with autonomic failure using a head-tilt upright method (Bondar et al., 1997), in patients with stroke (Robinson, et al., 2003) and in congestive heart failure and other cardiovascular disease (Davies, Colhoun, Coats, Piepoli, & Francis, 2002; Nasr, et al., 2005). Little research using BRS has been conducted in patients with TBI. One study evaluated whether there was uncoupling of the autonomic and cardiovascular systems in acute brain injury in a pediatric patient population and showed changes in heart rate variability in a variety of injuries. Some patients in this study sustained a TBI but others sustained hemorrhage and infection, making this study difficult to apply to the adult TBI population (Goldstein, Toweill, Lai, Sonnenthal, & Kimberly, 1998). One other study in rats indicated that BRS was impaired after an induced mild or moderate TBI for up to 30 minutes after the injury. Severe TBI was not evaluated in this rat study (McMahon, Kenney, Bennett, Little, & Kirkman, 2011). The results of these studies indicate that impaired BRS is an indicator of poor prognosis in patients with stroke, congestive heart failure and other cardiovascular diseases. The two studies that evaluated BRS in TBI support the presence of disordered BRS in these patients.

Tank and colleagues assessed 262 healthy subjects in order to determine reference values for BRS as a function of age (Tank et al., 2000). These authors tested healthy

volunteers in six age groups with 127 women and 135 men while they were supine for seven minutes and also while deep breathing (six breaths/minute for 15 cycles). Results of the testing identified age delineated BRS that can be used in comparing healthy subjects to those who are not. Because patients in this research study were no longer in the ICU, non-invasive measures were used. Advantages of non-invasive testing include the ability to conduct the study on less critically ill subjects, position changes can be used as the challenge more easily and the results can be applied to a specific patient population. Because positioning of patients may lead to a decrease in BP or CPP and lead to secondary brain injury, particularly in those who are critically ill, conducting this research on patients housed on the acute care unit may decrease this possibility.

Positioning

One of the most common nursing procedures is positioning the patient. Changes in position include moving from the supine (flat) position to the upright (90°) position. Research conducted by nurse scientists regarding positioning of the patient with TBI has focused on its effect on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) (Fan, 2004; March, Mitchell, Grady, & Winn, 1990; Mitchell & Mauss, 1978; Mitchell, Ozuna, & Lipe, 1981). These studies on ICP and positioning indicate that ICP increases with nursing activities and those activities should be spaced to prevent the cumulative effects of increased ICP. Measurement of CPP during position changes indicates that the head of bed position should be individualized for patients with brain injury. However, these studies did not examine BRS or CA status. Other studies have examined BRS in stroke or other cardiovascular disease (Bondar, et al., 1997; Nasr, et al., 2005; Robinson,

et al., 2003) but no research has focused on the effect of positioning on BRS in the patient with TBI. While the research did not focus on position changes, movement of the patient in and out of bed is a common and frequent bedside activity performed by all levels of health care providers (nurses, therapists, physicians). Baroreflex sensitivity may provide information that will assist the bedside clinician in knowing the optimal time for mobilizing the patient, thereby assuring cerebral blood flow and limiting secondary brain injury.

Cognition/Memory

One result of TBI is impaired cognition. Cognition is the ability to perceive, know, problem solve, and involves short term memory, learning and information processing (McAllister, 2011). Individuals who sustain a TBI can have a variety of cognitive impairments that affect ability to return to work or functioning in society (Nicholl & LaFrance, 2009; Vakil, 2005). Specifically, patients with TBI have problems with short-term memory, remote memory and post-traumatic amnesia (Levin, et al., 1979).

Many of the cerebral pathways that participate in memory are injured during the TBI. These pathways overlap with those for BRS and CA in the following areas: prefrontal cortex, thalamus, hypothalamus, nucleus tractus solitarii, insular cortices, and hippocampi (McAllister, 2011; Niendam et al., 2012) (Figure 1- 6). The GOAT is an instrument that measures cognitive status in patients with TBI in three areas: orientation, post-traumatic amnesia and remote amnesia. Subjects answer questions and incorrect answers are subtracted from a total score of 100 points. A score of < 75 indicates that post-traumatic amnesia has not resolved. The GOAT is simple to use and can be readily available to the bedside clinician with little preparation. In comparing the GOAT to the Orientation-Log, another assessment of memory and orientation, the authors determined that the GOAT would be better for cognitive assessment in those with TBI (Novack, Dowler, Bush, Glen, & Schneider, 2000). Other assessments of cognition such as those used by neuropsychologists require a longer period of time to administer and skilled clinicians to do so.

In summary, TBI is a devastating neurological injury in which secondary brain injury prevention is paramount. Knowledge of cerebral blood flow and cerebrovascular autoregulation are important components in prevention of secondary brain injury but are not currently easily measured at the bedside outside of the ICU. Surrogate measures for CA (ICP monitoring and TCD) are used in the ICU, but once the patient leaves the ICU, only TCD is available for use and then only by a skilled technician. Baroreflex sensitivity or the GOAT may be ways to determine CA in those with TBI. Measurement of BRS and the GOAT may provide the bedside clinician with readily available information that can be used to decrease morbidity and mortality and improve outcomes.

Thus the specific aims of this study were to:

Aim 1: Examine the association between a gold standard measure of CA [(CBFV) of bilateral MCAs as measured by TCD)] and BRS in adult patients who have sustained moderate to severe TBI.

Hypothesis 1: There will be a positive relationship between TCD measures of CA and BRS, with BRS defined as a dichotomous variable (normal, abnormal) in a population of adult patients with moderate to severe TBI.

Aim 2: Compare BRS in adult subjects who have sustained a moderate to severe TBI and a group of age and gender matched healthy controls.

Hypothesis 2: BRS will be worse in subjects who have sustained a moderate to severe TBI compared to healthy controls using BRS as a dichotomous variable (normal, abnormal).

Aim 3: Examine the relationship of selected covariates (such as age, gender, post-resuscitation Glasgow Coma Scale [GCS] score, Galveston Orientation and Amnesia Test [GOAT], CBFV of the bilateral MCAs as measured by TCD, and time since TBI) and BRS and CA.

Hypothesis 3: In logistic and linear regression models, covariates such as age, gender, post-resuscitation GCS, GOAT, time since TBI and CBFV of the bilateral MCAs as measured by TCD will be predictors of BRS and CA (normal, abnormal) in subjects with TBI.

Chapter 2

Review of the Literature

This chapter will review the literature related to traumatic brain injury, cerebrovascular autoregulation, baroreflex sensitivity, cognition, and the relationships among them.

Traumatic Brain Injury

Traumatic brain injury (TBI) affects 1.7 million people in the United States annually. Of these, 275,000 will be hospitalized, 1.1 million will be treated and released from the hospital and 52,000 will die. Males are twice as likely to sustain a TBI. The majority of TBIs are caused by firearms, motor vehicle crashes and falls while sports related injury is also a significant cause. While TBI affects individuals of all ages, the highest incidence is in those aged 0 - 4 and 15-19, with the highest death rate from TBI in those who are over 65 years of age. Most individuals are injured during the most productive years of their lives and the long term cost to survivors is incalculable. Direct and indirect medical costs in 2006 were estimated to be \$60 billion (Centers for Disease Control and Prevention, 2011). This figure includes the impact of lost work productivity due to death or disability. Of those who survive to be discharged from the hospital, 40% have persistent unmet needs one year after injury. These needs include cognitive, emotional, sensory, motor and employment and have long term effects on the social life of survivors and their families (Centers for Disease Control and Prevention, 2011). The Centers for Disease Control and Prevention [CDC] (2011) estimate that there are 5.3 million people in the United States who have lifelong needs for assistance in activities of daily living due to TBI. These numbers do not include the members of the military who sustain a TBI during combat. There have been approximately 230,000 TBIs sustained by military personnel since 2000. While

most of these TBIs are mild, the impact of TBI on the returning soldier is just beginning to be addressed and understood (Department of the Defense, 2012). The mechanism of injury for those in the military is primarily related to blast injuries, although other injuries such as motor vehicle crashes also occur (Department of the Defense, 2012; Plurad, 2011).

The CDC defines TBI as caused by a blow to the head or a penetrating head injury (primary injury) that disrupts the normal functioning of the brain (Centers for Disease Control and Prevention, 2006). Traumatic brain injury has three mechanisms, blunt, penetrating or blast. Injury to the brain occurs due to transfer of energy to the brain tissue because of one of these mechanisms (March et al., 2004; Nolan, 2005). The energy transfer causes pressure on, and shearing of tissue, leading to cellular injury at the site of initial impact (primary brain injury) and to a portion of the brain opposite to the impact (contre-coup injury). Injury to brain tissue and pathways due to movement of the brain within the skull also occurs at the time of the initial impact (Werner & Engelhard, 2007). The brain initiates physiological responses to the injury that can lead to secondary brain injury (damage which occurs after the initial insult) including increased vascular permeability, breakdown of neuronal tight junctions, release of free radicals and inflammation leading to cerebral edema (Greve & Zink, 2009; Hariri, 1994; Werner & Engelhard, 2007) (Figure 1-1).

Secondary Brain Injury

Individuals who sustain a TBI are at high risk for secondary brain injury because of the physiological events that occur after the primary injury. Secondary brain injury leads to further damage of neuronal tissue and may prolong or exacerbate neurological deficits (Adams, 1951; Doberstein, Hovda, & Becker, 1998; Rangel-Castilla, Gasco, Nauta, , Okonkwo, & Robertson,

2008; Reilly, et al., 1975; Rose, et al., 1977; Verweij & Muizelaar, 1996). Researchers have indicated that patients who are talking on arrival to the emergency department and then deteriorate often died of their injuries. Their deaths were related to an avoidable secondary insult in approximately 75% of these patients (Miller, et al., 1978; Reilly, et al., 1975; Rose, et al., 1977). Systemic causes of secondary brain injury include hypoxia, hypotension, electrolyte imbalance and other causes such as hypoglycemia, hyperthermia and anemia. In addition, intracranial causes of secondary injury include increased intracranial pressure (ICP), brain edema, hyperemia, vasospasm, and seizures (Bayir, Clark, & Kochanek, 2003; Doberstein, et al., 1998; Werner & Engelhard, 2007).

While mortality from TBI has decreased because of improved technology (including seatbelt and helmet use) (National Highway Traffic Safety Administration, 2008, 2008) and standardized interventions (Brain Trauma Foundation, 2000), there is still a high risk for secondary brain injury in this group of patients (Andrews & Citerio, 2004; Rangel-Castilla, et al., 2008; Verweij & Muizelaar, 1996; Werner & Engelhard, 2007). Interventions to reduce secondary brain injury begin in the intensive care unit (ICU) but once the patient is transferred to the post-ICU area, the degree of monitoring decreases while the risks of hypoxemia, hypotension, hyperthermia, seizures and hypoglycemia continue. In addition, changes in cerebral blood flow (CBF) occur after TBI, which can affect the oxygenation and nutrition to the brain tissue. Reed and Welsh (2002) reported that TBI patients who developed secondary brain injury did so in the ICU and on the general wards. Patients in these areas, particularly the general care ward (post-ICU) have a longer length of stay compared to those who do not have episodes indicating secondary brain injury. Longer length of stay may lead to additional secondary brain

injury from episodes of hypoxia, hypotension or other causes and additional episodes of hypoxia or hypotension may lead to longer length of stay.

Secondary brain injury is estimated to occur in up to 40% of patients admitted with a severe TBI (Andrews & Citerio, 2004; Andrews, Piper, Dearden, & Miller, 1990; Rose, et al., 1977). More concerning is that the events that cause secondary brain injury may go unrecognized and unrecorded by current monitoring modalities or be undertreated and could result in a poor functional outcome (Rose, et al., 1977; Signorini, Andrews, Jones, Wardlaw, & Miller, 1999). Management of the patient with TBI is a collaborative effort between the bedside nurse and the multidisciplinary team. The bedside nurse needs to be aware of the purpose of the various monitoring modalities and the treatment required when the patient's condition changes. The patient in the ICU is well observed with ICP, cerebral perfusion pressure (CPP), mean arterial pressure (MAP), jugular venous oxygenation, brain tissue oxygenation being monitored on a continual basis (Czosnyka & Pickard, 2004; Littlejohns & Bader, 2005; Marmarou, Saad, Aygok, & Rigsbee, 2005). As a result, ICU nurses are able to determine if nursing procedures such as positioning, suctioning or other daily nursing activities affect these parameters in a deleterious fashion (Heath & Vink, 1999; Littlejohns & Bader, 2005). Once the patient leaves the ICU, these monitoring modalities are no longer in place and the bedside nurse must rely on physical findings or limited monitoring devices such as blood pressure (BP), heart rate (HR) and pulse oximetry. Unfortunately, none of these physiological markers by themselves are predictive of secondary brain injury risk.

One of the goals of care of patients who are no longer in the ICU is to increase mobility by getting the patient out of bed. Increased mobility (walking, sitting up in the chair) assists in

the prevention of pneumonia and deep vein thrombosis and has been thought to improve the neurological status of patients (Safaz, Alaca, Yasar, Tok, & Yilmaz, 2008; Vitaz, Jenks, Raque, & Shields, 2003). With limited monitoring occurring, the incidence of secondary brain injury due to hypoxia, hypo- or hyperperfusion, or hypotension related to these common nursing procedures is not known and these changes may not be recognized during mobility. Thus, the bedside nurse needs a method of identifying potential secondary brain injury events in order to prevent or decrease their occurrence. An important physiological factor for bedside nurses to consider when evaluating risk for secondary brain injury is cerebrovascular autoregulation (CA).

Cerebrovascular Autoregulation

Cerebrovascular autoregulation is defined as the ability of the brain to maintain a constant CBF and a stable environment in the cranial vault (brain, blood and cerebrospinal fluid) during changes in systemic arterial blood pressure (SABP) or CPP (Lang, Czosnyka, & Mehdorn, 2003). In the normal individual, CA is a complex physiological phenomenon that is not completely understood. It involves myogenic, neurogenic and metabolic mechanisms that act in concert to maintain CBF. The myogenic component is related to the intrinsic ability of the smooth muscle of the blood vessels to constrict or dilate in response to changes in pressure. The neurogenic mechanism occurs as a result of the innervation of the blood vessels and responds to autonomic (sympathetic) stimulation. The metabolic component is thought to affect the smaller, distal blood vessels and respond to changes in carbon dioxide (CO₂) or oxygen (O₂) concentrations (Czosnyka, Smielewski, Piechnik, Steiner, & Pickard, 2001; Kirkness, Mitchell, Burr, & Newell, 2001; Myburgh, 2004; Rangel-Castilla, et al., 2008; Vavilala, Lee, & Lam,

2002; Zhang et al., 2002). This section will discuss measures, patterns and research related to CA as it applies to this research.

Patterns of Cerebrovascular Autoregulation

There are two identified patterns of autoregulation, static and dynamic. Static measurements provide information about the overall efficiency of autoregulation but not about the time in which this change is achieved (Tiecks, Lam, Aaslid, & Newell, 1995). Since this research used measures of dynamic CA, further discussion will focus in that area. Measurement of dynamic CA has become possible since the development of TCD techniques. This method uses rapid drops in arterial blood pressure (ABP) caused by manipulation of thigh cuffs or position changes and then compares ABP and CBF velocity (as measured by TCD). Use of CBF velocity (CBFV) has been validated as a surrogate for measurement of CBF (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989; Aaslid, et al., 1991; Lindegaard, Lundar, Wiberg, Sjoberg, & Aaslid, 1987; Newell, Aaslid, Lam, Mayberg, & Winn, 1994; Ringelstein, Sievers, Ecker, Schneider, & Otis, 1988). Dynamic measurement also provides information about the time that it takes for a change in CBF or CBFV related to a position change to occur. Research has indicated that measurement of CA yields similar results with either static or dynamic methods, which becomes important in assessing patients in the post-ICU setting where invasive monitoring is not available (Tiecks, et al., 1995). In order to apply research to practice in the area of CA, nurses need to understand the difference between the methods of measurement of static or dynamic CA. Given that static CA measures require the use of invasive monitoring devices and manipulation of medications such as vasopressors (inappropriate for assessment of non-ICU patients), these CA assessment techniques are not applicable for nurses to use in the post-ICU setting. Measures of

dynamic CA that include position change are more applicable to the post-ICU areas because mobility and positioning are easier CA assessment methods and often are included as important care activities in the non-ICU patient care setting.

Studies using dynamic methods (upright tilt; position change from lying to standing; thigh cuff release) have been conducted in patients with TBI (Czosnyka, et al., 1996; Hlatky, Valadaka, & Robertson, 2006; Lang, & Chesnut, 2000; Lang, et al., 2003; Muller, et al., 2003; Ng, Lim, & Wong, 2004; Panerai et al., 2004; Steiner, Coles, Czosnyka, et al., 2003; Steiner, Coles, Johnston, et al., 2003; Ter Minassian et al., 2002) and in those with cerebrovascular disorders (stroke and carotid disease) (Panerai, White, Markus, & Evans, 1998; Reinhard et al., 2005; Simpson, Panerai, Evans, & Naylor, 2001). These studies indicate that measurement of dynamic CA is possible and requires minimal equipment or monitoring devices which makes this method more desirable in comparison to static CA assessment in the post-ICU area.

Standard Measures of Cerebrovascular Autoregulation

One of the purposes of measuring CA is to determine if patients are at risk for decreased cerebral perfusion and secondary brain injury. Assessment of CA provides information that assists in the clinical management of patients particularly related to CBF. Multiple physiological variables have an effect on CA and no one measure is considered perfect, but there are assessment techniques that have been frequently used for determining CA. Authors have proposed several ways of indirectly assessing CA, including measurement of CBF and CPP (Myburgh, 2004; Vavilala, et al., 2002). In the individual with TBI and abnormal CA, changes in CA will lead to changes in CBF.

Measures of cerebral blood flow. Cerebral blood flow can be measured using patient inhalation of nitrous oxide or xenon¹³³ (Xe^{133}). These gases provide information about regional blood flow by measuring the time course of the appearance of the isotope in the cerebral venous blood and mapping blood flow changes (Myburgh, 2004). The gases are readily diffusible out of the brain and the techniques are easily reproducible for mapping changes in CBF (Myburgh, 2004; Vavilala, et al., 2002). Limitations of this method include limited repeatability, cost of isotopes, low availability of the equipment at the bedside for the test, and the potential for inaccurate results due to underlying pathology.

Other measures of CBF include Doppler ultrasonography using transcranial bone windows to access the vasculature of the Circle of Willis and laser Doppler flowmetry which examines the flow through the microcirculation. Light is provided through a fiber optic cable that measures shifts in frequency due to red blood cell movement in a small area of brain tissue. Limitations of this method include the small area of measurement such that flow assessed in this discrete region may not be indicative of flow throughout the brain and that there can be high variability in the ability of the operator to obtain the desired information in a consistent manner. In addition, measurement of cerebral blood velocity is not the same as measurement of CBF but changes in velocity generally correlate well with changes in CBF (Myburgh, 2004; Vavilala, et al., 2002).

Additional measures of CBF include the use of positron emission tomography (PET), magnetic resonance imaging (MRI) and computerized tomography (CT) scans. Positron emission tomography is a nuclear imaging method that provides information about function of various structures of the body, including the brain. A biologically active tracer isotope is injected into the

patient's blood stream and the molecule becomes concentrated in the tissues that are to be examined. Approximately one hour after injection, the patient is transported to the PET scanner and the scan is conducted. The main limitation of this method is the high cost of the cyclotron that is required to make the isotope and the need for a location to make the radiopharmaceutical that will be used in the test. In addition, the half-life of the isotope is approximately two hours so it needs to be used in a timely manner (Bybel et al., 2006; Kapoor, McCook, & Torok, 2004).

Magnetic Resonance Imaging (MRI) is used to identify structures of the body and provides greater contrast between tissues than does CT scanning and it is especially useful for imaging brain structures. Magnetic Resonance Imaging uses a magnetic field to align the nuclear magnetization of hydrogen atoms in water in the body. The advantage of MRI is that there is no radiation involved in the scanning process. Limitations include claustrophobia for the patient, the need for MR compatible equipment for patients who come from the ICU, and verification that any implants are compatible with MR scanning (Riederer, 2004).

Computerized tomography scanning uses digital geometry and radiation to reconstruct images. Current scanners can provide three dimensional reconstruction images of various body parts. Limitations of CT scanning include a high amount of radiation exposure and artifact (Beckmann, 2006). All of these imaging methods require that the patient be moved from their location and transported through the hospital to the location of the scanner. As transportation of a critical or acutely ill patient can potentially be a time of high risk, these tests are not ideal for the measurement of CBF and do not lend themselves to frequent assessment by the bedside nurse.

Measures of cerebral perfusion pressure. Cerebral perfusion pressure is the difference between the mean arterial pressure (MAP) and the ICP. Obtaining an accurate MAP is essential

in the measurement of CPP. This can be obtained through the use of an intra-arterial catheter placed in the radial artery that is connected to a calibrated transducer and leveled to the phlebostatic axis or the Foramen of Munro. In addition, an ICP monitor is required. The ICP monitor is placed in the ventricles or in the brain parenchyma. Placement in the ventricles allows for drainage of cerebrospinal fluid (CSF) which is an important modality in controlling increased ICP. The calibrated transducer is connected to the intraventricular catheter and leveled to the Foramen of Monro. Intraparenchymal catheters are placed if the ventricles are inaccessible due to edema or midline shift. While the intraparenchymal catheter provides measures of ICP and calculation of CPP, the “gold” standard is the intraventricular catheter (Brain Trauma Foundation, 2000). Measurement of CPP provides indirect information about CBF and has been used in many centers as a surrogate for CBF. The difficulty with using CPP as a surrogate for CBF is that once the monitoring devices are removed and the patient is no longer in the ICU, determining this information is difficult and is not routinely part of post-ICU care.

In summary, while several researchers have attempted to determine the most effective measure of CA and the effects on patients, most of the studies have been conducted on either healthy volunteers or with patients who are critically ill and in the ICU (Hlatky, et al., 2006; Kirkness, et al., 2001; Lang & Chesnut, 2000; Steiner, Coles, Czosnyka, et al., 2003; Tiecks, et al., 1995). No studies have determined if or how CA can be measured in patients who are in the acute care setting but no longer in the ICU and none indicate the impact of common nursing procedures, such as position change, on CA. The standard measures described in this section are expensive, invasive; require movement of the patient out of the ICU and the results are not readily accessible to the bedside clinician. In addition, performance of these methods requires

knowledgeable individuals with extensive training and cannot reasonably be performed by the bedside clinician during the course of daily care of the patient.

Baroreflex Sensitivity

Under normal conditions, repositioning an individual from supine to upright stimulates the baroreflex. Receptors located in the carotid artery and aortic arch recognize a change in BP and respond by sending impulses to the NTS in the brainstem which then leads to a correction of BP through change in HR (increase or decrease) to return BP to normal. The ANS also responds to signals from the NTS sent through the hypothalamus and leading to vasodilation or vasoconstriction to modulate BP (Wieling & Karemaker, 2000). Since CA may be impaired after TBI and the baroreflex and ANS work in concert to maintain blood flow to the brain, BRS may be a non-invasive method of assessing CA at the bedside.

Baroreflex sensitivity can be measured both invasively and non-invasively. Invasive measures require the placement of an arterial monitoring device and measurement is often performed using vasoactive agents to stimulate a high blood pressure (Wieling & Karemaker, 2002). This method of measurement is appropriate for those patients who are in an intensive care unit but is not practical in non-intensive care units or out-patient settings.

Methods of Measurement of Baroreflex Sensitivity

Instruments. Numerous devices have been identified that can measure BRS and include non-invasive blood pressure devices such as Finapres[®], tonometry and sphygmomanometry. Measurement of BRS necessitates the ability to measure beat by beat blood pressure and heart rate. Use of the sphygmomanometer does not allow for beat by beat measures but can provide information about trends of blood pressure in an individual. The information provided by the

sphygmomanometer is useful in the day to day measurement of blood pressure but is not helpful in patients who require more concise diagnosis of autonomic function. The Finometer Pro[®] (FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands) is based upon the volume-clamp method which allows measurement of blood pressure on a beat by beat basis non-invasively using the finger (Bondar, et al., 1997; Davies, et al., 2002; Robinson, et al., 2003). Another technique that is available is the use of a tonometric blood pressure device (Colin Medical, San Antonio, TX) that measures blood pressure non-invasively from a pressure sensor placed over the radial artery (Zion et al, 2003). The Finometer Pro[®] was used in this research. Normal values for BRS are measured in heart rate in ms/mm Hg and are used to determine baroreflex control of the heart rate. Normal values range from 7 ms/mmHg to 49 ms/mmHg depending on the age and gender of the subject (Tank, 2000).

Testing baroreflex sensitivity. Various physiologic systems contribute to the maintenance of blood pressure. These systems include the neurocardiovascular (neural), humorocardiovascular (humoral), capillary-fluid shift system and the renal-angiotensin-aldosterone system (RAAS) (Wieling & Karemaker, 2002). The neural system is the fastest acting and the RAAS is the slowest for regulation of blood pressure. For those individuals where autonomic failure is suspected, the arterial baroreflex is most commonly assessed.

Commonly used methods for determining BRS in non-critically ill subjects include head up tilt or upright standing, Valsalva maneuver and phenylephrine challenge. These methods decrease venous return and cardiac output and cause the baroreflex to work toward stabilization of the blood pressure (Pickering, Gribbin, Petersen, Cunningham, & Sleight, 1972; Smyth, Sleight, & Pickering, 1969; Wieling & Karemaker, 2002). An abrupt change in the position of

the subject will stimulate the baroreflex. Information about BRS may be obtained while monitoring blood pressure and heart rate while observing the vagal change in heart rate after the position change. Vagal changes are faster than the sympathetic effects on the vascular system. The information obtained can be evaluated based on the relationship between the change in blood pressure and heart rate (Critchley, 2005).

In healthy individuals, upon standing, the heart rate increases abruptly and peaks at about three seconds, increases further to a second peak at about 12 seconds, declines to a relative bradycardia at about 20 seconds and then rises again. The primary heart rate is a response due to the voluntary contraction of muscles on initial rising. Inhibition of cardiac vagal tone and an increase in sympathetic outflow due to baroreflex activity causes the secondary rise in heart rate. The final decrease in heart rate is due to recovery of the arterial pressure and is mediated through the baroreflex due to an increase in vagal output. Because it may be difficult to quantify the primary peak, the secondary peak is usually used to determine the HR response to the position change. The highest HR in the first 15 seconds after position change is determined and expressed as the increase from baseline (Δ HRmax). This result provides the magnitude of the HR change and provides information regarding instantaneous HR control (Steinback, 2005; Wieling, 2002).

Changes in blood pressure that occur on standing in healthy individuals include an increase in diastolic pressure by about 10 mmHg and minimal or no change in systolic blood pressure. A decrease in arterial blood pressure upon standing can be due to changes in either the systolic and diastolic pressure together or only systolic blood pressure changes. Changes in blood pressure that are due to autonomic changes are usually in both systolic and diastolic pressures. An abnormal blood pressure response to standing is more than a 20 mmHg drop in systolic

pressure and/or a drop in diastolic pressure of more than 5-10 mmHg. These results are considered abnormal regardless of the age of the subject. Those with high supine systolic blood pressures are likely to have larger drops in blood pressure in the upright standing position (Steinback et al., 2005; Wieling & Karemaker, 2002).

Tank and colleagues (2000) tested healthy volunteers in six age groups with 127 women and 135 men while they were supine for seven minutes and also while deep breathing (six breaths/minute for 15 cycles). Results of the testing identified age delineated BRS that can be used in comparing healthy subjects to those who are not. The results of Tank and colleagues research were used as the reference values in this research.

Baroreflex sensitivity is quantified as the quotient of induced change in pulse interval over the change in systolic blood pressure, providing a measure in ms/mmHg. For this study, the change in pulse was the difference in heart rate (in ms) as measured by the electrocardiogram for 30 seconds while supine (at the end of 10 minutes in supine position) and immediately upon sitting up (from supine to the torso suddenly raised to a 90° angle). Change in systolic blood pressure was based upon the blood pressure (as measured by the Finometer Pro[®]) taken at the same time as the pulse rate in the supine and sitting up positions. (Tank et al, 2000; Wieling & Karemaker, 2002).

To determine the changes in BP, the magnitude of the response was measured. This measurement is obtained by examining the systolic and diastolic trough and the systolic and diastolic overshoot. An initial decrease in systolic BP of more than 20 mm Hg or in the diastolic BP of more than 5 mm Hg is considered abnormal. The time of measurement of this information was 30 seconds after the position change (Wieling & Karemaker, 2002).

In the subject who has sustained a head injury and is not in the ICU, changing position to a head upright state should provide information about BRS without overly taxing the subject or placing that person at increased risk for injury. It may be difficult to elicit a Valsalva maneuver in someone who has sustained a TBI due to inability to fully comprehend instructions or lack of ability to perform the maneuver if there is a motor deficit. Therefore, this research study used a head up maneuver (lying supine to sitting with the assistance of the investigator).

Findings in Neurological Diagnoses

Research in BRS in neurological disorders has primarily been conducted in patients with cerebrovascular or cardiac disease (Goldstein, et al., 1998; Johnson, Shore, Potter, Panerai, & James, 2006; Maturri, et al., 2005; Nasr, et al., 2005; Robinson, et al., 2003), healthy volunteers (Ainslie, Celi, McGrattan, Peebles, & Ogoh, 2008; Pickering, et al., 1972; Smyth, et al., 1969; Steinback, et al., 2005; Tank, et al., 2000; Tzeng, Lucas, Atkinson, Willie, & Ainslie, 2010; Zion et al., 2003), autonomic failure (Bondar, et al., 1997) and heterogeneous samples which included pediatric TBI patients (Goldstein, et al., 1998). One study evaluated the relationship between BRS and CA in healthy subjects using head-tilt, thigh cuff release and phenylephrine challenge. The results indicated that those individuals with attenuated dynamic CA had greater BRS indicating that there might be a compensatory mechanism of interaction between BP and CA in humans (Tzeng, Lucas, Atkinson, Willie, & Ainslie, 2010).

Studies in cerebrovascular disease have predominated and have indicated that cardiac BRS is impaired in stroke leading to increased mortality and a poor long term prognosis (Nasr, et al., 2005; Robinson, et al., 2003). One study conducted in healthy volunteers established baseline values for BRS for six age groups. In addition, the study indicated that there was a decrease in

BRS in those aged between 40 and 50 years; heart rate increased and blood pressure decreased in women and BRS was similar in males and females as they aged (Tank, et al., 2000). These reference values were used in this research for comparison purposes.

Findings in Traumatic Brain Injury

In the study conducted by Goldstein and colleagues (Goldstein, et al., 1998), 24 pediatric patients with brain injury (TBI, anoxic/ischemic injury, CNS infection and intracranial hemorrhage) were studied to determine if there was uncoupling of heart rate variability (HRV) and BRS in neurological injury. There were 14 girls and 10 boys with an age range of 0.2 to 17.5 years. The average GCS score was 9. Correlations were present between GCS and mean HR ($r = 0.212$, $p = 0.006$,); Glasgow Outcome Score and mean HR ($r = 0.234$, $p = 0.02$,); survival and mean HR ($r = 0.294$, $p = 0.004$,); and brain death with mean HR ($p = 0.02$). The research indicated that there was uncoupling between autonomic and cardiovascular systems at various locations including the brain, sinoatrial (SA) node, peripheral vasculature and the arterial baroreceptors and were completely uncoupled in brain death indicating that the heart and the ANS no longer communicated with one another and were independent from each other. The limitations of this study were the small sample size, the variety of neurological insults and that the patients were children, not adults. If all of the patients had sustained a TBI, it would be easier to determine the applicability of the research to the TBI patient population; however, inferences can be made that BRS changes with an acute TBI which can lead to changes in blood pressure and heart rate, and therefore, CBF. In addition, these patients were in the pediatric age group which is different than the adult population, particularly with regards to plasticity of the brain,

however, that there were BRS changes in this patient population may indicate that similar changes would occur in the adult population of patients with brain injury.

In a pre-clinical animal study, McMahon and colleagues (2011) evaluated BRS after mild and moderate TBI using a phenylephrine challenge. Severe TBI was not evaluated in this particular study. The results indicated that BRS was abnormal and that the abnormality was sustained for up to 30 minutes after the TBI. This study has more applicability to human TBI as the rats only had TBI. Unfortunately, severe TBI was not evaluated, thus, it is not clear if disordered BRS would be similar in human subjects with more severe injury.

Impact of Nursing Procedures on Autoregulation

The above cited studies were conducted in a variety of subjects (rats, healthy volunteers, TBI and cerebrovascular disease) and in various settings, including out-patient and ICU. The care of these subjects, particularly those in the acute in-patient setting was provided by nurses. The research studies considered nursing care issues in the context of the study and some researchers did not perform the research protocols if the patient had to receive any nursing care such as suctioning, physical therapy, chest percussion or other disturbances (Czosnyka, et al., 1996; Lang, E. W. & Chesnut, 2000; Lang, E. W., Mehdorn, Dorsch, & Czosnyka, 2002) whereas, others did not indicate if the subjects received any of these interventions during the study (Hlatky, et al., 2006; Steiner, Coles, Czosnyka, et al., 2003). In addition, most of the research reviewed was conducted by individuals who are not nurses and may not have taken nursing care issues into consideration. Therefore, it is not known what the impact of nursing care is on CA.

Positioning. Positioning of patients with the head of the bed elevated to 30° after TBI has become a routine component of nursing practice. Research conducted since 1978 has indicated that ICP decreases when the head of the bed is elevated and the head is maintained in neutral, mid-line position (Mitchell & Mauss, 1978; Sullivan, 2000; Winkelman, 2000). Other studies have indicated that positioning of the patient should be individualized based upon the response of the patient to a change in head of bed elevation, particularly when examining the effect of positioning on CPP (March, et al., 1990; Simmons, 1997). Studies were conducted in patients with TBI, stroke and other cerebrovascular disorders (Ng, et al., 2004; Schneider, v. Helden, Franke, Lanksch, & Unterberg, 1993; Wojner-Alexandrov, Garami, Chernyshev, & Alexandrov, 2005; Wojner, El-Mitwalli, & Alexandrov, 2002). None of the studies conducted examined CA and the effect of positioning on CA.

Positioning of the patient may lead to decreased CBF, CPP or oxygenation. These data are carefully monitored in the ICU. Given that CA is abnormal after TBI and can lead to a poorer outcome (Czosnyka, et al., 1996; Golding, Robertson, & Bryan, 1999), it is important to be able to determine if routine position changes affect CBF and CA. Patients with abnormal CA are dependent on systemic BP to maintain adequate CBF. Changes in position, particularly sitting upright, may lead to a decrease in systemic BP causing decreased CBF or CPP and changes in oxygenation which then may lead to abnormalities in neurological status and secondary brain injury.

Cognition/Memory

Cognition is a broad term that includes various functions of the brain, including memory, judgment, reasoning, personality and emotion. It has been reported that TBI leads to changes in

cognition (Benedictus, Spikman, & van der Naalt, 2010; Davis, 2000; Jorge, 2005; McCullagh & Feinstein, 2005; Nicholl & LaFrance, 2009; Novack, Anderson, Bush, Meythaler, & Canupp, 2000; Oh & Seo, 2009) which then affects quality of life and return to functioning in society (Novack, et al., 2000; Oh & Seo, 2009; Ono, Yamaura, Kubota, Okimura, & Isobe, 2001). Pathways for CA regulation include the hypothalamus, the insular cortices, nucleus tractus solitarii and the neural control of memory overlaps many of these pathways through the subcortical white matter tracts (McAllister, 2011; McCullagh & Feinstein, 2005) (Figure 1- 7). Given this overlap, it is possible that a cognitive assessment tool, such as the GOAT, could provide information about CA status and assist in identifying the appropriate timing of nursing care procedures.

The GOAT measures temporal orientation (time, place, and person) and estimations of the time before the injury (retrograde amnesia [RA]) and the time after the event for which the patient has no memory (post-traumatic amnesia [PTA]). Patients are questioned regarding the day of the week, the date (month, day and year) and the time of the day. The GOAT also asks about the biographical data (name, birthdate, address). There are a total of 10 questions with error points assigned to each question. If the patient misses the answer, the error points are subtracted from 100 to provide a final score (Levin, et al., 1979).

In the development of the GOAT, 50 subjects with mild TBI were questioned using the tool. Patients were evaluated near the time of hospital discharge in order to assure that they had recovered sufficiently to answer the questions. Based on the results, patients were determined to be borderline abnormal if their score was between 66 and 75 and defective if their score was less than 66. Reliability of the GOAT was determined using two examiners who obtained 21 pairs of

scores from 13 hospitalized TBI subjects. Analysis of the pairs of GOAT scores revealed a Kendall r correlation coefficient of $r = .99$ ($p < 0.001$). Validity of the GOAT was determined by administering the test to patients with TBI over time, until they reached a score of 75 or greater and evaluating the Glasgow Coma Scale (GCS) score. Components of the GCS (eye opening, best motor response, best verbal response) were then evaluated with the GOAT score. Impaired eye opening was highly related to orientation on the GOAT ($X^2 = 21.09$, $p < 0.00001$). Impaired motor response was also highly related to performance on the GOAT ($X^2 = 18.98$, $p < 0.00001$). Expressive language dysfunction and GOAT performance were also related ($X^2 = 19.53$, $p < 0.00001$) (Levin, et al., 1979).

The GOAT is an easily administered tool that can be used on a daily basis to assess the patient's memory and cognition. Once the score is ≥ 75 , it is possible that this may provide information about CA status. In a study by Zafonte and colleagues, the length of PTA, as assessed by the GOAT, predicted outcomes for TBI patients in the areas of disability, functional status, cognitive and motor status at the time of discharge from the rehabilitation setting (Zafonte et al., 1997). Research by another group identified that the duration of PTA assessed by the GOAT affects long term outcome after TBI (Ellenberg, Levin, & Saydjari, 1996).

Summary

This literature review has focused on TBI, CA, BRS and cognition. Injury to the brain can be significant in patients with TBI and it is known that CA is impaired after a TBI. What is not known is when CA returns. In addition, impaired CA may mean that the patient will be unable to regulate blood flow in a way that prevents secondary brain injury. One way of regulating blood flow is with the physiological responses of the baroreceptors. If the

baroreceptors remain intact, CBF should be maintained. Research has indicated that BRS may not be intact and CBF will be blood pressure dependent. The effect of this is that positioning of the patient may lead to a drop in CBF, secondary brain injury and a poorer outcome. Nurses position patients routinely and need to be aware of the effect of BRS on TBI and CA so that interventions can be provided that prevent or decrease secondary brain injury.

Chapter 3

Theoretical Framework

This chapter will describe the theoretical framework of the research project. The concepts of baroreflex sensitivity (BRS), autonomic regulation of cerebral circulation and cerebrovascular autoregulation (CA) will be discussed. Fawcett (2000) describes the Conceptual-Theoretical-Empirical (CTE) system of nursing knowledge as the “translation of components of the structural hierarchy of contemporary nursing knowledge for the real world of clinical nursing practice”. (Fawcett, 2000, p. 37). The concepts identify the phenomenon of interest, the theoretical component is composed of the propositions that state relatively concrete and specific relations between concepts and the empirical indicators are conditions or instruments that are used to measure the concepts (Fawcett, 2000). These aspects of theory analysis will be used to describe the proposed research in the context of the General System Theory (GST) (von Bertalanffy, 1968).

General System Theory

Constructs

The GST was proposed by von Bertalanffy in 1968. Von Bertalanffy describes the increasing specialization of science such that individuals in diverse fields were developing theories that were similar but not known to one another. In addition, he stated that the

...organismic conception is basic for modern biology. It is necessary to study not only the parts and processes in isolation, but also to solve the decisive problems found in the organization and order unifying them, resulting from dynamic interaction of parts, and making

the behavior of parts different when studied in isolation or within the whole (von Bertalanffy, 1968, p. 31).

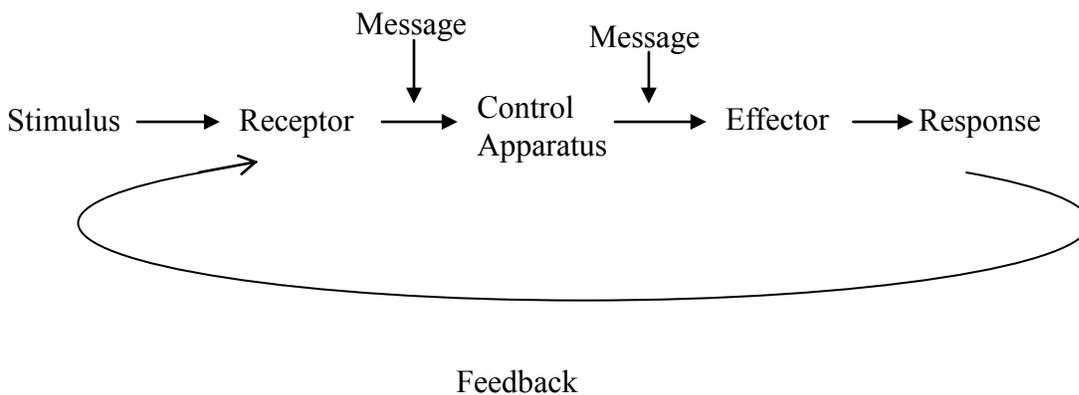
He further suggests that rather than choose from a specific field, principles that apply to systems in general should be prescribed. The aims of GST are to include integration of the various sciences, to be an important means for determining theory in nonphysical fields of science, and to develop unifying principles through science leading to integration in scientific education (von Bertalanffy, 1968).

The GST was developed to include many scientific disciplines but this research will applied the GST as it pertains to biological systems. The GST describes the organism as an open system (a system that maintains itself in a continuous exchange with the environment) (von Bertalanffy, 1968). Open systems are able to maintain a steady state where the system remains constant. This can be applied to man and environment but also to components of the internal environment, such as the brain. Studying the brain within the context of its interaction with its environment will provide different information than studying the brain outside of it. The GST is applicable to the research as the brain, ANS, baroreflexes and CA are part of a system that interacts within a whole. This theory has additional application to patients with TBI as the GST proposes that when certain aspects of a system are unknown, one can explain the phenomenon without knowing all aspects of the process (von Bertalanffy, 1968). The GST addresses the phenomenon of homeostasis, where organisms are maintained in a steady state. This is a feedback model and a circular process where information is relayed back to the input (Figure 3-1) and makes the system self-regulating. The following components are considered essential in feedback systems: (a) regulation is based on pre-established structures, (b) linear and uni-

directional causal trains and (c) “open” feedback (homeostatic) phenomena with respect to incoming information. Physiologically, the feedback model accounts for “secondary regulations” in metabolism, neurohormonal control or cell metabolism (von Bertalanffy, 1968, pp. 161-163). As this research examined the results of feedback between CA and BRS, this framework was appropriate.

The feedback loop delineated in Figure 3-1 shows the constructs developed by von Bertalanffy. A stimulus initiates the feedback loop and influences the receptor. The receptor is a sense organ which sends a message in the form of nerve conduction to the control apparatus. The control apparatus acts as the relay center and transmits messages to the effector. The effector responds to the incoming message in such a way as to have an output of energy. The response of the effector is sent back to the receptor. This process makes the system self-regulating and guarantees direction of action or stabilization (von Bertalanffy, 1968).

Figure 3-1. Schematic of General System Theory

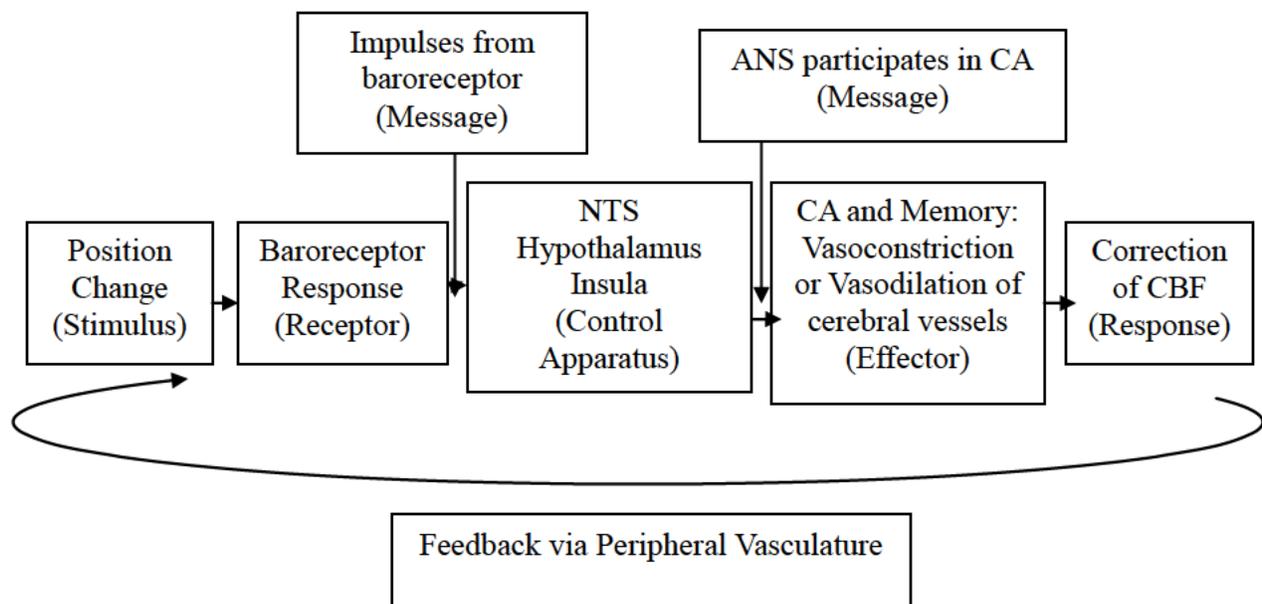


Adapted from von Bertalanffy, L. (1968). *General system theory: Foundations, development, applications*. New York: George Braziller.

Concepts

General System Theory is a theory of wholeness and homeostasis. This theory is applicable to the patient with TBI particularly in the context of BRS, CA and autonomic influence on cerebral circulation as they work in concert to assure that blood flow to the brain is maintained through a variety of changes in blood pressure and heart rate. While this research evaluated these connections, determining if there is an identifiable measure of BRS that can easily be used by the bedside clinician is the ultimate goal. These concepts are outlined in Figure 3-2.

Figure 3-2. Schematic of General System Theory with Baroreflex Sensitivity, Cerebrovascular autoregulation and Memory



Adapted from von Bertalanffy, L. (1968). *General system theory: Foundations, development, applications*. New York: George Braziller.

For this research, the elements of the concepts included position change as the stimulus, baroreflex sensitivity and CA as the responses, the NTS, insular cortices and the hypothalamus

are the control apparatus, change in vessel diameter is the effector and the response is the change in CBF.

Baroreflex. Under normal conditions, changes in systemic blood pressure are sensed by the arterial baroreceptors located in the carotid arteries and the aortic arch. These receptors are stretch receptors that respond to increases and decreases in blood pressure (response). Arterial baroreceptors cause excitation of the cardiac vagal centers and inhibition of the sympathetic vasomotor centers in the brainstem. This leads to a decrease in arterial blood pressure, because of decreased vagal excitation and sympathetic inhibition which causes an increase in heart rate, cardiac contractility and vasomotor tone in an effort to restore blood pressure to normal. In addition, if the baroreceptors are stimulated as a result of an increase in arterial pressure, adjustments occur to oppose that increase in blood pressure. Changes that occur as a result of baroreceptor activity occur quickly, often in less than two to three seconds (Weiling & Karemaker, 2002).

Nucleus tractus solitarii, hypothalamus and insular cortices. The NTS is located in the brainstem and relays information to the hypothalamus. This information includes that from the baroreceptors (control apparatus). The hypothalamus then sends information to the insular cortices which stimulate ANS function causing a change in the diameter of the cerebral blood vessels (effector). The change in diameter regulates blood flow to the brain. In addition, the heart is stimulated to regulate its rate, depending on whether the BP needs to be raised or lowered. All of these parts work in concert to maintain homeostasis and CBF.

Cerebrovascular autoregulation. Implied in the framework is CA as the effector. Cerebrovascular autoregulation is the ability of the blood vessels of the brain to maintain a

constant blood flow regardless of the systemic BP. Blood flow to the brain is maintained due to variations in cerebrovascular resistance in response to changes in blood pressure, and under normal circumstances is relatively independent from systemic blood pressure (Aaslid et al, 1989; Diehl et al, 1998; Lavinio et al, 2007). In the injured brain, blood flow is dependent on systemic BP because CA is impaired.

Cerebrovascular autoregulation is influenced by the ANS. Information from the NTS is transmitted to the hypothalamus and then to the insular cortices. The insular cortices have central control of the ANS, whereas peripheral control is determined through the sympathetic and parasympathetic ganglia that are situated along the spinal column. The neurological pathways that regulate CA adjust the caliber of the cerebral blood vessels without changes in perfusion pressure and are composed of two systems, intrinsic and extrinsic. The intrinsic system is made up of nerves that arise within the brain and pass through the substance of the brain to innervate the parenchymal vessels. The extrinsic system is the part of the ANS that influences CBF. Influence from the trigeminal nerve (CN V) reflexively controls vasodilator effects in the cerebral circulation (Edvinsson et al, 1994; Franchini et al, 2004; Goadsby, 2004). Correction of the HR, BP and CBF occur as a result of the interaction of the baroreflexes and the ANS and has an impact on CA.

Empirical Indicators

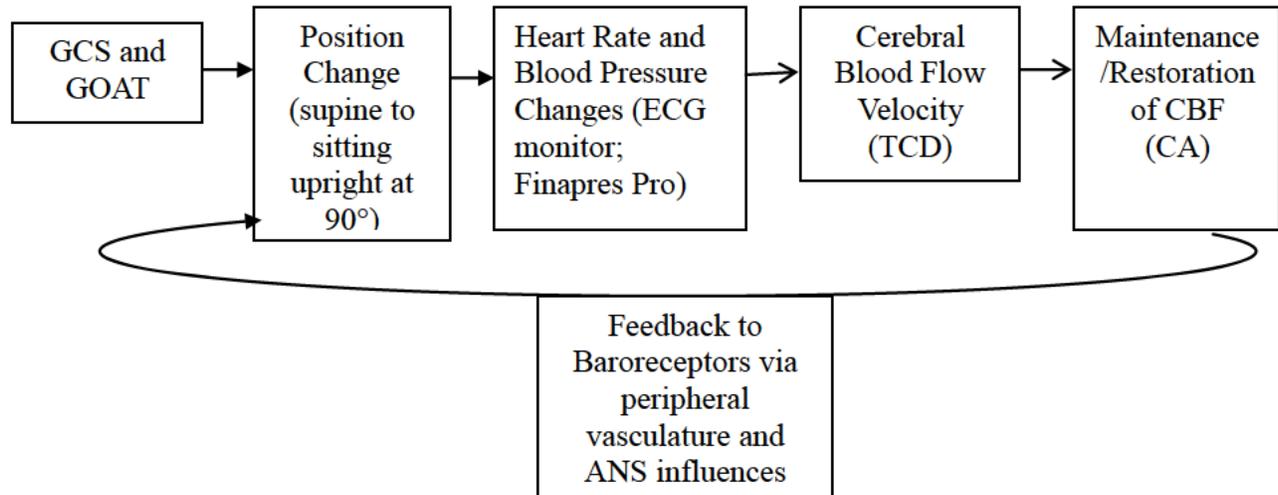
For this research there were several empirical indicators that assisted in identifying whether or not BRS can be used as a surrogate measure for CA. Heart rate and BP are routinely measured in the patient with TBI from the time admission until discharge. These standard physiological measures are determined either through the use of an electrocardiographic (ECG)

monitor or by counting a pulse (heart rate) or using a sphygmomanometer or electronic non-invasive BP device.

Cerebral blood flow velocity was measured using a transcranial Doppler (TCD) ultrasound device. The TCD measures CBFV in various components of the cerebral vasculature and provides information about CBF and CA status.

The Glasgow Coma Scale (GCS) score provides information about the severity of the brain injury. Those with a moderate TBI have GCS scores of 9-12 whereas, those with severe TBI have GCS scores ≤ 8 (Teasdale & Jennett, 1974). Severity of injury may affect CA. The Galveston Orientation and Amnesia Test (GOAT) was developed to assess cognition in patients who have sustained a TBI. The GOAT measures the major components of orientation, estimation of post-traumatic amnesia (PTA) and an estimate of the time interval before the injury for which the patient has no recall (remote amnesia [RA]) (Levin, et al., 1979). For the research, the GOAT was used to determine the ability of the subjects to provide informed consent. A score < 75 indicates that the subject continues to have PTA and therefore cannot provide informed consent. The GOAT will also be used to assess CA status. The empirical indicators are shown in Figure 3-3.

Figure 3-3. Schematic Using Empirical Indicators



Adapted from von Bertalanffy, L. (1968). *General system theory: Foundations, development, applications*. New York: George Braziller.

In summary, the GST provides a framework for the research that is holistic and focuses on maintaining homeostasis. The constructs and empirical indicators fit into the framework in a manner that allows the organism to adapt via a feedback loop to the event that is occurring namely, response to position changes.

Chapter 4

Research Methodology

This chapter will describe the study design, the settings and sample, instruments used for measurement of variables, data collection procedures and the methods of statistical analysis.

Study Design

This study used a two group comparative design to examine the relationships between baroreflex sensitivity (BRS), cerebrovascular autoregulation (CA) and cognition.

Settings

Data for this study were collected from the neuroscience unit and the acute brain injury unit at Ronald Reagan UCLA Medical Center (UCLA) and Rancho Los Amigos National Rehabilitation Center (Rancho). The neuroscience unit at UCLA is a 26 bed unit that cares for patients with various neurological and neurosurgical diagnoses including TBI. The acute brain injury unit at Rancho is a 30 bed rehabilitation unit that provides rehabilitation for patients who have sustained a TBI or other brain injury such as stroke.

Sample

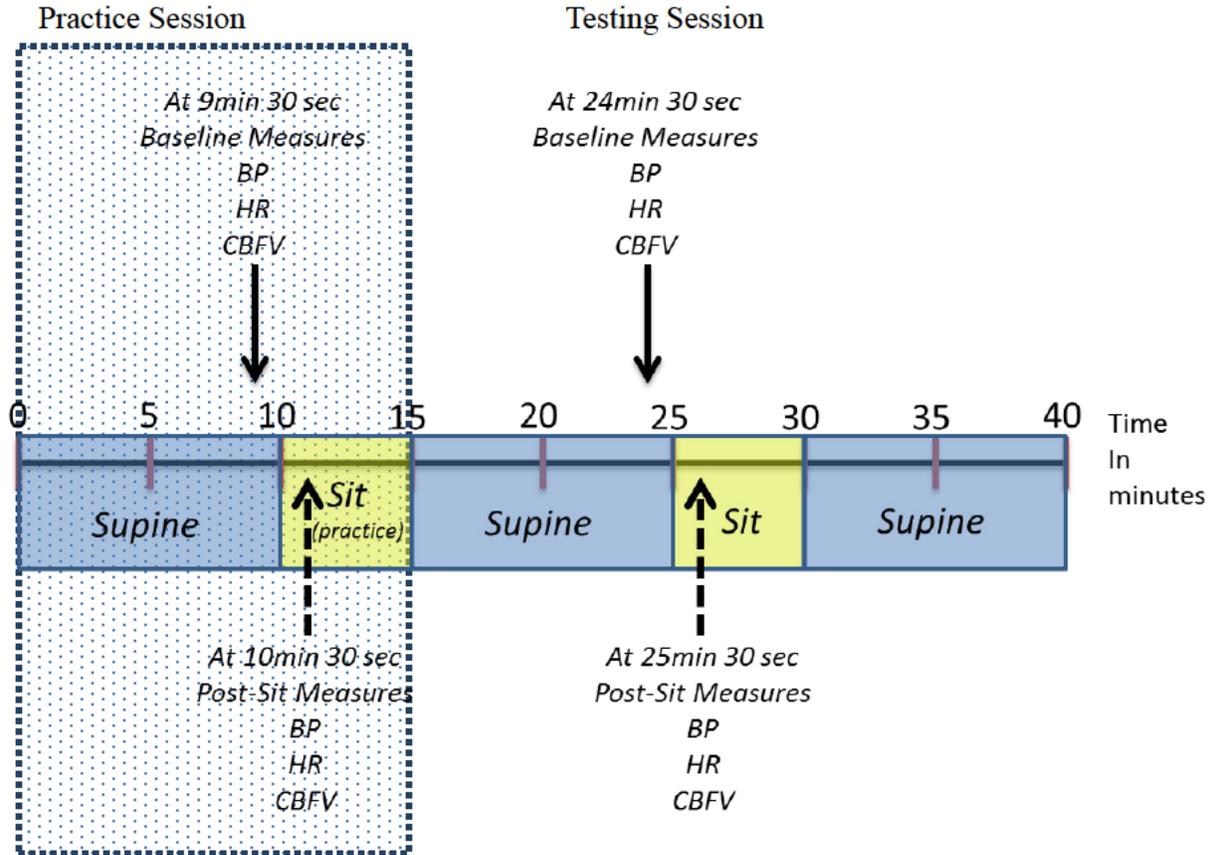
Traumatic brain injury subjects were recruited from UCLA and Rancho. Healthy subjects (controls/healthy volunteers [HV]) were recruited from staff and students at UCLA. The convenience sample consisted of 52 subjects (26 TBI and 26 age- and gender-matched HV). The TBI subjects were included in the study if they were 18 – 65 years of age, had recently sustained a moderate to severe TBI (Glasgow Coma Scale score [GCS] ≤ 12), were able to provide informed consent or had a proxy surrogate available who could provide consent, could read and follow instructions in English, had a physician order for out of bed activity and were no longer

being cared for in the intensive care unit (ICU). Healthy subjects were age- and gender-matched to the TBI group, had no history of a TBI, were able to provide informed consent and could read and follow instructions in English. Subjects in either group were excluded if they had atrial fibrillation or pre-existing heart disease (heart failure or myocardial infarction). These exclusions were identified because they affect BRS and it would be difficult to determine if one of these had an effect on the results versus assessing BRS alone. A GOAT score of < 75 and proxy consent that could not be obtained were also exclusion criteria for the TBI subjects.

Screening for potential subjects occurred as follows. For the TBI group, potential subjects were identified by the charge nurse on the unit. A chart review determined appropriateness of the subject for the study and included review of the history and physical, radiology reports (CT scan and MRI), current medications and co-morbid conditions. The TBI subjects were also administered the GOAT to determine if proxy consent would be needed. In the HV group, subjects were screened for previous TBI, stroke, cardiac arrhythmias, medication use and hypertension once they arrived for the scheduled testing time.

Head injured subjects were tested in their hospital bed, while HV subjects were tested in the neurophysiology lab at UCLA away from hospital activity. In order to assure that the subjects were comfortable with the study procedure and equipment, a practice position change was conducted using all equipment 15 minutes before actual data acquisition. Data collection occurred at two time points (30 seconds prior to the position change and 30 seconds after the position change) (Figure 4-1).

Figure 4-1. Timeline for study protocol



Legend: BP = blood pressure reading from Finometer Pro[®]; HR = heart rate; CBFV = cerebral blood flow velocity from TCD

Measurement of Variables

Baroreflex sensitivity reflects peripheral ANS activity and is calculated as heart rate/blood pressure (Tank, et al., 2000; Wieling & Karemaker, 2002). Baroreflex sensitivity was measured using a non-invasive device (Finometer Pro[®] [FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands]) to obtain heart rate and blood pressure measures. The Finometer Pro[®] consists of two cuffs. One cuff was placed on the upper arm and the other was placed on the middle finger of the same extremity. The device continuously measures HR and BP in a beat to

beat method. It uses the volume clamp and return to flow methodology to obtain the pressures and the HR (Finometer Pro[®] [FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands]). Use of the Finometer has been shown to be a valid substitute for intra-arterial blood pressure measurement in several studies with correlations as high as $r = .94$ (Guelen et al., 2003; La Rovere, Mortara, & Schwartz, 1995; Schutte, Huisman, van Rooyen, Oosthuizen, & Jerling, 2003; Zion, et al., 2003). Baroreflex sensitivity was manually calculated as heart rate in ms/mean arterial blood pressure in mmHg and obtained at the same time as CBFV measures (Figure 4-1). Baroreflex sensitivity was measured as a continuous variable and was also categorized as normal and abnormal based on published norms (Tank, et al., 2000). Normal values for BRS range from 3 to 49 ms/mmHg in adult subjects and vary depending on the age and gender of the individual (Tank, et al., 2000; Wieling & Karemaker, 2002). For example, in a 40 – 49 year old female, the normal range would be 6 – 12 ms/mmHg whereas in a 50 – 59 year old male, the normal range would be 3 – 9 ms/mmHg (Tank, et al., 2000). This method of BRS calculation has been validated (Tank, et al., 2000) and has high reliability ($r = .644 - .895$, $p < 0.05$) (Jíra, Závodná, Honzík, Nováková, & Fišer, 2006).

Cerebrovascular autoregulation was defined as CBFV through the bilateral middle cerebral arteries (MCA) (Hlatky, et al., 2006; Newell, et al., 1994). Cerebrovascular autoregulation was measured in the bilateral MCAs using a TCD headset with 2 MHz probes (Spencer Technologies, Seattle, WA). A technician with over 18 years of experience with TCD techniques performed all of the TCD studies for this research. The average of the left and right MCA CBFVs was used as the CA value in the analysis. For this study, the CA data was used as a continuous variable and also categorized as normal or abnormal. Categorization of CA was based

on published norms using numbers from DeWitt and colleagues (DeWitt & Wechsler, 1988). Use of CBFV has been validated as a surrogate measure of CA. In 1988, Ringelstein and colleagues evaluated CA status using vasomotor reactivity in patients with carotid disease. Vasomotor reactivity indicates the ability of the blood vessels to constrict or dilate to maintain perfusion. When vasomotor reserve is depleted, the vessels are unable to respond to any vasodilator stimulus which can lead to ischemia. These authors found that MCA flow increased during periods of hypercapnea (by 52%) and decreased 35.3% during hypocapnea. Evaluation of healthy subjects compared to individuals with bilateral or unilateral carotid disease indicated that there were significant differences between the healthy group, the group with unilateral occlusion and the group with bilateral disease ($p < 0.0001$) (Ringelstein, et al., 1988). The authors concluded that the use of TCD techniques can provide valuable information about cerebrovascular blood flow dynamics and may provide information regarding vasomotor reserve (CA). Reliability of TCD measures of CBFV is high (repeated measures of TCD with correlations of $r = .78$ to $.97$) (Totaro, Marini, Cannarsa, & Prencipe, 1992).

Severity of TBI was measured using the ICU admission GCS score. The GCS evaluates three categories of brain functioning: eye opening, best motor response and best verbal response. Summed scores range from 3 – 15 with 15 indicating an alert and oriented patient with no deficits (Teasdale & Jennett, 1974). Scores are categorized as follows ≤ 8 indicates severe injury, 9 – 12 indicates moderate injury and 13 – 14 indicates a mild TBI. In the original research, Teasdale and colleagues did not provide information regarding the validity of the scale items or scoring. They classified interrater reliability in terms of levels of disagreement, with low levels defined as between 0 and 0.299, and high levels between 0.3 and 0.5. Seven neurosurgeons

showed low levels of disagreement in their assessments of 12 ICU patients using the GCS. Levels of disagreement for eye opening were 0.143, verbal response was 0.0054 and motor response was 0.109 (Kornbluth & Bhardwaj, 2011; Teasdale, Knill-Jones, & van der Sande, 1978). Additional tests of interrater reliability have shown that the GCS has moderate to high agreement, especially when performed by experienced users (Heron, Davie, Gillies, & Courtney, 2001; Juarez & Lyons, 1996; Teasdale & Jennett, 1974).

The GOAT was used as an assessment of cognitive status and to determine the ability of the TBI subject to provide informed consent. The GOAT consists of 10 questions that assess orientation and time intervals before and after injury for which events are unable to be recalled. The patient begins with 100 points and earns “error” points for each incorrect answer. These points are subtracted from 100 to obtain the final GOAT score. The higher the patient scores, the better the patient’s orientation and cognition (Levin, et al., 1979). The GOAT was administered by the principal investigator (PI) at the time of study screening and recruitment in the TBI patients. For this study, a score of > 75 was considered appropriate for obtaining informed consent from the patient.

Levin and colleagues (1979) determined validity using GOAT scores from post-TBI patients. Patients were categorized based on length of time to eye opening with 14 days as the point of division. Using the initial hospital GCS as the criterion for acute injury severity and evaluating the categories of eye opening, best motor response and best verbal response, the results indicated that impaired eye opening was significantly related to a delay in regaining orientation on the GOAT ($X^2 = 21.09$, $p < 0.00001$). Patients were assessed on their motor response on the day of admission and the duration of PTA over 14 days was compared to the

initial motor response. The results indicated that a poor motor response score on admission and performance on the GOAT was significant ($X^2 = 18.98$, $p = < 0.00001$). Lastly, assessment of the verbal response on admission (those identified as confused, incomprehensible or absent) indicated that the more severely disrupted the verbal response, the longer the time for PTA to resolve, thus affecting the GOAT score ($X^2 = 19.53$, $p < 0.00001$) (Levin, et al., 1979). To establish reliability, Levin (1979) evaluated 21 pairs of GOAT scores obtained by two examiners simultaneously. The Kendall r correlation coefficient for the two scores was 0.99 ($p < 0.001$).

Data Collection Procedures

The study was approved by the University of California Los Angeles (UCLA) and the Rancho Los Amigos National Rehabilitation Center (Rancho) Institutional Review Boards (IRB). Once subjects were screened for inclusion/exclusion criteria (including administration of the GOAT in the TBI subjects), they (or their surrogate [$n = 7$]) read and signed the informed consent documents. After all documents were complete, the subject was connected to the Finometer Pro[®] and the TCD. A practice sitting up session was performed in order to familiarize the subject with the equipment and protocol in order to limit the sympathetic nervous system activation during the supine/resting period (baseline for the study). For both the practice and data collection sessions, the subjects reclined supine for 10 minutes (in their hospital bed or on a gurney) in order to maximize the sympathetic stimulation at the position change. At the end of this 10 minute resting period, each subject was elevated to an upright sitting position in less than one second by the PI and a research assistant who placed the flat of their hands behind the subject's back and lifted the subject to an upright (90° angle) sitting position. This upright sitting position was sustained for five minutes, after which the subject was laid supine in less than one

second followed by 10 minutes in the supine position. Data was collected at two time points: 30 seconds prior to the position change and 30 seconds after the position change because McMahon and colleagues (2011) using a phenylephrine challenge in their pre-clinical rat study indicated that BRS was abnormal up to 30 minutes after a TBI. It was difficult to obtain valid and reliable measures on TCD prior to the 30 second interval as the TCD equipment available for this study did not collect continuous data during the position change. At the end of the study period, the TBI subject was disconnected from all equipment and returned to the care of their nurse. The HV subjects were disconnected and allowed to return to their previous activity.

Statistical Analyses

Statistical analyses consisted of descriptive statistics, Pearson's correlations, t-tests, Chi square, logistic and linear regression (Statistical Package for the Social Sciences version 18, IBM SPSS, Inc., Somers, NY). Significance was set at $p < 0.05$. There were three specific aims for this study. The first specific aim was to examine the association between a gold standard measure of CA [(CBFV) of bilateral MCAs as measured by TCD] and BRS in adult patients who have sustained moderate to severe TBI. Pearson's correlations were performed on the continuous variables. Power analysis indicated that a sample size of 26 subjects would allow detection of a large effect (0.50) on a two-tailed Pearson's correlation test at an alpha of 0.05 and a power of 0.80 (Faul, Erdfelder, Lang, & Buchner, 2007). Sensitivity and specificity for BRS determination of abnormal CA were also calculated to determine clinical utility.

The second specific aim was to compare BRS in adult subjects who have sustained a moderate to severe TBI and a group of age and gender matched healthy controls. T-tests, Chi-square and Pearson's correlations were performed. Power analysis

indicated that a sample size of 39 subjects (18 in each group) would allow detection of a large effect size (0.5) on a X^2 test, at an alpha of 0.05 and a power of 0.80 (Erdfelder, Faul & Buchner, 2007).

The final specific aim was to examine the relationship of selected covariates (such as age, gender, post-resuscitation Glasgow Coma Scale [GCS] score, Galveston Orientation and Amnesia Test [GOAT], CBFV of the bilateral MCAs as measured by TCD, and time since TBI) and BRS and CA. The logistic regression model used was forward stepwise Likelihood Ratio because this model is best for small sample sizes (Agresti, 2007). Linear regression was also performed to determine the magnitude of the effect of variables on BRS and CA. Power analysis indicated that a sample size of 22 subjects would allow detection of a large effect size (0.35) in a logistic regression, at an alpha of 0.05 and a power of 0.80 (Erdfelder, Faul & Buchner, 2007).

Chapter 5

Results

This chapter will review the sample characteristics and the results of the research. The results will be presented in the order of the specific aims of the research project. The specific aims of the project were to:

1) Examine the association between a gold standard measure of cerebrovascular autoregulation (CA) and baroreflex sensitivity (BRS) in adult patients who have sustained moderate to severe traumatic brain injury (TBI).

2) Compare BRS in adult subjects who have sustained a moderate to severe TBI and a group of age and gender matched healthy controls.

3) Examine the relationship of selected covariates (such as age, gender, post-resuscitation Glasgow Coma Scale [GCS] score, Galveston Orientation and Amnesia Test [GOAT], cerebral blood flow velocity [CBFV] of the bilateral middle cerebral arteries [MCAs] as measured by TCD and time since TBI) and BRS and CA.

Subject Characteristics

There were 52 subjects in the study. Twenty-six had TBI, and 26 were healthy volunteers (HV). All of the HV subjects were age and gender matched to the TBI subjects. Tables 5-1 and 5-2 present baseline demographic and clinical characteristics of each group. Between the two groups, there was a significant difference in ethnicity, with more Caucasians and fewer Hispanics in the HV group compared to the TBI group. There were also more Asians in the HV group and more African Americans in the TBI group ($X^2 = 10.38$; $p = 0.016$). In addition the TBI group had more subjects with hypertension

($X^2 = 3.90$; $p = 0.048$), history of seizures ($X^2 = 5.532$; $p = 0.019$), alcohol use ($X^2 = 6.783$; $p = 0.009$) and use of beta blockers ($X^2 = 6.783$; $p = 0.009$). In the TBI group, the majority of subjects had severe, bilateral injuries with hematomas (18 severe vs. 8 moderate). The average time since injury was 52 days and the average GOAT score was 69.

Table 5-1. Comparison of Demographic and Clinical Characteristics by Group (Traumatic Brain Injury [TBI] vs. Healthy Volunteer [HV])

Characteristic	TBI Group (n = 26) Mean ± SD	Healthy Group (n = 26) Mean ± SD	p-value
<i>Age (years)</i> Range 18 – 64	37.04 ± 14.51	37.00 ± 14.45	0.992
	N (%)	N (%)	
<i>Gender</i> Male Female	18 (69.2) 8 (30.8)	18 (69.2) 8 (30.8)	1.0
<i>Ethnicity</i> Caucasian African American Asian Hispanic	6 (23.1) 3 (11.5) 3 (11.5) 14 (53.9)	13 (50) 0 (0) 7 (26.9) 6 (23.1)	0.016*
<i>Cerebrovascular autoregulation</i> Normal Abnormal	14 (53.8) 12 (46.2)	17 (65.4) 9 (34.6)	0.397
<i>Baroreflex Sensitivity</i> Normal Abnormal	20 (76.9) 6 (23.1)	21 (80.8) 5 (19.2)	0.734

Characteristic	N (%)	N (%)	p-value
Coronary Artery Disease	2 (7.7)	0 (0)	0.149
Diabetes	2 (7.7)	0 (0)	0.149
Hypertension	9 (34.6)	3 (11.5)	0.048*
Seizures	5 (19.2)	0 (0)	0.019*
Schizophrenia	1 (3.8)	0 (0)	0.313
Depression	3 (11.5)	0 (0)	0.074
Tobacco Use	4 (15.4)	1 (3.8)	0.158
Alcohol Use	6 (23.1)	0 (0)	0.009*
Angiotensin Converting Enzyme Inhibitors	3 (11.5)	3 (11.5)	1.0
Angiotensin II Receptor Blocker	1 (3.8)	0 (0)	0.313
Calcium Channel Blocker	0 (0)	1 (3.8)	0.313
Hydrochlorothiazide	1 (3.8)	2 (7.7)	0.552
Beta Blockers	6 (23.1)	0 (0)	0.009*
Selective Serotonin Reuptake Inhibitors	0 (0)	1 (3.8)	0.313
History of Migraine	1 (3.8)	0 (0)	0.313

* Significant results
SD = Standard Deviation

Table 5-2. Characteristics of the TBI group (n=26)

Characteristic	TBI Group Mean ± SD
<i>GOAT Score</i> Range 0 - 100	68.92 ± 31.56
<i>Post-injury Day</i> Range 14 – 209	51.62 ± 44.65
	N (%)
<i>Glasgow Coma Scale Score</i> Severe TBI (GCS ≤ 8) Moderate TBI (GCS 9 - 12)	18 (69.2) 8 (30.8)
<i>Location of Injury</i> Bilateral Right hemisphere Left hemisphere Posterior fossa	15 (57.7) 2 (7.7) 8 (30.8) 1 (3.8)
<i>Type of Injury</i> Diffuse Hematoma Hemorrhage Contusion	8 (30.8) 11 (42.3) 3 (11.5) 4 (15.4)

SD = Standard deviation

In the TBI group, 12 individuals (46.2%) had abnormal CA and 6 (23.1%) had abnormal BRS. There was one subject in the TBI group with had both abnormal BRS and abnormal CA. Of those with abnormal CA, 10 (38.5%) were from Rancho, and therefore had survived an extended period since their injuries. The average time since injury of the patients at Rancho was 54.88 ± 36.07 days, whereas the average time since injury for the patients at Ronald Reagan was 46.40 ± 57.63 days ($p = 0.683$). In the HV group, there

were nine (34.6%) subjects with abnormal CA and five (19.2%) with abnormal BRS. There was one subject in the HV group with both abnormal BRS and abnormal CA. Interestingly, in this study, when comparing the HV and TBI group on normal or abnormal CA, nearly an equal number in each group had abnormal CA, indicating that there are a number of healthy individuals in the community with abnormal CA. While this number was slightly higher in the TBI group than in the HV group (12 vs. 9), these differences were not statistically significant.

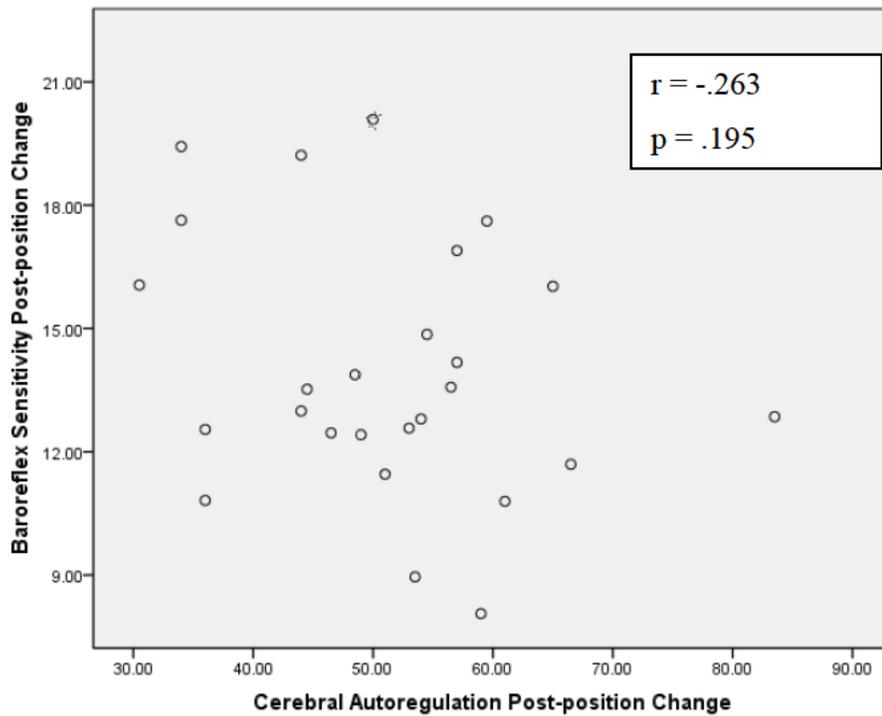
Specific Aim # 1

In the TBI subjects, there were no correlations between CA and BRS (Figure 5-1). However, correlations with other variables were noted. These significant correlations were BRS and GCS ($r = -.542, p = 0.004$); BRS and GOAT ($r = -.606, p = 0.001$) and CA and GOAT ($r = .421, p = 0.032$). In evaluating the TBI group for differences related to CA status (normal or abnormal), there were no significant differences between those with normal or abnormal CA status. Of the 12 subjects with disordered CA status, ten were evaluated in the rehabilitation setting. Sensitivity and specificity of BRS was calculated for clinical utility. Sensitivity of BRS (ability to identify abnormal CA) was low (23%) but specificity of BRS (ability to identify normal CA) was high (77%).

Pearson's correlations were performed on the continuous variables for this specific aim. A priori power analysis indicated that a sample size of 26 subjects in each group would allow detection of a large effect (0.50) on a two-tailed Pearson's correlation test at an alpha of 0.05 and a power of 0.80 (Faul, et al., 2007). The actual effect size (post-hoc) for this aim was 0.51, which would require a sample size of 25 subjects to

avoid a Type II error. Therefore, our sample of 26 TBI subjects was adequate to avoid a false negative conclusion for this specific aim.

Figure 5-1. Scatterplot of Correlation of Baroreceptor Sensitivity and Cerebrovascular Autoregulation in TBI subjects (n = 26)



Specific Aim # 2

To evaluate specific aim # 2, all subjects (n = 52; TBI and HV) were compared on BRS status (normal or abnormal). T-tests were performed to evaluate the difference between the groups based on BRS status. These results indicated there were no significant differences between those who had normal and abnormal BRS status on age, GCS score, GOAT score, post-injury day or CA status (Table 5-5). Chi-square analysis was performed on the categorical variables. These results indicated that there were significant differences in diabetes ($X^2 = 7.75$; $p = 0.005$) when compared on BRS status.

These results indicate that those individuals with diabetes are more likely to have abnormal BRS.

The sample was compared based on their CA status (normal or abnormal). T-tests and Chi-square were performed. Results of the t-tests indicated that there were no significant differences between the normal or abnormal CA groups on age, GCS score, GOAT score, post-injury day, or BRS (Table 5-3). Chi-square analysis was performed on the categorical variables. These results indicated that there were significant differences in gender ($X^2 = 4.49$; $p = 0.034$) and the use of ACE-Inhibitors ($X^2 = 5.19$; $p = 0.023$) when compared on CA status (Table 5-4). These results indicate that males and persons taking ACE-Inhibitors are more likely to have abnormal CA.

Table 5-3. T-tests for All Subjects with Baroreflex Sensitivity Classified as Normal (n = 41) or Abnormal (n = 11)

Characteristic	Normal BRS Mean ± SD	Abnormal BRS Mean ± SD	p-value
Age (in years)	35.10 ± 13.17	44.18 ± 16.83	0.120
GCS Score	11.39 ± 4.32	10.73 ± 4.17	0.649
GOAT	88.22 ± 22.49	70.45 ± 38.07	0.165
Post Injury Day	210.66 ± 163.11	199.55 ± 161.65	0.842
CA	53.11 ± 12.71	50.00 ± 11.36	0.443

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Table 5-4. Chi-Square for All Subjects with Baroreflex Sensitivity Classified as Normal (n= 41) or Abnormal (n= 11)

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
<i>Gender</i>			
Male	26 (63.41)	10 (90.91)	0.079
Female	15 (36.69)	1(9.09)	
<i>Ethnicity</i>			
Caucasian	17 (41.46)	2 (18.18)	0.296
African American	2 (4.88)	1 (9.09)	
Asian	6 (14.63)	4 (36.36)	
Hispanic	16 (39.02)	4 (36.36)	
<i>GCS (categorized)</i>			
No Injury	21 (51.22)	5 (45.45)	0.641
Moderate	7 (17.07)	1 (9.09)	
Severe	13 (31.71)	5 (45.45)	
<i>Location of Injury</i>			
No Injury	21 (51.22)	15 (45.45)	0.877
Bilateral	11 (26.83)	4 (36.36)	
Right hemisphere	2 (4.88)	0 (0)	
Left hemisphere	6 (14.63)	2 (18.18)	
Posterior fossa	1 (2.44)	0 (0)	
<i>Type of Injury</i>			
No Injury	21 (51.22)	5 (45.45)	0.788
Diffuse	6 (14.63)	2 (18.18)	
Hematoma	8 (19.51)	3 (27.27)	
Hemorrhage	2 (4.88)	1 (9.09)	
Contusion	4 (9.76)	0 (0)	
Diabetes	0 (0)	9 (81.81)	0.005*

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
Coronary Artery Disease	1 (2.44)	1 (9.09)	0.308
Hypertension	8 (19.51)	4 (36.36)	0.239
Seizures	3 (7.32)	2 (18.18)	0.278
Schizophrenia	1 (2.44)	0 (0)	0.601
Depression	2 (4.88)	1 (9.09)	0.595
Tobacco Use	4 (9.76)	1 (9.09)	0.947
Alcohol Use	4 (9.76)	2 (18.18)	0.437
ACE-Inhibitors	4 (9.76)	2 (18.18)	0.437
ARBs	0 (0)	1 (9.09)	0.051
Calcium Channel Blockers	1 (2.44)	0 (0)	0.601
Hydrochlorothiazide	4 (9.76)	0 (0)	0.355
Beta-blockers	4 (9.76)	2 (18.18)	0.437
SSRIs	1 (2.44)	0 (0)	0.601
History of Migraine	1 (2.44)	0 (0)	0.601
CA	18 (43.90)	3 (27.27)	0.318

* Significant results

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation; ARB: Angiotensin II Receptor Blocker

Table 5-5. T-tests for All Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n = 31) or Abnormal (n = 21)

Characteristic	Normal CA Mean ± SD	Abnormal CA Mean ± SD	p-value
Age (in years)	35.13 ± 14.65	39.81 ± 13.74	0.247
GCS Score	12.00 ± 3.69	10.14 ± 4.88	0.147
GOAT	89.77 ± 19.70	76.62 ± 34.39	0.124
Post Injury Day	220.39 ± 165.42	190.48 ± 157.23	0.513
BRS	12.09 + 2.93	12.73 + 3.02	0.406

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Table 5-6. Chi-Square for All Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n=31) or Abnormal (n=21)

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
<i>Gender</i>			
Male	18 (58.06)	18 (85.71)	0.034*
Female	13 (41.94)	3 (14.29)	
<i>Ethnicity</i>			
Caucasian	15 (48.39)	4 (19.04)	0.134
African American	1 (3.22)	2 (9.52)	
Asian	4 (12.90)	6 (28.57)	
Hispanic	11 (35.48)	9 (42.86)	
<i>GCS (categorized)</i>			
No Injury	17 (54.84)	9 (42.86)	0.583
Moderate	5 (16.12)	8 (38.09)	
Severe	9 (29.03)	18 (85.71)	
<i>Location of Injury</i>			
No Injury	17 (54.84)	9 (42.86)	0.695
Bilateral	9 (29.03)	6 (28.57)	
Right hemisphere	1 (3.22)	1 (4.76)	
Left hemisphere	4 (12.90)	4 (19.04)	
Posterior fossa	0 (0)	1 (4.76)	

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
<i>Type of Injury</i>			
No Injury	17 (54.84)	9 (42.86)	0.234
Diffuse	4 (12.90)	8 (38.09)	
Hematoma	4 (12.90)	11(52.38)	
Hemorrhage	3 (9.67)	3 (14.29)	
Contusion	3 (9.67)	4 (19.04)	
Diabetes	1 (3.22)	1 (4.76)	0.777
Coronary Artery Disease	1 (3.22)	1 (4.76)	0.777
Hypertension	5 (16.12)	7 (33.33)	0.149
Seizures	3 (9.67)	2 (9.52)	0.985
Schizophrenia	1 (3.22)	0 (0)	0.406
Depression	1 (3.22)	2 (9.52)	0.339
Tobacco Use	1 (3.22)	2 (9.52)	0.347
Alcohol Use	3 (9.67)	3 (14.29)	0.610
ACE-Inhibitors	1 (3.22)	5 (23.80)	0.023*
ARBs	1 (3.22)	0 (0)	0.406
Calcium Channel Blockers	0 (0)	1 (4.76)	0.220
Hydrochlorothiazide	1 (3.22)	2 (9.52)	0.339
Beta-blockers	3 (9.67)	3 (14.29)	0.610
SSRIs	1 (3.22)	0 (0)	0.406
History of Migraine	1 (3.22)	0 (0)	0.406
BRS	8 (25.81)	3 (14.29)	0.318

The group of HV subjects was evaluated on the same measures as the entire group of subjects. When the HV subjects were categorized as normal or abnormal on BRS, there were no statistically significant differences on any variables, including age and CA (Tables 5-7 and 5-8).

Table 5-7. T-tests for Healthy Subjects with Baroreflex Sensitivity Classified as Normal (n = 21) or Abnormal (n = 5)

Characteristic	Normal BRS Mean ± SD	Abnormal BRS Mean ± SD	p-value
Age (in years)	36.24 ± 13.37	40.20 ± 19.92	0.690
CA	54.52 ± 12.84	50.90 ± 15.06	0.639

Table 5-8. Chi-Square for Healthy Subjects with Baroreflex Sensitivity Classified as Normal (n = 21) or Abnormal (n = 5)

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
<i>Gender</i>			
Male	13 (61.9)	5 (100)	0.097
Female	8 (38.1)	0 (0)	
<i>Ethnicity</i>			
Caucasian	12 (57.1)	1 (20)	0.161
African American	0 (0)	0 (0)	
Asian	4 (19)	3 (60)	
Hispanic	3 (14.3)	1 (20)	
<i>GCS (Categorized)</i>			
No Injury	21 (100)	5 (100)	---
Diabetes	0 (0)	0 (0)	---
Coronary Artery Disease	0 (0)	0 (0)	---

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
Hypertension	3 (14.3)	0 (0)	0.369
Seizures	0 (0)	0 (0)	---
Schizophrenia	0 (0)	0 (0)	---
Tobacco Use	1 (4)	0 (0)	0.619
Alcohol Use	0 (0)	0 (0)	---
ACE-Inhibitors	3 (14.3)	0 (0)	0.369
ARBs	0 (0)	0 (0)	---
Calcium Channel Blockers	1 (4)	0 (0)	0.619
Hydrochlorothiazide	2 (9.5)	0 (0)	0.473
Beta-Blockers	0 (0)	0 (0)	---
SSRIs	1 (4)	0 (0)	0.619
History of Migraine	0 (0)	0 (0)	---
CA	8 (38.1)	1 (20)	0.445

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Evaluation of the group of HV related to normal vs. abnormal cerebrovascular autoregulation, there were no statistically significant differences in any variables except hypertension ($p = 0.011$) and the use of ACE-I ($p = 0.011$)(Table 5-9 and 5-10).

Table 5-9. T-tests for Healthy Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n = 17) or Abnormal (n = 9)

Characteristic	Normal CA Mean ± SD	Abnormal CA Mean ± SD	p-value
Age (in years)	33.88 ± 14.58	42.89 ± 12.98	0.124
BRS	10.89 ± 1.88	10.54 ± 1.18	0.571

Legend: SD: Standard deviation; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Table 5-10 Chi-Square for Healthy Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n = 17) or Abnormal (n = 9)

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
<i>Gender</i>			
Male	10 (58.8)	8 (88.8)	0.114
Female	7 (41.2)	1 (11.1)	
<i>Ethnicity</i>			
Caucasian	10 (58.8)	3 (33.3)	0.449
African American	0 (0)	0 (0)	
Asian	4 (23.5)	3 (33.3)	
Hispanic	3 (17.6)	3 (33.3)	
<i>GCS (Categorized)</i>			
No Injury	17 (100)	9 (100)	---
Diabetes	0 (0)	0 (0)	---
Coronary Artery Disease	0 (0)	0 (0)	---
Hypertension	0 (0)	3 (33.3)	0.011*
Seizures	0 (0)	0 (0)	---
Schizophrenia	0 (0)	0 (0)	---

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
Tobacco Use	0 (0)	1 (11.1)	0.161
Alcohol Use	0 (0)	1 (11.1)	0.161
ACE-Inhibitors	0 (0)	3 (33.3)	0.011*
ARBs	1 (5.8)	0 (0)	0.345
Calcium Channel Blockers	0 (0)	1 (11.1)	0.161
Hydrochlorothiazide	1 (5.8)	1 (11.1)	0.634
Beta-Blockers	0 (0)	0 (0)	---
SSRIs	1 (5.8)	0 (0)	0.458
History of Migraine	0 (0)	0 (0)	---
BRS	4 (23.5)	1(11.1)	0.445

* Significant results

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation; ARB: Angiotensin II Receptor Blocker;

Table 5-11. T-tests for TBI Subjects with Baroreflex Sensitivity Classified as Normal (n = 20) or Abnormal (n = 6)

Characteristic	Normal BRS Mean ± SD	Abnormal BRS Mean ± SD	p-value
Age (in years)	33.90 ± 13.12	47.50 ± 14.84	0.80
GCS Score	7.60 ± 3.14	7.17 ± 1.17	0.614
GOAT	75.85 ± 27.39	45.83 ± 36.04	0.103
Post Injury Day	48.60 ± 45.11	61.67 ± 45.57	0.554
CA	51.63 ± 12.73	49.25 ± 8.68	0.611

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Evaluation of the group of TBI subjects showed no statistically significant differences when BRS was classified as normal or abnormal except diabetes ($p = 0.007$).

Table 5-12. Chi-Square for TBI Subjects with Baroreflex Sensitivity Classified as Normal ($n = 20$) or Abnormal ($n = 6$)

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
<i>Gender</i>			
Male	13 (65)	5 (83.3)	0.393
Female	7 (35)	1 (16.7)	
<i>Ethnicity</i>			
Caucasian	5 (25)	1 (16.7)	0.915
African American	2 (10)	1 (16.7)	
Asian	2 (10)	1 (16.7)	
Hispanic	11 (55)	3 (50)	
<i>GCS (categorized)</i>			
Moderate	7 (35)	1 (16.7)	0.393
Severe	13 (65)	5 (83.3)	
<i>Location of Injury</i>			
Bilateral	11 (55)	4 (66.7)	0.795
Right hemisphere	2 (10)	0 (0)	
Left hemisphere	6 (30)	2 (33.3)	
Posterior fossa	1 (5)	0 (0)	
<i>Type of Injury</i>			
Diffuse	6 (30)	2 (33.3)	0.681
Hematoma	8 (40)	3 (50)	
Hemorrhage	2 (10)	1 (16.7)	
Contusion	4 (20)	0 (0)	
Diabetes	0 (0)	2 (33.3)	0.007*

Characteristic	Normal BRS N (%)	Abnormal BRS N (%)	p-value
Coronary Artery Disease	1 (5)	1 (16.7)	0.347
Hypertension	5 (25)	4 (66.6)	0.060
Seizures	3 (15)	2 (33.3)	0.318
Schizophrenia	1 (5)	0 (0)	0.576
Depression	2 (10)	1 (16.7)	0.654
Tobacco Use	3 (15)	1 (16.7)	0.921
Alcohol Use	4 (20)	2 (33.3)	0.497
ACE-Inhibitors	1 (5)	2 (33.3)	0.057
ARBs	0 (0)	1 (16.7)	0.063
Calcium Channel Blockers	0 (0)	0 (0)	---
Hydrochlorothiazide	1 (5)	0 (0)	0.576
Beta-blockers	4 (20)	2 (33.3)	0.497
SSRIs	0 (0)	0 (0)	---
History of Migraine	1 (5)	0 (0)	0.576
CA	10 (50)	2 (33.3)	0.473

* Significant results

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation; ARB: Angiotensin II Receptor Blocker

When classifying the TBI subjects with normal or abnormal CA, there were no statistically significant differences on any variables (Tables 5-13 and 5-14).

Table 5-13. T-tests for TBI Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n = 14) or Abnormal (n = 12)

Characteristic	Normal CA Mean ± SD	Abnormal CA Mean ± SD	p-value
Age (in years)	36.64 ± 15.14	37.50 ± 14.39	0.884
GCS Score	8.36 ± 2.31	6.50 ± 3.06	0.100
GOAT	77.36 ± 24.34	59.08 ± 36.98	0.161
Post Injury Day	44.79 ± 50.94	59.58 ± 36.54	0.399
BRS	13.54 ± 3.36	14.48 ± 2.88	0.448

Legend: SD: Standard deviation; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; BRS: Baroreflex sensitivity; CA: Cerebrovascular autoregulation

Table 5-14. Chi-Square for TBI Subjects with Cerebrovascular Autoregulation Status Classified as Normal (n = 14) or Abnormal (n = 12)

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
<i>Gender</i>			
Male	8 (57.1)	10 (83.3)	0.149
Female	6 (42.9)	2 (16.7)	
<i>Ethnicity</i>			
Caucasian	5 (35.7)	1 (8.3)	0.104
African American	1(7)	2 (16.7)	
Asian	0 (0)	3 (25)	
Hispanic	8 (57.1)	6 (50)	
<i>GCS (categorized)</i>			
Moderate	5 (35.7)	3 (25)	0.555
Severe	9 (64.3)	9 (75)	
<i>Location of Injury</i>			
Bilateral	9 (64.3)	6 (50)	0.693
Right hemisphere	1 (7)	1(8.3)	
Left hemisphere	4 (28.5)	4 (33.3)	
Posterior fossa	0 (0)	1 (8.3)	

Characteristic	Normal CA N (%)	Abnormal CA N (%)	p-value
<i>Type of Injury</i>			
Diffuse	4 (28.5)	4 (33.3)	0.196
Hematoma	4 (28.5)	7 (58.3)	
Hemorrhage	3 (21.4)	0 (0)	
Contusion	3 (21.4)	1 (8.3)	
Diabetes	1 (7)	1 (8.3)	0.910
Coronary Artery Disease	1 (7)	1 (8.3)	0.910
Hypertension	5 (35.7)	4 (33.3)	0.899
Seizures	3 (21.4)	2 (16.7)	0.759
Schizophrenia	1 (7)	0 (0)	0.345
Depression	1 (7)	2 (16.7)	0.449
Tobacco Use	2 (14.2)	2 (16.7)	0.867
Alcohol Use	3 (21.4)	3 (25)	0.829
ACE-Inhibitors	1 (7)	2 (16.7)	0.449
ARBs	1 (7)	0 (0)	0.345
Calcium Channel Blockers	0 (0)	0 (0)	---
Hydrochlorothiazide	0 (0)	1 (8.3)	0.271
Beta-blockers	3 (21.4)	3 (25)	0.829
SSRIs	0 (0)	0 (0)	---
History of Migraine	1 (7)	0 (0)	0.345
BRS	4 (28.5)	2 (16.7)	0.473

A prior power analysis indicated that a sample size of 39 subjects (18 in each group) would allow detection of a large effect size (0.5) on a X^2 test, at an alpha of 0.05 and a power of 0.80 (Erdfelder, Faul & Buchner, 2007). The post-hoc effect size for the second aim was 0.88 with a total of 52 subjects (26 in each group). This indicates that the sample size was large enough to avoid a Type II error for this aim.

Specific Aim # 3

As mentioned and reported in the tables for Specific Aim # 1, in the bivariate analyses BRS correlated negatively with both the GCS ($r = -.542$, $p = 0.004$) and the GOAT ($r = -.606$, $p = 0.001$). Cerebrovascular autoregulation correlated positively with the GOAT ($r = .421$, $p = 0.032$).

To identify independent predictors of BRS, results from the bivariate correlations, t-test and Chi-square were evaluated and the significant results were entered into the equation. These variables include GCS score, diabetes, GOAT score and CA. Cerebrovascular autoregulation was entered into the equation due to its relationship with the GOAT. Only diabetes entered into the equation but it was not significant (Table 5-15), thus none of the variables are independent predictors of BRS.

To identify independent predictors of CA status, significant results from the bivariate correlation, Chi-square and t-tests from the comparisons between normal and abnormal CA groups (described in Specific Aim #2) were evaluated and the significant variables were entered into the equation. These variables included gender, ACE-Inhibitors, diabetes, GCS score, GOAT score and BRS. Baroreflex sensitivity was entered into the equation due to its relationship to the GCS and GOAT. The following

variables entered into the model: gender, GOAT score and use of ACE-inhibitors (Table 5-16). These results indicate that as the GOAT score increases, the likelihood of having abnormal CA decreases. In addition, if the patient is not taking ACE-Inhibitors, the likelihood of having abnormal CA decreases. Finally, if the subject is female, they are less likely to have abnormal CA.

Table 5-15. Logistic Regression for the Prediction of Abnormal BRS (n= 52)

Covariates in Regression	Mean ± SD	Bivariate p value	Multivariate p value	B value
GCS	10.73 ± 4.17	0.004*	0.915	---
GOAT	70.45 ± 38.07	0.001*	0.085	---
CA	50.00 ± 11.36	0.443	0.538	---
	N (%)	Bivariate p value	Multivariate p value	B value
Diabetes	2 (3.84)	0.005*	0.999	-22.72

*Significant results

Legend: GOAT: Galveston Orientation and Amnesia Test; GCS: Glasgow Coma Scale

Table 5-16. Logistic Regression for the Prediction of Abnormal CA Status (n = 52)

Covariates in Regression	Mean ± SD	Bivariate p value	Multivariate p value	B value
GCS	10.14 ± 4.88	0.147	0.776	---
GOAT	76.62 ± 34.39	0.032*	0.047*	-.029
BRS	12.73 ± 3.02	0.406	0.931	---
	N (%)	Bivariate p value	Multivariate p value	B value
Diabetes	2 (3.85)	0.777	0.213	---
ACE-Inhibitors	6 (11.54)	0.023*	0.031*	-3.157
<i>Gender</i>				
Female	16 (30.77)	0.034*	0.025*	-2.301
Male	36 (69.23)			

*Significant results

Legend: GOAT: Galveston Orientation and Amnesia Test; GCS: Glasgow Coma Scale; BRS: Baroreflex sensitivity

Linear regression was performed to determine the magnitude of the relationship between selected variables. Based on the results from the bivariate correlation, GCS and GOAT were entered into the equations to evaluate both CA and BRS. In the linear regression related to BRS status (Table 5-17), both the GOAT and the GCS entered into the model. These results indicate that for every unit change in GOAT, BRS will change in the opposite direction. For example, for every unit increase in the GOAT, BRS will decrease by 0.05. For each unit increase in the GCS score, BRS will decrease by 0.27.

In the linear regression related to CA, only the GOAT entered into the model (Table 5-18). This indicates that for every unit change in the GOAT, CA will change by 0.16.

Table 5-17. Linear Regression for BRS (n = 52)

Covariates in Regression	Mean ± SD	Bivariate p value	Multivariate p value	B value
GOAT	70.45 ± 38.07	0.001*	0.002*	-0.046
GCS	10.73 ± 4.17	0.004*	0.005*	-0.267
CA	50.00 ± 11.36	0.443	0.838	---

* Significant results

Legend: GOAT: Galveston Orientation and Amnesia Test; GCS: Glasgow Coma Scale; CA: Cerebrovascular autoregulation

Table 5- 18. Linear Regression for CA Status (n = 52)

Covariates in Regression	Mean ± SD	Bivariate p value	Multivariate p value	B value
GOAT	76.62 ± 34.39	0.032*	0.025*	0.160
GCS	10.14 ± 4.88	0.147	0.967	---
BRS	12.73 ± 3.02	0.406	0.355	---

*Significant results

Legend: GOAT: Galveston Orientation and Amnesia Test; GCS: Glasgow Coma Scale; BRS: Baroreflex Sensitivity

From the results of both Specific Aims # 2 and # 3, use of the GOAT is helpful in assessing CA status. In order to determine a score that will provide information to the bedside clinician, quartile scores were calculated on the GOAT in all subjects (Table 5-19). The quartile scores for all subjects indicated that a GOAT score of 100 would

provide information regarding CA status. Since 100 is the score for post-TBI subjects with resolved PTA and RA, this was not helpful. Thus, quartile scores for the TBI subjects alone were also calculated (Table 5-20).

Table 5-19. Quartiles for GOAT and Abnormal CA in All Subjects (n = 21)

Percentiles	GOAT Score
25	69
50	90
75	100

Table 5-20. Quartiles for GOAT and Abnormal CA in TBI Subjects (n = 12)

Percentiles	GOAT Score
25	15
50	76.5
75	85

These results indicated that a score of ≤ 85 would identify 75% of those who had abnormal CA. Given that the GOAT was developed for TBI patients, this seems to be reasonable. A plot of the GOAT scores and CA status for all subjects was done (Figure 5-2). An additional plot of just the TBI sample was also done (Figure 5-3) with the cut-off score of 85 indicated.

Figure 5-2. Scatterplot of All Subjects with Cerebrovascular Autoregulation Classified as Normal vs. Abnormal

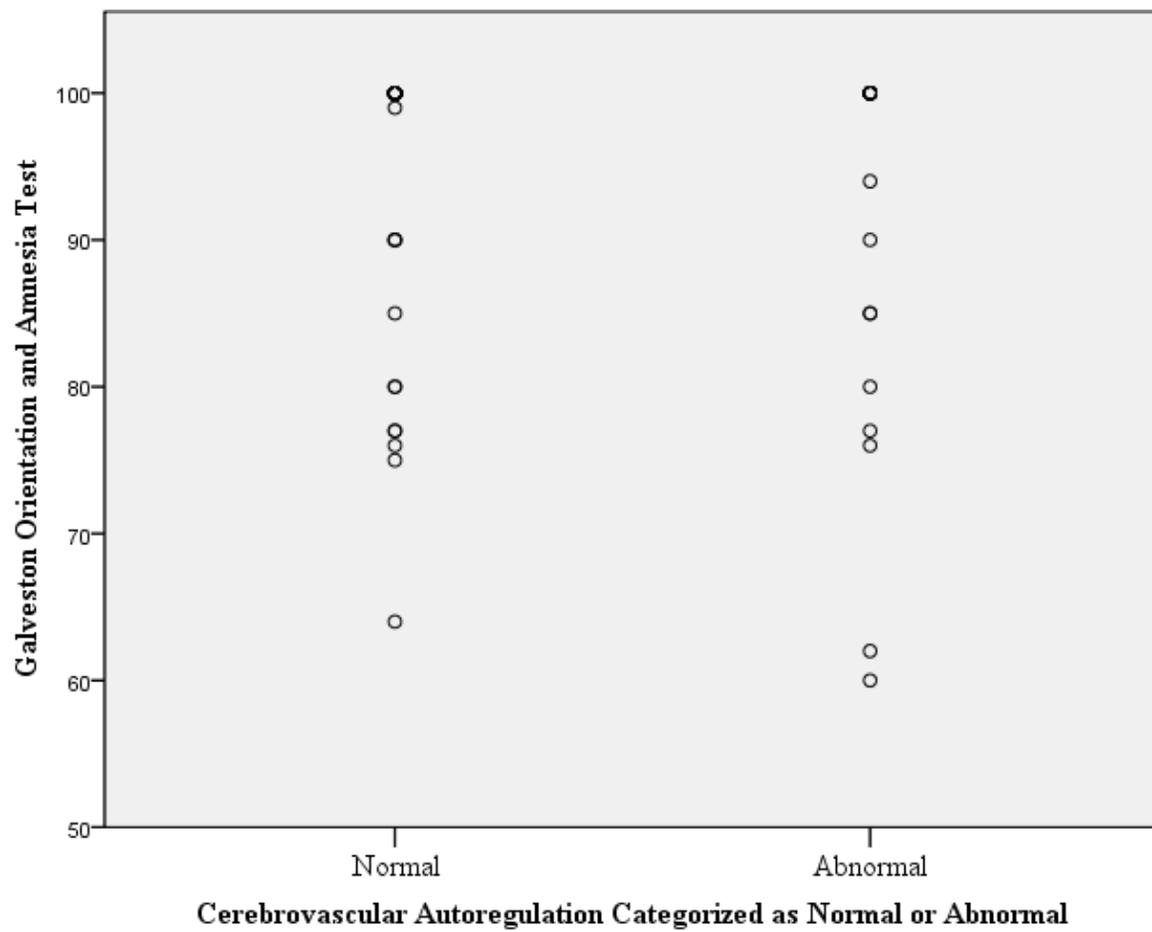
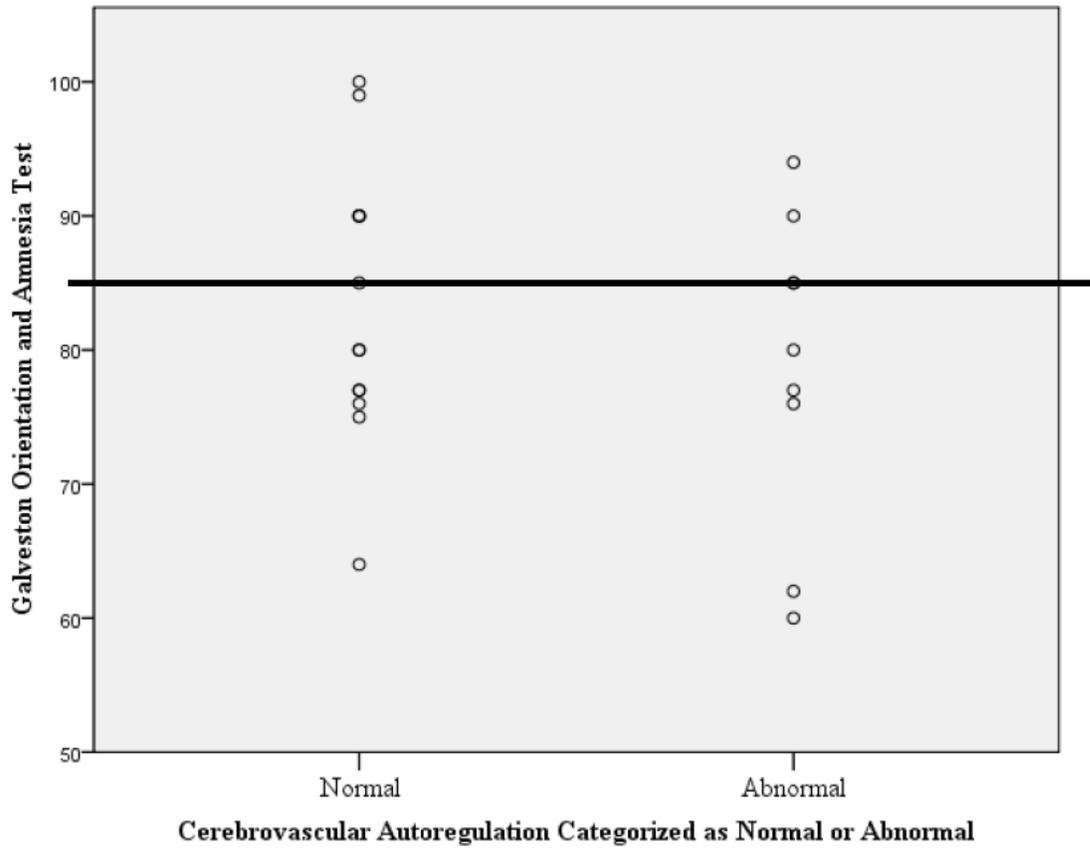


Figure 5-3. Scatterplot of GOAT scores in TBI subjects with Cerebrovascular Autoregulation Classified as Normal vs. Abnormal



The other variables that entered into the logistic regression (gender and ACEI) may be helpful in identifying individuals who might have abnormal CA in both TBI patients and in those who have not sustained a TBI. A high index of suspicion for abnormal CA might be needed for those taking ACE-Inhibitors in view of the impact of this variable in predicting CA.

Gender also had a large impact in predicting CA and it would be important to evaluate males since they are more likely to have abnormal CA. These variables are

likely to be very important in the TBI patient as they could easily identify those at high risk for abnormal CA.

Chapter 6

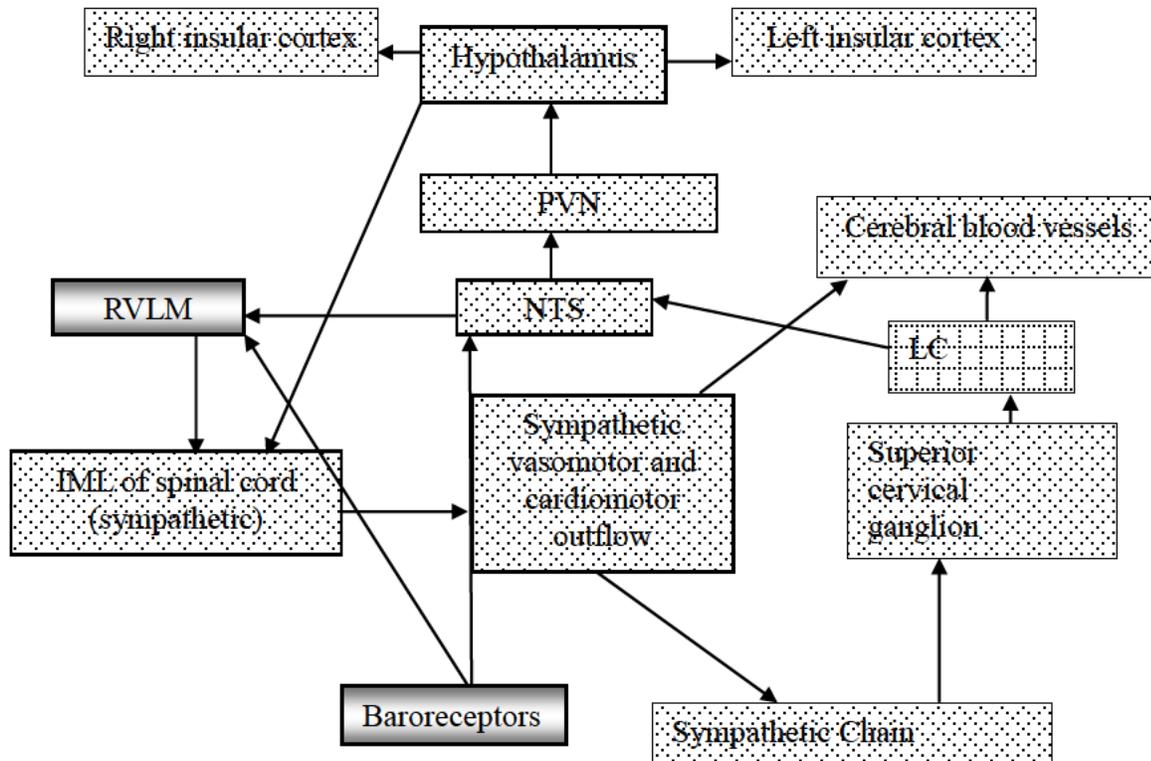
Discussion

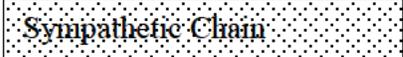
This chapter presents discussion of the major findings and limitations of the study, the clinical implications and suggestions for future research.

Baroreflex Sensitivity and Cerebrovascular Autoregulation in Traumatic Brain Injury

The purpose of this study was to identify a non-invasive surrogate measure of cerebrovascular autoregulation (CA) in patients with traumatic brain injury (TBI). It was anticipated that baroreflex sensitivity (BRS) would be such a surrogate; however, there were no correlations between CA and BRS in the TBI group, the HV group or the combined groups. Given previous studies in neurological disorders, such as stroke and carotid disease (Maturri, et al., 2005; Nasr, et al., 2005; Robinson, et al., 2003) that indicated that BRS was disordered after a stroke, and an animal study that indicated BRS was abnormal after TBI (McMahon, et al., 2011) the lack of correlation of BRS and CA in the current study was surprising. Because CA and BRS share some neurological pathways (Figure 6-1), through the NTS, hypothalamus, insular cortices and IML of the spinal cord it was anticipated that there would be a relationship between these variables. The results of this study seem to indicate that while BRS and CA share these pathways, there may be other pathways of the either the baroreflex or the regulation of CA (such as within the blood vessels) that are not shared. These non-shared pathways may play a larger role in the baroreflex and CA than is currently understood.

Figure 6-1. Major Common Cortical and Sub-cortical Pathways of Baroreflex Sensitivity and Cerebrovascular Autoregulation



Legend: RVLM = rostral ventrolateral medulla; NTS = nucleus tractus solitarii; PVN = Periventricular nucleus IML = intermediolateral column; BRS pathways = ; CA pathways overlapping with BRS pathways = ; CA pathways = 

Previous studies in healthy subjects have indicated a relationship between CA and BRS (Ainslie, et al., 2008; Tzeng, et al., 2010). These studies included thigh cuff release and the use of phenylephrine and nitroprusside as the autonomic stimulus for the baroreflex. The use of thigh cuff release and vasopressors may provide a more drastic autonomic challenge than would be desirable or clinically practical on a daily basis in patients with TBI. With the thigh cuff release, the cuffs are inflated for two minutes at a BP that is higher than the patient's systolic BP (Aaslid,

et al., 1989). It may be difficult to maintain this inflation in the patient with TBI due to their inability to remain focused on the procedure and due to the pain that can be induced during this maneuver. The use of vasopressors may also be a less than desirable autonomic challenge because if the patient has abnormal CA, cerebral blood flow is reliant upon the systemic BP. To increase or decrease the patient's BP in such a rapid method may cause additional secondary brain injury in those patients who are the most vulnerable. The current study used a position change challenge which may not have been a strong enough stimulus to elicit an autonomic challenge sufficient to demonstrate a relationship between CA and BRS. Further research is needed to identify the strength of the autonomic challenge that would be required to achieve a correlation on these measures.

There were six subjects in the TBI group that were taking beta-blockers, three of them had normal CA status and three had abnormal CA status. In addition, two of these subjects had abnormal BRS and four had normal BRS. Beta-blockers block the adrenergic impulses to the heart decreasing the force of cardiac contraction leading to a drop in BP. Given that beta blockers affect autonomic status by blocking sympathetic stimulation, it is likely that in these subjects the study's autonomic challenge was not enough to identify a relationship.

Interestingly, when sensitivity and specificity of BRS was calculated for clinical utility, sensitivity (ability of BRS to identify abnormal CA) was low (23%) but the specificity (ability to identify normal CA) was high (77%). Thus, if a patient has normal BRS, it is likely that they will have normal CA status and bedside clinicians could safely mobilize patients as their risk for secondary brain injury would be low. Unfortunately, it did not follow that those with abnormal BRS would also have abnormal CA status. While it is important to identify patients with normal

CA status, the patients with abnormal CA status remain vulnerable to secondary brain injury from any activity, such as getting out of bed or participating in rehabilitation therapies, whether in the acute or rehabilitation settings. Thus, it is important to identify a method of assessing these patients.

Another interesting study finding was the persistence of abnormal CA. Previous researchers had reported that abnormal CA persists for up to 23 days in those who have sustained a TBI (Sviri, et al., 2009). In the current study, there were 10 patients in the rehabilitation setting (mean days from injury 64 ± 38.45 days) and two patients in the acute care setting (mean days from injury 46.40 ± 57.63) who continued to demonstrate abnormal CA. The finding of abnormal CA in these settings was unexpected as it has been assumed that patients who are no longer in the ICU do not continue to have problems with CA. Once patients are out of the ICU, they experience increased activity to prepare for their transfer to a rehabilitation setting and a return to a functional role in society. This includes multiple trips in and out of bed and increasing exercise, both in the acute setting and while in the rehabilitation setting. The CA status of patients admitted to a post-ICU or a rehabilitation facility is not regularly assessed, thus this is an unknown situation for TBI subjects. If patients in the post-ICU area have abnormal CA status, they could continue to be vulnerable to secondary brain injury because of the activity required in this location. After patients are admitted to rehabilitation their activity increases substantially to approximately six hours of activity each day. No study has evaluated normalization of CA after TBI beyond 23 days and based on the results of the current study, further research is needed in an effort to identify those who may continue to be at risk for secondary brain injury after leaving the ICU setting.

Incidence of Abnormal Cerebrovascular Autoregulation in Healthy Subjects

The group of healthy volunteers (HV) in this study showed surprising results. There were nine subjects with abnormal CA status, five with abnormal BRS and one who had abnormalities in both measures. These findings were unexpected as none of the HV subjects had a prior TBI, stroke or history of migraine, all of which have been shown to alter CA. Previous studies have indicated that migraine can alter CA (Müller & Marziniak, 2005; Vernieri et al., 2008) and that hypertension can alter the upper limit of CA (Beevers, Lip, & O'Brien, 2001; Strandgaard & Paulson, 1989) however, use of anti-hypertensive medication can return CA status to normal (Beevers, et al., 2001; Strandgaard & Paulson, 1989). Three subjects in the HV group had a history of hypertension but this was less than the nine in the TBI group. In addition, three of the HV group was taking ACE-Inhibitors (equal to the TBI group), two were taking hydrochlorothiazide and one was taking a calcium channel blocker. The differences between the TBI group and HV group on these variables were not statistically significant thus it is unclear as to why the HV group had such abnormality in CA.

The results of abnormal CA status in the HV group is concerning. It was not expected that healthy individuals would have abnormal CA. In fact, the proportion of HV with abnormal CA was the same as that in the TBI group. These healthy individuals may be at higher risk for neurological events during medical procedures such as cardiopulmonary bypass, hemodialysis, and hypovolemic states or after a TBI. A decrease in blood pressure during these types of events in patients with unknown CA status may lead to decreased cerebral blood flow and secondary brain injury. While it

may not currently be feasible or cost-effective to evaluate CA status in every patient who is admitted to the hospital, it might be important to reconsider this. The unusual finding of abnormal CA in healthy individuals may warrant further evaluation of patients who are admitted for procedures that are known to decrease CBF, such as surgery, anesthesia or hemodialysis. This would be especially important in those individuals who are male and taking an ACE-Inhibitor. Certainly females taking an ACE-Inhibitor should also be evaluated but the higher risk appears to be in the male population. An assessment of CA status using TCD with CO₂ reactivity would provide information about CA and would provide information to those who are conducting procedures that may alert them to protect the patient's brain. A change in policy related to this finding is important for the health of patients who unknowingly have poor CA status. Additional research to identify the incidence of abnormal CA status in healthy individuals is warranted.

Assessment of Cerebrovascular Autoregulation Status

Linear regression was conducted to determine the magnitude of the relationship between variables. Only the GOAT showed a relationship to CA status. Thus, the GOAT could be a useful tool to assess not only cognition but CA. Patients who have poor scores on the GOAT would have poor cognitive and CA status. In determining the appropriate GOAT score for identifying abnormal CA status in all subjects, the cutoff score may be higher (100) and not especially helpful. If one considers only TBI subjects, then the cutoff GOAT score to identify abnormal CA is slightly higher (≤ 85) than the abnormal cognitive status (GOAT < 75). Since the GOAT was developed specifically for assessment of the individual with TBI and is not likely to be pertinent or accurate in non-

TBI subjects, the differences in cutoff GOAT scores for abnormal CA vs. assessment of PTA and cognition were different than expected. Patients with TBI will need to score > 85 to assure that their CA status is normal. For those with no history of TBI, another assessment will be necessary to determine CA status. As indicated previously, TCD with CO₂ reactivity testing is likely the best alternative. CO₂ reactivity testing provides information regarding the status of the cerebrovascular bed. Administration of CO₂ causes dilation of the cerebral resistance vessels leading to increased CBF/CBFV. Maximal dilation of the blood vessels occurs during periods of ischemia and during dilation, the ability of the arterioles to compensate is lost. Thus, the CO₂ challenge provides information regarding the ability of the smaller arterioles to respond to CO₂ and to provide blood flow to the brain. Additional methods of assessment include breath holding or administration of acetazolamide (Diamox[®]), both of which assess vasodilation, or hyperventilation which assesses vasoconstriction.

The advantage of the GOAT is that it is easy for the bedside clinician to use on a daily basis. It takes less than 10 minutes to administer and provides information regarding memory and cognition. In testing memory with the GOAT, it is possible that CA status can also be tested because of these overlapping anatomical areas which include the NTS, hypothalamus, and insular cortices (Figure 6-2). Currently, the GOAT is only used for the assessment of memory and cognition; it has not been evaluated as a tool for identifying CA status.

(Figure 5-2) for all of the subjects in this study, impaired CA status would be identified with a GOAT score of less than 100 which is not helpful in identifying those with impaired CA as 100 is the total score possible. For those with TBI, a GOAT score of ≤ 85 would indicate poor CA status (Figure 5-3). As previously stated, the GOAT was not developed to assess healthy individuals but could provide valuable information regarding CA status in TBI patients. Administration of the GOAT on a daily basis could provide trended information that would indicate improvement in cognitive and CA status. As the GOAT score improved, cognition and CA status would improve. The GOAT takes little time to perform and it can be performed on a daily basis allowing for the monitoring of trends, and may provide prediction of the patient's ability to participate in daily nursing care activities without secondary brain injury. Knowing the CA status of the patient should allow the bedside clinician to make a determination of the appropriate activity status for the patient.

Another interesting study finding was the fact that ACE-I use was an independent predictor of abnormal CA. There have been limited studies on the use of ACE-I in TBI. One animal study reported that ACE-I impaired the degrading of substance P which led to increased injury caused by substance P (Harford-Wright, Thornton, & Vink, 2010). This single study might indicate that if there is increased brain injury from substance P, there could potentially be additional problems with CA. Studies in patients with hypertension indicate that ACE-I lower the CA threshold to normal (Beevers, et al., 2001) but this has not been examined in TBI subjects. In the current study, patients who are taking ACE-I were more likely to have abnormal CA. With

such limited research related to ACE-I and TBI further research in this area is needed, particularly in human subjects.

Gender has been evaluated in several studies related to TBI outcome (Berry et al., 2009; Farace & Alves, W. M., 2000; Groswasser, Cohen, & Keren, 1998; Kraus, Peek-Asa, & McArthur, 2000; Moore, Ashman, Cantor, Krinick, & Spielman, 2010; Roof, Duvdevani, & Stein, 1993) with mixed results. Some studies indicate that women fare better after TBI (Groswasser, et al., 1998; Roof, et al., 1993) and others state that women do worse (Farace & Alves, W., 2000; Kraus, et al., 2000). None of these studies on outcome based on gender evaluated CA status. In the current study, the results indicate that males are more likely to have abnormal CA. Further research is needed to better elucidate the relationship of gender and CA status.

The results of this study indicated that BRS is not related to CA status in TBI or HV subjects. While BRS was able to identify those with normal CA status, it is more important to identify those with abnormal CA status. Upon admission to the acute care setting after a TBI, patients could be evaluated on their GOAT score, gender and the pre-existing use of ACEI in an effort to identify those who may be at more risk for secondary brain injury as they progress through the hospital experience. Additional research is needed to assure that these findings are generalizable across the population of TBI subjects. In addition, since healthy subjects also had abnormal CA status, evaluation of gender and ACEI in these individuals along with TCD studies could provide information regarding the CA status of healthy subjects. It would be interesting to determine if some individuals just “have” abnormal CA.

Limitations of the Study

While every effort was made to minimize the limitations, some exist. The first limitation was in relation to the sample size. Power analysis for each of the statistical tests indicated that the sample obtained would have sufficient power to detect large differences. It is likely however, that with a larger sample correlations of BRS and CA may be found. In fact, a recent study found significant correlations between BRS and CA in healthy individuals (Tzeng et al, 2010). Further study in larger samples of TBI survivors to determine if there is a relationship between BRS and CA in human subjects is needed.

Another limitation was the timing of variable measurements. Research has shown that the baroreflex activates rapidly after a position change, within 10-15 seconds (Wieling & Karemaker, 2002). In this study, measurements were taken at 30 seconds after the position change, which may have been too long to detect any change. The Finometer Pro[®] measures data continuously, but the TCD device available for this study did not. Further study with continuous measurement devices is needed to confirm and extend the current findings.

A third limitation was the use of only two sites for the study. The use of two sites assisted with enrollment of subjects, but the results are not generalizable beyond these two sites. In a larger study, use of more sites might produce more patients with TBI and increase the ability to generalize the results.

An additional limitation was that it was not possible for the current study to enroll subjects with TBI who were in the military. The mechanism of injury for most military TBI is a blast. The majority of subjects in the current study were falls or motor vehicle crashes. The

mechanism of blast injuries (Plurad, 2011) is different than the majority of civilian TBI and it would be important to examine the results of the current study in military personnel with TBI.

Finally, the GOAT was used as an assessment of the ability of the subject to provide informed consent for the study. This was a one-time measurement and trends over time were not obtained. Future research should observe trends over time.

Implications for Nursing Practice

There were several interesting findings in this study. The ability of BRS to identify normal CA status can be important for identifying the patients that are appropriate for increased activity with minimal risk for secondary brain injury. The calculation of BRS could readily be added to the electronic health record (EHR) and calculated on a daily basis. By including the norms based on age and gender in the EHR, the bedside clinician would be able to determine normal CA status for their patient.

The next finding of long-term abnormal CA in TBI subjects outside of the ICU was unexpected and thus it indicates that it would be important to integrate an assessment of CA into practice. The GOAT was able to predict abnormal CA status in all of the subjects and it could be easily used for this assessment. The GOAT could be used on a daily basis to assess cognition (resolution of post-traumatic amnesia) and CA. The results would allow the bedside clinician to determine the activity appropriate for the patient and provide activity that would be less likely to decrease CBF and lead to secondary brain injury. These results may also be applicable to those in the military who have sustained TBI as the GOAT could be readily used and trended. However, further study using the GOAT and its relationship to CA in military TBI is needed.

Patients identified with abnormal CA could be assessed with additional modalities such as TCD with CO₂ reactivity to more clearly determine the cerebrovascular reserve of the patient.

The finding of the impact of ACEI on CA also needs to be further evaluated. In the current study, those on ACEI were more likely to have abnormal CA. In light of the previous animal study and the current study results it is possible that ACE-I contributes to abnormal CA. Given the very limited research in this area, further investigation into the relationship of ACE-I and CA needs to be conducted.

The most surprising finding in this study was the several of the healthy subjects had abnormal CA. This finding warrants further study in healthy subjects but in the meantime, it would be important for patients who are being admitted to the hospital for procedures that would decrease CBF to be evaluated with TCD testing. It would truly be horrible for someone to needlessly have an adverse neurological outcome after a procedure that would seem to not affect the brain in any way. In those patients who are undergoing anesthesia, cardiopulmonary bypass, hemodialysis or other procedures that affect BP, this assessment should be part of the pre-operative/pre-procedure clearance. In addition, it is not clear if these healthy subjects have always had disordered CA and this research should be repeated in healthy children to determine if abnormal CA is pre-existing at a younger age than these subjects. Given the results of this study, additional research in children with TBI should also be conducted.

The effect of gender on CA status is not clear. While it would appear that males are more likely to have abnormal CA, this finding needs further investigation.

Future Research

Very little research has been conducted on the relationship of BRS and CA in healthy subjects (Ainslie, et al., 2008; Tzeng, et al., 2010) or on this relationship in brain injury (Goldstein, et al., 1998; McMahon, et al., 2011). Future research should examine this relationship further in a larger group of subjects with TBI because the results of the current study conflict with results in the healthy subjects and in one animal study. In addition, examination of these results in children with TBI would add to the science as little research has been conducted in children (Goldstein, et al., 1998). Examination of BRS and CA in those with TBI who are in the military may clarify this relationship in those with a different mechanism of injury (Plurad, 2011). Future studies should be conducted at multiple sites that treat patients with TBI including military hospitals, county hospitals and other trauma centers. In view of the findings of the length of time that CA remains abnormal, it would be important to conduct research in the rehabilitation and home settings to determine when CA returns to normal. It will also be important to further explore the relationship of the GOAT to CA status. Examination of long term outcome in TBI patients, both civilian and military, with disordered CA would also be important as this is not yet understood.

Further studies are needed to evaluate CA status in TBI patients in the post-ICU area. This would be important in civilians who go to rehabilitation settings and those who are returning from war as by the time they are returned to the United States, they are no longer in the ICU setting. In addition, it would be interesting to evaluate CA and BRS status in other HVs to determine if the findings in the current study remain supported. Additional research is also needed to determine if there is an effective mechanism for returning CA to normal.

Overall Summary

The purpose of this study was to identify a non-invasive surrogate measure for determining CA status in patients with TBI after they leave the ICU. The GOAT is a simple tool already in use by many bedside clinicians and could be readily incorporated into practice to assess patients on a daily basis related to CA status. Calculation of BRS could be incorporated into the EHR, thus simplifying the assessment for the clinician and increasing the availability of the results to identify those with normal CA. This research project indicates that BRS and CA can be measured in patients with TBI and that ongoing study is needed to determine the effectiveness of using BRS to identify normal and abnormal CA. The results of this study show promise for improving the evaluation of CA status in patients with TBI and could improve the outcomes for these patients. In addition, the identification of abnormal CA in healthy individuals warrants change in health care policy so that injury does not occur unnecessarily in those whose CA status is unknown.

Appendix A: IRB Approval from University of California Los Angeles, Medical IRB 3



APPROVAL NOTICE

OFFICE FOR PROTECTION OF RESEARCH SUBJECTS
11000 Kinross Avenue, Suite 102
169407
www.oprs.ucla.edu

DATE: October 1, 2009

TO: Norma D. McNair, MSN, RN
Principal Investigator

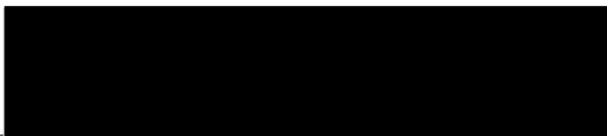
FROM: James McGough, M.D.
Chair, Medical Institutional Review Board 3

RE: UCLA IRB #06-11-119-03A
Approved by Expedited Review
(Approval Period from 10/01/2009 through 03/04/2010)
Baroreceptor Sensitivity During Positional Changes in Patients with Acute Traumatic Brain Injury [Revised exclusion and inclusion criteria]

Please be notified that the UCLA Institutional Review Board (UCLA IRB) has approved the above referenced research project involving human subjects in research. The UCLA's Federalwide Assurance (FWA) with the Department of Health and Human Services, Office for Human Research Protections is FWA00004642.

PLEASE COMPLY WITH THE FOLLOWING CODICIL(S) IMPOSED BY THE IRB:

- 1. The UCLA IRB waived the requirement for signed informed consent for screening under 45 CFR 46.117(c)(2).**
- 2. Upon the expected enrollment of non-English speaking subjects, appropriate translation(s) of the consent form must be forwarded to the M-IRB. All consent documents must be reviewed and approved by the M-IRB prior to implementation.**
- 3. This study is approved for use of non-emergency proxy informed consent as set forth in CA Health & Safety Code 24178.**



Approval Signature of the UCLA IRB Chair

PRINCIPLES TO BE FOLLOWED BY PRINCIPAL INVESTIGATORS:

As the Principal Investigator, you have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the UCLA IRB. You must abide by the following principles when conducting your research:

1. Perform the project by qualified personnel according to the approved protocol.
2. Do not implement changes in the approved protocol or consent form without prior UCLA IRB approval (except in a life-threatening emergency, if necessary to safeguard the well-being of human subjects.)
3. If written consent is required, obtain the legally effective written informed consent from human subjects or their legally responsible representative using only the currently approved UCLA-IRB stamped consent form.
4. Promptly report all undesirable and unintended, although not necessarily unexpected adverse reactions or events, that are the result of therapy or other intervention, within ten working days of occurrence. All fatal or life-threatening events must be reported to the UCLA IRB in writing within 2 working days after discovery.
5. In clinical medical research, any physician(s) caring for your research subjects must be fully aware of the protocol in which the subject is participating.
6. No subjects may be identified, contacted, recruited, or enrolled until the contract with the sponsor is finalized by the University.
7. Ensure that all individuals who will interact with subjects and/or have access to identifiable research data have completed the UCLA Protection of Human Research Subjects Certification.
8. Ensure that all individuals who will access subjects' medical records have completed the UCLA HIPAA Research Training Certification.
9. If non-UCLA sites or personnel are involved, follow all study-specific requirements and consent processes approved by the UCLA IRB.

FUNDING SOURCE(S):

According to the information provided in your application, the funding source(s) for this research project may include the following: extramural.

PI of Contract/Grant: Norma McNair

Funding Source: Sigma Theta Tau International Honor Society of Nursing, Gamma Tau Chapter

APPROVAL NOTICE
IRB #06-11-119-03A

Contract/Grant No: Funding has been awarded. Ther
Contract/Grant Title: Baroreceptor Sensitivity During Positional Changes in Patients with Acute Traumatic
Brain Injury



APPROVAL NOTICE

OFFICE OF THE HUMAN RESEARCH PROTECTION PROGRAM
11000 Kinross Avenue, Suite 102
Campus Mail Code: 169407
www.research.ucla.edu/ohrpp

DATE: February 4, 2010

TO: Norma D. McNair, MSN, RN
Principal Investigator

FROM: James McGough, M.D.
Chair, Medical Institutional Review Board 3

RE: UCLA IRB #06-11-119-04
Approved by Expedited Review
(Approval Period from 02/04/2010 through 02/03/2011)
Baroreceptor Sensitivity During Positional Changes in Patients with Acute Traumatic Brain Injury [Revised exclusion and inclusion criteria]

Please be notified that the UCLA Institutional Review Board (UCLA IRB) has approved the above referenced research project involving human subjects in research. The UCLA's Federalwide Assurance (FWA) with the Department of Health and Human Services, Office for Human Research Protections is FWA00004642.

PLEASE COMPLY WITH THE FOLLOWING CODICIL(S) IMPOSED BY THE IRB:

- 1. The UCLA IRB waived the requirement for signed informed consent for screening under 45 CFR 46.117(c)(2).**
- 2. The UCLA IRB approved the use of surrogate consent in a non-emergency situation in accordance with California Health & Safety Code 24178.**
- 3. Please submit translated copies of your recruitment, screening and consent documents as an amendment(s) before recruiting or consenting any subjects for whom these translations are required. If a medical study is being conducted in California, be sure to provide subjects with the appropriate translated Research Participant's Bill of Rights. Numerous translations are available for download on the HRPP website at <http://www.oprs.ucla.edu/human/bill-of-rights>.**
- 4. The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110, categories 4 and 7.**

APPROVAL NOTICE
IRB #06-11-119-04

5. **The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110, categories 4 and 7.**



Approval Signature of the UCLA IRB Chair

PRINCIPLES TO BE FOLLOWED BY PRINCIPAL INVESTIGATORS:

As the Principal Investigator, you have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the UCLA IRB. You must abide by the following principles when conducting your research:

1. Ensure that the personnel **performing the study are qualified and appropriately trained**, key personnel have completed the CITI training program and will adhere to the provisions of the approved protocol.
2. Implement **no changes** in the approved protocol or consent process or documents without prior UCLA IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notify the IRB as soon as possible afterwards.)
3. Obtain the **legally effective informed consent** from human subjects or their legally authorized representative (when approved), and use only the currently approved consent process and stamped consent documents, as required by the IRB.
4. **Report unanticipated problems** related to the protocol to the IRB in writing within the appropriate time period (2 days to 10 working days).
5. Assure that **adequate resources** to protect research subjects (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if such resources become unavailable.
6. **Arrange for a co-investigator** to assume direct responsibility of the study if at any time you will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as a co-investigator on this application, or you will advise the IRB by letter in advance of such arrangements.

FUNDING SOURCE(S):

According to the information provided in your application, the funding source(s) for this research project may include the following: extramural.

PI of Contract/Grant: Norma McNair

APPROVAL NOTICE
IRB #06-11-119-04

Funding Source: Sigma Theta Tau International Honor Society of Nursing, Gamma Tau Chapter
Contract/Grant No: Funding has been awarded. Ther
Contract/Grant Title: Baroreceptor Sensitivity During Positional Changes in Patients with Acute Traumatic Brain Injury

Appendix B: Recruitment Flyer for Healthy Volunteers

Research Study

“Baroreceptor Sensitivity During Positional Changes after Traumatic Brain Injury”

We’re Looking for Volunteers!!

We want to know how change in position affects heart rate and blood pressure in persons with Traumatic Brain Injury and in Healthy Volunteers.

You will qualify if you are between the ages of 18-65 years, do not have atrial fibrillation, high blood pressure or history of a recent stroke or heart attack or are taking the type of drug called beta-blockers.

Healthy volunteers should **not** have had a traumatic brain injury.

We will look at your heart rate, blood pressure and blood flow to your brain during a position change from flat to upright. The entire study will take about 60 minutes to complete.

Volunteers will be reimbursed for their time and effort for the study.

If you are interested or have questions, please contact:
Norma D. McNair, MSN, RN
UCLA School of Nursing



UCLA IRB #: 06-11-119-03A

Expiration Date:

MAR 04 2010

Appendix C: Recruitment Flyer for TBI Subjects at Ronald Reagan UCLA Medical
Center

Research Study

Effect of Changes in Position on Heart Rate and Blood Pressure in Patients with a Traumatic Injury to their Brain

("Baroreceptor Sensitivity during Positional Changes after Traumatic Brain Injury")

Volunteers Are Needed!!

For a study about how change in position affects heart rate and blood pressure in persons with Traumatic Brain Injury and in Healthy Volunteers.

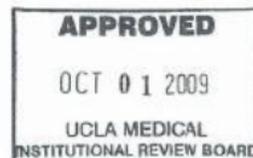
You will qualify if you are between the ages of 18 - 65 years, **have** sustained a traumatic brain injury, and do not have atrial fibrillation, high blood pressure or history of a recent stroke or heart attack or are taking the type of drug called beta-blockers.

We will look at your heart rate, blood pressure and blood flow to your brain during a position change from flat to upright. The entire study will take about 60 minutes to complete.

Volunteers will be reimbursed for their time and effort for the study.

If you are interested or have questions, please contact:

Norma D. McNair, MSN, RN
UCLA School of Nursing



UCLA IRB #: 06-11-119-03A
Expiration Date: MAR 04 2010

Appendix D: Screening Script for Healthy Volunteers

University of California, Los Angeles

CONSENT SCRIPT TO SCREEN FOR RESEARCH

Effect of changes in Position on Heart Rate and Blood Pressure in Patients with a
Traumatic Injury to their Brain

Baroreceptor Sensitivity During Positional Changes in Patients with Traumatic Brain
Injury

Thank you for calling. My name is Norma McNair and I am a nurse and doctoral student in the UCLA school of nursing. The study that you called about is about the effect of changes in position on heart rate and blood pressure in patients with a traumatic injury to their brain.

I need to ask you a few questions in order to determine whether you may be eligible for the research. I will ask you about your recent medical history, particularly in regards to your heart and blood pressure. Before I begin I would like to tell you a little bit about the research.

The research compares healthy people to people with traumatic brain injury. It will specifically compare heart rate and blood pressure during changes in your position from lying down to sitting up. If you are eligible, your participation in the research will consist of a one time visit of approximately 60 minutes and will include measuring your heart rate, your heart rhythm, your blood pressure and your blood flow to your brain.

Would you like to continue with the screening? The screening will take about 5 minutes.

You may feel uncomfortable answering questions about your medical history. You do not have to answer any questions you do not wish to answer and you may stop at any time.

Your participation in the screening is voluntary. A decision whether or not to participate in the screening will not affect your relationship with UCLA. You will not directly benefit from the screening.

Your answers will be confidential. No one will know the answers except for the research team.

If you do not qualify for the study, your answers will be kept in a confidential location without any identifying information for five years after the completion of the study.

If you do qualify for the study and you come for an appointment, your information will be kept with all of your research data in a secure location for five years after the completion

Date of Preparation: February 1, 2010

UCLA IRB #09-02-007-02

Expiration: February 3, 2011

of the study. There will be no personal identifying information on the screening form, except a unique identifier that I will determine.

Would you like to continue with the screening?

If no, thank the person and hang-up.

If yes, continue with the screening as follows:

What is your age?

Are you a man or a woman?

Please do not answer the following questions individually. When I am finished asking them, you may say "yes" if one or more questions in the group apply.

Have you ever had a traumatic brain injury?

Do you have the heart irregularity known as atrial fibrillation?

Do you have congestive heart failure?

Have you ever had a heart attack?

Have you ever had a stroke?

Do you have high blood pressure?

Do you take medications known as beta-blockers?

Thank you for answering the screening questions.

The subject will be told if they are eligible or not. If they are not eligible, they will be told why. If they are eligible, and they want to participate, an appointment will be scheduled for them to come to the hospital for the research study.

Do you have any questions about the screening or the research? I am going to give you a couple of telephone numbers to call if you have any questions later. Do you have a pen?

If you have questions about the research screening, you may call me, Norma McNair at [REDACTED] and we will answer your questions.

If you have questions about your rights as a research subject, please call the UCLA Office for Protection of Research Subjects at [REDACTED]

Thank you again for your willingness to answer my questions.

Date of Preparation: February 1, 2010

UCLA IRB #09-02-007-02

Expiration: February 3, 2011

Appendix E: Screening Script for Traumatic Brain Injury Subjects

Script for Direct Recruitment of TBI subjects

Once TBI subjects have been identified as potential research subjects, the PI will approach the patient in the privacy of their in-patient room.

Hello, my name is Norma McNair. I am a nurse and a doctoral student in the UCLA School of Nursing.

I am conducting a research study on the effects of changes in position on blood pressure, heart rate and blood flow to the brain. The study will require the attachment of some pieces of equipment to measure your heart rate, blood pressure and blood flow to the brain. The study will be performed with you in your bed, so you will not have to go anywhere for this. I will ask you to sign consent and to complete some other tests.

Would you be agreeable to hearing more about the study?

- If yes, further details about the study will be provided including position change and time frame.
- If no, the subject will be asked if they have any questions or concerns about what they have heard.
- If yes, questions will be answered and the question about hearing more about the study will be repeated.
- If no, the subject will be thanked and the PI will leave the room.

If the subject would like to hear more, additional information will be provided and then the subject will be asked if they would like to participate.

- If yes, the consent forms will be signed, the GOAT, BDI –II and the CDT will be provided. Once these documents are completed, the patient will be connected to the monitoring devices and the study will begin.
- If no, the patient will be thanked and the PI will leave the room.

Appendix F: Consent for Healthy Volunteers

CONSENT TO PARTICIPATE IN RESEARCH

Effect of Changes in Position on Heart Rate and Blood Pressure in Patients with a Traumatic Injury to their Brain

Baroreceptor Sensitivity During Positional Changes in Patients with Traumatic Brain Injury

Healthy Volunteer Subject Form

You are asked to participate in a research study conducted by Norma D. McNair, MSN, RN and Mary A. Woo, DNSc, RN, from the School of Nursing at the University of California, Los Angeles. You have been asked to participate in this study because you are a healthy individual whose results will be used for comparison to patients who have sustained a traumatic brain injury. Your participation in this study is entirely voluntary. This study is funded by a grant from Sigma Theta Tau, Gamma Tau chapter. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

• PURPOSE OF THE STUDY

Common medical and nursing procedures in traumatic brain injury can include having patients change position (turn on their side or sit up). It is unknown how such changes in position affect important blood flow factors in persons who recently have had traumatic brain injury. The purpose of this study is to determine if a change in position affects heart rate and blood pressure (“baroreceptor sensitivity”) in persons with traumatic brain injury differently than in persons who do not have a traumatic brain injury. Your participation in this study will last approximately 60 minutes. You will be asked to participate only one time. The study will enroll a total of 52 subjects at Ronald Reagan UCLA Medical Center and UCLA campus.

• PROCEDURES

If you volunteer to participate in this study, we would ask of you the following:

1. All study procedures involving you will be performed in the Clinical Neurophysiology Lab at Ronald Reagan UCLA Medical Center.
2. You will be asked not to drink any caffeine or use any tobacco products for 12 hours prior to the study procedure (which will take place in the morning).
3. You will be asked to complete the following documents: the Galveston Orientation and Amnesia Test (GOAT), the Watson Clock Drawing Test and the Beck Depression Inventory - II.
 - a. If it is determined that you are depressed (BDI-II score above 13) you will be asked if you wish to continue with

Protocol ID:IRB#11-000499 UCLA IRB Approved Approval Date: 2/28/2012 Through: 2/27/2013 Committee: Medical IRB 3

the study. If it is determined that you are moderately to severely depressed (BDI-II score > 18), you will be referred for treatment with a psychiatrist. If you are actively suicidal, you will not be enrolled in the study and you will be escorted to the Emergency Department for treatment.

4. You will be connected to the cardiac monitor with wires that are provided with the monitor for this purpose using electrodes that are specifically used for cardiac monitoring, and connected to the blood pressure monitoring device and it will be attached to your wrist to measure your blood pressure. In addition, the transcranial Doppler measuring device will be placed on your head and secured with a band that will hold the device steady. The blood pressure and cardiac monitors provide continuous, non-invasive monitoring of your heart rate and blood pressure throughout the research study. The transcranial Doppler measuring device will provide continuous, non-invasive monitoring of the blood flow to your brain in the right and left middle cerebral arteries (the main arteries to the brain).

5. Your monitoring devices will be connected to a personal computer which will record the data for analysis.

6. You will be asked to lie down flat on the bed, with a lifting pad under your back, resting quietly for 10 minutes. During that time, the monitors will measure heart rate, blood pressure and blood flow to your brain.

7. At the end of the 10 minute period, you will be sat up straight in the bed (bending at the waist – your head and upper body will be upright, your legs will remain flat on the bed) by 2 researchers (Norma McNair and a research assistant) using the lifting pad (in less than one second). The position will be kept for five (5) minutes, while your heart rate, blood pressure, and changes in blood flow to your brain are recorded.

8. Then, you will be laid back down flat on the bed to rest again for 10 minutes.

9. The sitting up procedure will be repeated as described in step # 6, one more time.

10. After the second time sitting up, you will rest flat on the bed for 10 minutes.

11. After this last 10 minute rest, you will be disconnected from the monitors and your study participation will be completed.

The total time for this testing will be 60 minutes (hookup of equipment, test procedures).

• POTENTIAL RISKS AND DISCOMFORTS

Connection to the monitoring devices should cause no discomfort. The electrodes for the monitoring devices may cause some itchiness of the skin. The transcranial Doppler monitoring device may feel tight on your head. Sitting straight up suddenly may cause momentary dizziness or lightheadedness. If dizziness or lightheadedness should persist

longer than one minute, you will be laid back down flat until your symptoms (the dizziness/lightheadedness) go away.

The test maneuvers performed for this study may involve risks that are currently unforeseeable.

• ANTICIPATED BENEFITS TO SUBJECTS

Based on experience with this procedure in patients with similar disorders, researchers believe it may be of benefit to subjects with traumatic brain injury. Comparing patients with traumatic brain injury to those of healthy subjects may provide better information on the care of the patient with traumatic brain injury. There will be no direct benefit to you as a healthy subject.

• ANTICIPATED BENEFITS TO SOCIETY

The anticipated benefits will be to future patients who have sustained a traumatic brain injury as we may have a better understanding of how position changes affect heart rate and blood pressure, and blood flow to the brain.

• ALTERNATIVES TO PARTICIPATION

There are no alternatives to participation other than to not participate in the study.

• PAYMENT FOR PARTICIPATION

There will be payment of \$20 to subjects who participate in the research study. Subjects will also be paid the current rate for parking.

• FINANCIAL OBLIGATION

There will be no financial obligation on the part of you or your insurance provider for participation in this study or for procedures performed solely for this study.

Neither you nor your insurance company will be billed for your participation in this research.

• EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures not done primarily for your own benefit, you will receive treatment at no cost. The University of California does not normally provide any other form of compensation for injury.

• PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team. No information about you, or provided by you during the research will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law.

Authorized representatives of the UCLA Office for Protection of Research Subjects may need to review records of individual subjects. As a result, they may see your name, but are bound by rules of confidentiality not to reveal your identity to others.

When the results of the research are published or discussed in conferences, no personal information will be included that would reveal your identity. If photographs, videos, or audio-tape recordings of you will be used for educational purposes, your identity will be protected or disguised. No personal identification information will be collected from you. Instead, a unique study code will be assigned to your data and the code sheet will be kept in a locked cabinet separate from the study data. Data will be destroyed in a secure manner five (5) years after the completion of the study.

• PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

• WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing. If your initial blood pressure is over 140 systolic or 90 diastolic or less than 100 systolic or 60 mmHg diastolic, you will not be eligible for the study and will not be able to continue with the study. If you experience any of the following side effects: persistent lightheadedness or dizziness, change in your blood pressure or heart rate that is not normal and does not resolve, or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Norma D. McNair, MSN, RN, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid for your participation at the \$20 remuneration.

• NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

• IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact Norma D. McNair, MSN, RN at [REDACTED] or [REDACTED] or Mary A. Woo, DNSc, RN, at [REDACTED] at the UCLA School of Nursing, 700 Tiverton Avenue, Los Angeles, CA 90095-1702.

• RIGHTS OF RESEARCH SUBJECTS

If you wish to ask questions about your rights as a research participant or if you wish to voice any problems or concerns you may have about the study to someone other than the researchers, please call the Office of the Human Research Protection Program at [REDACTED] or write to the Office of the Human Research Protection Program, UCLA, 11000 Kinross Avenue, Suite 102, Box 951694, Los Angeles, CA 90095-1694.

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

Name of Subject

Name of Legal Representative (if applicable)

Signature of Subject or Legal Representative Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject or his/her legal representative, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

Name of Investigator

Signature of Investigator Date (must be the same as subject's)

Appendix G: Permission to Use Personal Health Information for Research at UCLA

University of California
Permission to Use Personal Health Information for Research

Study Title (or IRB Approval Number if study title may breach subject's privacy):

Baroreceptor Sensitivity During Positional Changes in Patients with Traumatic Brain Injury

Principal Investigator Name:

Norma D. McNair, MSN, RN

Sponsor/Funding Agency (if funded):

N/A

A. What is the purpose of this form?

State and federal privacy laws protect the use and release of your health information. Under these laws, the University of California or your health care provider cannot release your health information to the research team unless you give your permission. The research team includes the researchers and people hired by the University or the sponsor to do the research. If you decide to give your permission and to participate in the study, you must sign this form as well as the Consent Form. This form describes the different ways that the researcher, research team and research sponsor may use your health information for the research study. The research team will use and protect your information as described in the attached Consent Form. However, once your health information is released it may not be protected by the privacy laws and might be shared with others. If you have questions, ask a member of the research team.

B. What Personal Health Information will be released?

If you give your permission and sign this form, you are allowing: [UCLA](#) to release the following medical records containing your Personal Health Information. Your Personal Health Information includes health information in your medical records and information that can identify you. For example, Personal Health Information may include your name, address, phone number or social security number.

Entire Medical Record

Outpatient Clinic Records

Pathology Reports

EKG

Laboratory Reports

Dental Records

Operative Reports

Radiology Reports

Emergency Medicine Center Reports

Health Care Billing Statements

Diagnostic Imaging Reports

History & Physical Exams

Progress Notes

Radiologic & MR
Scans

Consultations

Discharge
Summary

Psychological Tests

Other (describe):

C. Do I have to give my permission for certain specific uses?

Yes. The following information will only be released if you give your specific permission by putting your initials on the line(s).

___ I agree to the release of information pertaining to drug and alcohol abuse, diagnosis or treatment.

___ I agree to the release of HIV/AIDS testing information.

___ I agree to the release of genetic testing information.

___ I agree to the release of information pertaining to mental health diagnosis or treatment as follows:

D. How will my Personal Health Information be used?

Your Personal Health Information may be released to these people for the following purposes:

1. To the research team for the research described in the attached Consent Form;
2. To others at UC who are required by law to review the research;
3. To others who are required by law to review the quality and safety of the research, including: U.S. government agencies, such as the Food and Drug Administration, the research sponsor or the sponsor's representatives, or government agencies in other countries. These organizations and their representatives may see your Personal Health Information. They may not copy or take it from your medical records unless permitted or required by law.

E. How will my Personal Health Information be used in a research report?

If you agree to be in this study, the research team may fill out a research report. (This is sometimes called "a case report".) The research report will **not** include your name, address, or telephone or social security number. The research report may include your date of birth, initials, dates you received medical care, and a tracking code. The research report will also include information the research team collects for the study. The research team and the research sponsor may use the research report and share it with others in the following ways:

1. To perform more research;
2. Share it with researchers in the U.S. or other countries;
3. Place it into research databases;
4. Use it to improve the design of future studies;
5. Use it to publish articles or for presentations to other researchers;
6. Share it with business partners of the sponsor; or
7. File applications with U.S. or foreign government agencies to get approval for new drugs or health care products.

F. Does my permission expire?

This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over. Research reports can be used forever.

G. Can I cancel my permission?

You can cancel your permission at any time. You can do this in two ways. You can write to the researcher or you can ask someone on the research team to give you a form to fill out to cancel your permission. If you cancel your permission, you may no longer be in the research study. You may want to ask someone on the research team if canceling will affect your medical treatment. If you cancel, information that was already collected and disclosed about you may continue to be used. Also, if the law requires it, the sponsor and government agencies may continue to look at your medical records to review the quality or safety of the study.

H. Signatures

Subject

If you agree to the use and release of your Personal Health Information, please print your name and sign below. You will be given a signed copy of this form.

Subject's Name (print)--required

Subject's Signature

Date

Parent or Legally Authorized Representative (where IRB approved)

If you agree to the use and release of the above named subject's Personal Health Information, please print your name and sign below.

Parent or Legally Authorized Representative's Name
(print)

Relationship to the Subject

Parent or Legally Authorized Representative's Signature

Date

Witness

If this form is being read to the subject because s/he cannot read the form, a witness must be present and is required to print his/her name and sign here:

Witness' Name (print)

Witness' Signature

Date

Appendix H: Obtaining Consent from Legally Authorized Representative

Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research

Section 1:

I am willing to serve as a surrogate decision maker for

_____ (Potential Subject)

to participate in **_Baroreceptor Sensitivity During Positional Changes in Patients with Traumatic Brain Injury_** IRB # **_ 11-000499** _____

(Title of research project and IRB #)

research conducted by **_Norma D. McNair, MSN, RN_** _____

(Principal Investigator)

Section 2:

Category of Potential Surrogate

For the categories listed above yours, provide the name(s) of other relatives. (For example, if you are the adult son or daughter of the potential subject, provide the names of adults, if any, who are best described by categories 1-4 only)

1. Agent named in the potential subject's advanced health care directive.

1. _____

2. Conservator or guardian of the potential subject, with authority to make health care decisions for the potential subject

2. _____

3. Spouse of the potential subject.

3. _____

4. Domestic partner of the potential subject.

4. _____

5. Adult son or daughter of the potential subject.

5. _____

6. Custodial parent of the potential subject

6. _____

7. Adult brother or sister of the potential subject

7. _____

8. Adult grandchild of the potential subject

8. _____

9. Adult whose relationship to the potential subject does not fall within one of the above listed categories and is best described as:

9. _____

(Example: cousin, aunt, etc.)

Section 3:

The following section information must be completed only for surrogate consent to participate in research in non-emergency settings:

(Check the statement which best describes the basis of your knowledge of the potential subject)

_____ I live with the potential subject and have done so for _____ years.

_____ I have discussed participation in research with the potential subject and believe that I can carry out his/her preferences.

_____ Other (please describe): _____

UNIVERSITY OF CALIFORNIA LOS ANGELES
OFFICE OF THE HUMAN RESEARCH PROTECTION PROGRAM
SUBJECT COMPREHENSION ASSESSMENT TOOL

Potential Subject: _____ Date: _____

IRB Protocol # **_11-000499** _____

Use these four elements to assess subject comprehension and/or decision-making capacity for this specific research protocol:

Understanding:

What is the purpose of the research study?

What will happen to you in this research study?

Appreciation:

What are the potential risks of this research study?

What are the potential benefits of this research study?

Reasoning:

What alternative is there if you choose not to participate in this study?

Investigator Evaluation:

Does the individual express a choice about whether or not to participate?

Yes No

Does the individual have the decision-making capacity to give informed consent for this study?

Yes No

Printed Name of Investigator

Signature of Investigator

Appendix I: Consent for Traumatic Brain Injury Subjects at Ronald Reagan UCLA Medical
Center

CONSENT TO PARTICIPATE IN RESEARCH

Effect of Changes in Position on Heart Rate and Blood Pressure in Patients with a Traumatic Injury to their Brain

Baroreceptor Sensitivity during Positional Changes in Patients with Traumatic Brain Injury

Traumatic Brain Injury Subject Form

You are asked to participate in a research study conducted by Norma D. McNair, MSN, RN, and Mary A. Woo, DNSc, RN from the School of Nursing at the University of California, Los Angeles because you have a diagnosis of a recent traumatic brain injury. Your participation in this study is entirely voluntary. This study is funded by a grant from Sigma Theta Tau, Gamma Tau chapter. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

• PURPOSE OF THE STUDY

Common medical and nursing procedures in traumatic brain injury can include having patients change position (turn on their side or sit up). It is unknown how such changes in position affect important blood flow factors in persons who recently have had traumatic brain injury. The purpose of this study is to determine if a change in position affects heart rate and blood pressure (“baroreceptor sensitivity”) in persons with traumatic brain injury differently than in persons who do not have a traumatic brain injury. Your participation in this study will involve approximately 60 minutes. You will be asked to participate only one time. The study will enroll 52 subjects at Ronald Reagan UCLA Medical Center and UCLA Campus.

• PROCEDURES

If you volunteer to participate in this study, we would ask of you the following:

- 1) All study procedures involving you will be performed in your room and in your assigned hospital bed.
- 2) You will be asked not to drink any caffeine or use any tobacco products for 12 hours prior to the study procedure (which will take place in the morning).
- 3) You will be asked to complete the Galveston Orientation and Amnesia Test (GOAT), the Watson Clock Drawing Test and the Beck Depression Inventory – II.
- 4) You will be connected to the cardiac monitor with wires that are provided with the monitor for this purpose using electrodes that are specifically used

for cardiac monitoring, and connected to the blood pressure monitoring device and it will be attached to your wrist to measure your blood pressure. In addition, the transcranial Doppler measuring device will be placed on your head and secured with a band that will hold the device steady. The blood pressure and cardiac monitors provide continuous, non-invasive monitoring of your heart rate and blood pressure throughout the research study. The transcranial Doppler measuring device will provide continuous, non-invasive monitoring of the blood flow to your brain in the right and left middle cerebral arteries (the main arteries to the brain).

5) Your monitoring devices will be connected to a personal computer which will record the data for analysis.

6) You will be asked to lie down flat on your bed, with a lifting pad under your back, resting quietly for 10 minutes. During that time, the monitors will measure heart rate, blood pressure and blood flow to your brain.

7) At the end of the 10 minute period, you will be sat up straight in the bed (bending at the waist – your head and upper body will be upright, your legs will remain flat on the bed) by 2 researchers (Norma McNair and a research assistant) using the lifting pad (in less than one second). The position will be kept for five (5) minutes, while your heart rate, blood pressure and changes in blood flow to your brain are recorded.

8) Then, you will be laid back down flat on the bed to rest again for 10 minutes.

9) The sitting up procedure will be repeated as described in step # 6, one more time.

10) After the second time sitting up, you will rest flat on the bed for 10 minutes.

11) After this last 10 minute rest, you will be disconnected from the monitors and your study participation will be completed.

The total time for this testing will be 60 minutes (hookup of equipment, test procedures).

• POTENTIAL RISKS AND DISCOMFORTS

Connection to the monitoring devices should cause no discomfort. The electrodes for the monitoring devices may cause some itchiness of the skin. The transcranial Doppler monitoring device may feel tight on your head. Sitting straight up suddenly may cause momentary dizziness or lightheadedness. If dizziness or lightheadedness should persist longer than one minute, you will be laid back down flat until your symptoms (the dizziness/lightheadedness) goes away.

The test maneuvers performed for this study may involve risks that are currently unforeseeable.

• ANTICIPATED BENEFITS TO SUBJECTS

Based on experience with this procedure in patients with similar disorders, researchers believe it may be of benefit to subjects with your condition in that we may discover the effects of positioning patients with traumatic brain injury. Of course, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

You should not expect your condition to improve as a result of participating in this research. You have the right to refuse to participate in this study.

• ANTICIPATED BENEFITS TO SOCIETY

The anticipated benefits will be to future patients who have sustained a traumatic brain injury as we may have a better understanding of how position changes affect heart rate and blood pressure, and blood flow to the brain.

• ALTERNATIVES TO PARTICIPATION

There are no alternatives to participation other than to not participate in the study or to have this procedure performed at another institution.

• PAYMENT FOR PARTICIPATION

There will be payment of \$20 to subjects who participate in this study.

• FINANCIAL OBLIGATION

There will be no financial obligation on the part of the patient or their insurance provider for participation in this study or for procedures performed solely for this study.

Neither you nor your insurance company will be billed for your participation in this research.

• EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures not done primarily for your own benefit, you will receive treatment at no cost. The University of California does not normally provide any other form of compensation for injury.

• PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team. No information about you, or provided by you during the research will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law.

Authorized representatives of the UCLA Office for Protection of Research Subjects may need to review records for individual subjects. As a result, they may see your name, but are bound by rules of confidentiality not to reveal your identity to others.

When the results of the research are published or discussed in conferences, no personal information will be included that would reveal your identity. No personal identification information will be collected from you. Instead, a unique study code will be assigned to your data and the code sheet will be kept in a locked cabinet separate from the study data. Data will be destroyed in a secure manner five (5) years after the completion of the study.

• PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you choose not to participate, this will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

If you consent to participate in this study and should your condition deteriorate, your legal representative will be asked to provide consent for your continuing participation in the study. If consent is being obtained from your legal representative because you are unable to provide informed consent, you will be asked for your consent to continue in the study when your condition improves and you are able to do so.

• WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If your initial blood pressure is over 140 systolic or 90 diastolic or less than 100 systolic or 60 mmHg diastolic, you will not be eligible for the study and will not be able to continue with the study. If you experience any of the following side effects: persistent lightheadedness or dizziness, change in your blood pressure or heart rate that is not normal and does not resolve, or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Norma D. McNair, MSN, RN, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid for your participation at the \$20 remuneration.

• NEW FINDINGS

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

ID:IRB#11-000499 UCLA IRB Approved Approval Date: 2/28/2012 Through: 2/27/2013 Committee: Medical IRB 3

• IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact Norma D. McNair, MSN, RN at [REDACTED] or Protocol [REDACTED] or Mary A. Woo, DNSc, RN, at [REDACTED] at the UCLA School of Nursing, 700 Tiverton Avenue, Los Angeles, CA 90095-1702.

• RIGHTS OF RESEARCH SUBJECTS

If you wish to ask questions about your rights as a research participant or if you wish to voice any problems or concerns you may have about the study to someone other than the researchers, please call the Office of the Human Research Protection Program at [REDACTED] or write to the Office of the Human Research Protection Program, UCLA, 11000 Kinross Avenue, Suite 102, Box 951694, Los Angeles, CA 90095-1694.

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

Name of Subject

Name of Legal Representative (if applicable)

Signature of Subject or Legal Representative Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject or his/her legal representative and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

Name of Investigator

Signature of Investigator Date (must be the same as subject's) Protocol ID:IRB#11-000499

Appendix J: IRB Approval from Rancho Los Amigos National Rehabilitation Center



LOS AMIGOS RESEARCH & EDUCATION INSTITUTE, INC.
RANCHO LOS AMIGOS NATIONAL REHABILITATION CENTER
P.O. BOX 3500
DOWNEY, CA 90242

INSTITUTIONAL REVIEW BOARD

Notification of Continuing Review Approval

Date: September 19, 2011
To: Primary Investigator Subinvestigators/Coordinators
McNair, Norma Luis Montes, M.D.

IRB#: IRB #086 **Study#:** BRS after TBI
Study Title: Baroreceptor Sensitivity during Position Changes in Patients with Traumatic Brain Injury

In response to your request for continued approval of the above named protocol, the IRB has reviewed all pertinent information reported/provided and has granted continued approval of your project.

Approval Date: 09/19/2011 **IRB approval expires:** 09/17/2012
Review Period: 12 months **Continuing review due:** 09/17/2012
Risk Assignment: Minimal
Subjects Approved: 30 **Controls Approved:** 0

IRB Recommendations: CONTINUING REVIEW UNANIMOUSLY APPROVED

This approval is for a period of 12 months. You should receive electronic notification 60 days prior to the expiration of this project's approval. However, it is your responsibility to insure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a final report of findings at the completion of the project.

Consent Form (if applicable): All subjects must use the approved and stamped consent form. You are responsible for maintaining signed consent forms for a period of at least three years after study completion.

Research Modifications: Please note that you are responsible for informing the IRB of any and all protocol modifications prior to implementing those changes; serious or unexpected adverse events, IND safety reports, and additional information pertinent to the risk, benefit, or desire for subjects to continue to participate.

IRB members abstaining for potential or actual conflict of interest: N/A

The Los Amigos Research & Education Inc. Institutional Review Board is duly constituted (fulfilling FDA requirements for diversity), allows only those IRB members who are independent of the investigator and sponsor of the study to vote/provide opinion on the study, has written procedures for initial and continuing review, prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirements defined in 21 CFR (Code of Federal Regulations) Parts 50 and 56, and ICH (International Conference on Harmonization) guidance relating to GCP's (Good Clinical Practice).

Signature applied by Marijke Weightman on 09/19/2011 03:36:06 PM PDT



LOS AMIGOS RESEARCH & EDUCATION INSTITUTE, INC.
RANCHO LOS AMIGOS NATIONAL REHABILITATION CENTER
P.O. BOX 3500
DOWNEY, CA 90242

**INSTITUTIONAL REVIEW BOARD
Notification of Approval**

Date: March 21, 2012

To: Primary Investigator Subinvestigators/Coordinators
McNair, Norma, R.N.

IRB Number: IRB #086 (This number is a LAREI number which should be used on all consent forms and correspondence.)
Study Number: BRS after TBI
Study Title: Baroreceptor Sensitivity during Position Changes in Patients with Traumatic Brain Injury

Approval Date: 10/18/2010

Risk Assignment: Minimal

Review Period: 12 Months

Expiration Date: 09/17/2012 (based upon date recommended for approval)

Subjects Approved: 30

Controls Approved: 0

IRB Recommendations: THE CONTINUING REVIEW REPORT, WITHOUT A NEW INFORMED CONSENT, FORM HAS BEEN UNANIMOUSLY APPROVED.

This approval is for a period of 12 months. You should receive electronic notification 60 days prior to the expiration of this project's approval. However, it is your responsibility to insure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a final report of findings at the completion of the project.

Consent Form (if applicable): The approved and stamped consent form must be used when enrolling subjects. You are responsible for maintaining signed consent forms for a period of at least three years after study completion.

Reporting: The principal investigator must report to the IRB any serious problem, adverse effect, or outcome that occurs with frequency or degree of severity greater than that anticipated. In addition, the principal investigator must report any event or series of events that prompt the temporary or permanent suspension of a research project involving human subjects.

Modifications: Changes or modifications in a research project must have prior approval by the IRB. When deemed necessary to prevent immediate harm to a subject, changes or modifications must be reported to the IRB within 24 hours.

IRB members abstaining from discussion/vote due to a potential, or actual, conflict of interest (if applicable): N/A

The Los Amigos Research & Education, Inc. Institutional Review Board is duly constituted (fulfilling FDA requirements for diversity), allows only those IRB members who are independent of the investigator and sponsor of the study to vote/provide opinion on the study, has written procedures for initial and continuing review, prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirements defined in 21 CFR (Code of Federal Regulations) Parts 50 and 56, and ICH (International Conference on Harmonization) guidance relating to GCP's (Good Clinical Practice).

Signature applied by Becky Mendoza on 03/21/2012 09:22:26 AM PDT

Appendix K: Recruitment Flyer for TBI Subjects at Rancho Los Amigos National Rehabilitation
Center

Research Study

Effect of Changes in Position on Heart Rate and Blood Pressure in Patients with a Traumatic Injury to their Brain

("Baroreceptor Sensitivity during Positional Changes after Traumatic Brain Injury")

Volunteers Are Needed!!

For a study about how change in position affects heart rate and blood pressure in persons with Traumatic Brain Injury and in Healthy Volunteers.

You will qualify if you are between the ages of 18-65 years, **have** sustained a traumatic brain injury, and do not have atrial fibrillation, high blood pressure or history of a recent stroke or heart attack or are taking the type of drug called beta-blockers.

We will look at your heart rate and blood pressure during a position change from flat to upright. The entire study will take about 60 minutes to complete.

Volunteers will be reimbursed for their time and effort for the study.

If you are interested or have questions, please contact:

Norma D. McNair, MSN, RN
UCLA School of Nursing

UCLA IRB #: 06-11-119-04A
Expiration Date:



IRB NUMBER: IRB #086

IRB APPROVAL DATE: 10/28/2010

Appendix L: Permission to Use Personal Health Information for Research at Rancho Los Amigos National Rehabilitation Center

**LOS AMIGOS RESEARCH AND EDUCATION INSTITUTE INC.
RANCHO LOS AMIGOS NATIONAL REHABILITATION CENTER**

**AUTHORIZATION TO ACCESS PROTECTED HEALTH INFORMATION FOR
RESEARCH PURPOSES**

Project title: Baroreceptor Sensitivity during Position Changes in Patients with Traumatic Brain Injury

Investigators: Norma D. McNair, PhD (c), RN and Luis Montes, MD

As a research participant, I authorize the above named researcher and the researcher's staff to disclose my individual health information for the purpose of conducting this project.

This health information disclosed by me or from records will be used to determine my eligibility and may include information collected from procedures that are carried out as part of this study. This information may include demographic information, results of physical exams, blood test, x-rays and other diagnostic and medical procedures as well as medical history. Also, if I receive compensation for participating in this study, identifying information about me may be used or disclosed as necessary to provide compensation.

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

I can change my mind and withdraw this authorization at any time by sending a written notice to above investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

My individual health information disclosed under this authorization may be subject to redisclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

IRB NUMBER: IRB #086

IRB APPROVAL DATE: 10/18/2010

I may not be allowed to review the information collected for this study, including information recorded in my medical record, until after the study is completed. When the

study is over, I will have the right to access the information again.

This authorization does not have an expiration date. You will be given a copy of this form for your files.

I am the research participant or personal representative authorized to act on behalf of the participant.

I have read this information, and I will receive a copy of this authorization form after it is signed.

signature of research participant or research
participant's personal representative

date

printed name of research participant or research
participant's personal representative

description of personal
representative's authority
to act on behalf of the
research participant

IRB NUMBER: IRB #086
IRB APPROVAL DATE: 10/18/2010

Appendix M: Consent for Traumatic Brain Injury Subjects at Rancho Los Amigos National
Rehabilitation Center

INFORMED CONSENT FORM

PROJECT TITLE: Baroreceptor Sensitivity During Position Changes in Patients with Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Norma D. McNair, PhD (c), RN

CO-PRINCIPAL INVESTIGATOR(S): Luis Montes, MD

ADDRESS: [REDACTED]

PHONE [REDACTED] subjects will be enrolled

SUBJECT'S NAME: _____

SUBJECT'S NUMBER: _____ **DATE:** _____

PURPOSE:

Common medical and nursing procedures in traumatic brain injury can include having patients change position (turn on their side or sit up). It is unknown how such changes in position affect important blood flow factors in persons who recently have had traumatic brain injury. The purpose of this study is to determine if a change in position affects heart rate and blood pressure ("baroreceptor sensitivity") in persons with traumatic brain injury differently than in persons who do not have a traumatic brain injury. Your participation in this study will involve approximately 60 minutes. You will be asked to participate only one time. The study will enroll 52 subjects at Ronald Reagan UCLA Medical Center and UCLA Campus and Rancho Los Amigos National Rehabilitation Hospital.

PROCEDURE:

All study procedures involving you will be performed in your room and in your assigned hospital bed or in the clinic on a gurney.

- 1) You will be asked not to drink any caffeine or use any tobacco products for 12 hours prior to the study procedure (which will take place in the morning).
- 2) You will be asked to complete the Galveston Orientation and Amnesia Test (GOAT), the Watson Clock Drawing Test and the Beck Depression Inventory – II.
 - a. If it is determined that you are depressed (BDI-II score above 13, you will be asked if you wish to continue with the study. If it is determined that you are moderately to severely depressed (BDI-II score > 18), your score will be discussed with your primary medical team. Your medical team will determine further treatment. If you are suicidal, you will not be enrolled in the study.
- 4) You will be connected to the cardiac monitor with wires that are provided with the monitor for this purpose using electrodes that are specifically used for cardiac monitoring, and connected to the blood pressure monitoring device and it will be attached to your wrist to measure your blood pressure. In addition, the transcranial Doppler measuring device will

IRB NUMBER: IRB #086
IRB APPROVAL DATE: 10/18/2010
IRB EXPIRATION DATE: 10/17/2011

be placed on your head and secured with a band that will hold the device steady. The blood pressure and cardiac monitors provide continuous, non-invasive monitoring of your heart rate and blood pressure throughout the research study. The transcranial Doppler measuring device will provide continuous, non-invasive monitoring of the blood flow to your brain in the right and left middle cerebral arteries (the main arteries to the brain).

5) Your monitoring devices will be connected to a personal computer which will record the data for analysis.

6) You will be asked to lie down flat on your bed/gurney, with a lifting pad under your back, resting quietly for 10 minutes. During that time, the monitors will measure heart rate, blood pressure and blood flow to your brain.

7) At the end of the 10 minute period, you will be sat up straight in the bed (bending at the waist – your head and upper body will be upright, your legs will remain flat on the bed) by 2 researchers (Norma McNair and a research assistant) using the lifting pad (in less than one second). The position will be kept for five (5) minutes, while your heart rate, blood pressure and changes in blood flow to your brain are recorded.

8) Then, you will be laid back down flat on the bed/gurney to rest again for 10 minutes.

9) The sitting up procedure will be repeated as described in step # 6, one more time.

10) After the second time sitting up, you will rest flat on the bed/gurney for 10 minutes.

11) After this last 10 minute rest, you will be disconnected from the monitors and your study participation will be completed.

The total time for this testing will be 60 minutes (hookup of equipment, test procedures).

RISKS:

Connection to the monitoring devices should cause no discomfort. The electrodes for the monitoring devices may cause some itchiness of the skin. The transcranial Doppler monitoring device may feel tight on your head. Sitting straight up suddenly may cause momentary dizziness or lightheadedness. If dizziness or lightheadedness should persist longer than one minute, you will be laid back down flat until your symptoms (the dizziness/lightheadedness) goes away.

The test maneuvers performed for this study may involve risks that are currently unforeseeable.

BENEFITS:

You should not expect your condition to improve as a result of participating in this research. You have the right to refuse to participate in this study.

Based on experience with this procedure in patients with similar disorders, researchers believe it may be of benefit to subjects with your condition in that we may discover the effects of positioning patients with traumatic brain injury. Of course, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case. The anticipated benefits will be to future patients who have sustained a traumatic brain injury as we may have a better understanding of how position changes affect heart rate and blood pressure, and blood flow to the brain.

These benefits may not happen and unexpected side effects may also develop.

FINANCIAL COMPENSATION TO PARTICIPANT:

You will be compensated for your time in the participation of the study in the amount of \$20.

ALTERNATIVES TO NON-PARTICIPATION:

There are no alternatives to participation other than to not participate in the study.

IRB NUMBER: IRB #086
IRB APPROVAL DATE: 10/18/2010
IRB EXPIRATION DATE: 10/17/2011

CONDITIONS FOR TERMINATION OF SUBJECT BY INVESTIGATOR:

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If your initial blood pressure is over 140 systolic or 90 diastolic or less than 100 systolic or 60 mmHg diastolic, you will not be eligible for the study and will not be able to continue with the study. If you experience any of the following side effects: persistent lightheadedness or dizziness, change in your blood pressure or heart rate that is not normal and does not resolve, or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Norma D. McNair, PhD (c), RN, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid for your participation at the \$20 remuneration.

SUBJECT'S PARTICIPATION IN OTHER RESEARCH STUDIES:

You should inform the investigator if you are or will be participating in any other research study at the same time. This is important because requirements of different studies may conflict with one another, possibly causing harm.

POTENTIAL RISK TO PREGNANCY:

There should be no risk to a pregnant woman or her fetus as a result of participation in this study. It may be difficult for a woman in the latter stages of pregnancy to participate due to the growth of the fetus and the need to sit straight upright during the position change.

STATEMENT OF CONFIDENTIALITY:

The results of this research may be published for the information of other physicians and scientists. Your name or photographs will not be published or used without your consent. To comply with Federal Regulations, we must inform you that your individual health information may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting of abuse or neglect, judicial proceedings, health oversight activities, and public health measures.

DISCLOSURE OF SUBSEQUENT FINDINGS:

Any subsequent findings which may alter your participation decision will be disclosed to you as they become available.

RESEARCH REVIEW, VOLUNTARY PARTICIPATION AND OFFER TO ANSWER QUESTIONS:

A committee (Institutional Review Board or Research Committee) of medical and non-medical people periodically reviews and approves this research for scientific and ethical merit. You will be told of any new information, which may affect your willingness to continue in this research. Your refusal to participate will in no way involve penalty or loss of benefits to which you are otherwise entitled. Your participation is strictly voluntary. You may withdraw from the research project at any time without jeopardizing your medical care at this hospital. If you have any questions now or later please ask us. You will be given a copy of this form to keep. If at any time you feel any infringement of your rights, you may contact the Medical Director at Rancho Los Amigos National Rehabilitation Center (telephone number: [REDACTED]) and/or the Research Committee (telephone number: [REDACTED]) for answers to any questions about the research and your rights.

IRB NUMBER: IRB #086
IRB APPROVAL DATE: 10/18/2010
IRB EXPIRATION DATE: 10/17/2011

STATEMENT OF EMERGENCY, MEDICAL TREATMENT AND FINANCIAL RESPONSIBILITY:

Emergency medical care will be made available at Rancho Los Amigos National Rehabilitation Center if you are an inpatient or while you are here undergoing a research procedure. Otherwise, you should use your usual medical resources (i.e., paramedics, emergency room, etc.).

If you need medical treatment as a result of physical injury arising from your participation in this study, the financial responsibility for such care will be yours.

SUBJECT'S CONSENT:

This consent form has been fully explained to me and I want to participate in this study. I have been given a copy of the consent form and the Subject's Bill of Rights.

Subject's Signature	Subject's Printed Name	Date
---------------------	------------------------	------

Witness' Signature	Witness' Printed Name	Date
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I certify that I have reviewed the contents of this form with the person signing above, who, in my opinion understood the explanation. I have explained the known side effects and benefits of the research.

Principal Investigator's Signature	Norma D. McNair, PhD (c), RN Doctoral Student Printed Name Title	Date
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This consent form will be used for English speaking persons.

IRB NUMBER: IRB #086
IRB APPROVAL DATE: 10/18/2010
IRB EXPIRATION DATE: 10/17/2011

Appendix N: Medical Record Screening Document

Data Collection Instrument

Screening Data for BRS in TBI Study

Inclusion Criteria:

1. Age (in years) _____
2. Diagnosis: _____
3. MD order present to allow out of bed or sitting: _____
4. Location: _____

Exclusion Criteria:

- | | | | | |
|----|------------------------------|----|-----|----------|
| 1. | Atrial Fibrillation | | Yes | No |
| 2. | Pre-existing cardiac disease | HF | Yes | No |
| | | MI | Yes | No |
| 3. | Previous stroke: | | Yes | No |
| 4. | History of HTN: | | Yes | No |
| 5. | Taking beta blockers: | | Yes | No |
| 6. | Abnormal blood pressure | | Yes | _____ No |

Appendix O: Data Collection Instrument

Data Collection Tool

Baroreceptor Sensitivity during Positional Changes in Patients with Traumatic Brain

Injury

Demographics:

Date: _____

Ht: ___ Wt: ___

Study ID: _____

HV: ___ TBI: _____

DOB: _____ Initials: _____

Location: _____

Age: _____ Gender: _____

Ethnicity: _____

Screening OK: _____; if No, Stop

Admission GCS: _____ Copy of MRI/CT results: _____ PID# _____

Current GCS: _____ GOAT: _____ Clock-Drawing: _____ BDI: _____

Type of TBI: _____ Tox Screen: _____

Co-Morbidities: CAD DM HTN ETOH Szs Schizophrenia

Depression Tobacco

Current Medications:

Appendix P: Galveston Orientation and Amnesia Test

The Galveston Orientation and Amnesia Test
Harvey S. Levin, Ph.D., Vincent M. O'Donnell, M.A., & Robert G. Grossman, M.D.

Question	Error Score	Notes
What is your name?	-2 _____	Must give both first name and surname.
When were you born?	-4 _____	Must give day, month, and year.
Where do you live?	-4 _____	Town is sufficient.
Where are you now:		
(a) City	-5 _____	Must give actual town.
(b) Building	-5 _____	Usually in hospital or rehab center. Actual name necessary.
When were you admitted to this hospital?	-5 _____	Date.
How did you get here?	-5 _____	Mode of transport.
What is the first event you can remember after the injury?	-5 _____	Any plausible event is sufficient (record answer)
Can you give some detail?	-5 _____	Must give relevant detail.
Can you describe the last event you can recall before the accident?	-5 _____	Any plausible event is sufficient (record answer)
What time is it now?	-5 _____	-1 for each half-hour error.
What day of the week is it?	-3 _____	-1 for each day error.
What day of the month is it? (i.e. the date)	-5 _____	-1 for each day error.
What is the month?	-15 _____	-5 for each month error.
What is the year?	-30 _____	-10 for each year error.
Total Error:		
Total Actual Score = (100 - total error) = 100 - _____ =		Can be a negative number.
76-100 = Normal / 66-75 = Borderline / <66 = Impaired		
Developed by Harvey Levin, Ph.D., Vincent M. O'Donnell, M.A., & Robert G. Grossman, M.D.		

Appendix Q: Glasgow Coma Scale

Glasgow Coma Scale

Eye Opening Response

- Spontaneous--open with blinking at baseline **4 points**
- To verbal stimuli, command, speech **3 points**
- To pain only (not applied to face) **2 points**
- No response **1 point**

Verbal Response

- Oriented **5 points**
- Confused conversation, but able to answer questions **4 points**
- Inappropriate words **3 points**
- Incomprehensible speech **2 points**
- No response **1 point**

Motor Response

- Obeys commands for movement **6 points**
- Purposeful movement to painful stimulus **5 points**
- Withdraws in response to pain **4 points**
- Flexion in response to pain (decorticate posturing) **3 points**
- Extension response in response to pain (decerebrate posturing) **2 points**
- No response **1 point**

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Appendix R: Research Participants Bill of Rights

**UNIVERSITY OF CALIFORNIA LOS ANGELES
RESEARCH PARTICIPANT'S
BILL OF RIGHTS**

These rights are the rights of every person who is asked to be in a medical research study. As a research participant, I have the following rights:

1. I have the right to be told what the research is trying to find out.
2. I have the right to be told about all research procedures, drugs, and/or devices and whether any of these are different from what would be used in standard practice.
3. I have the right to be told about any risks, discomforts or side effects that might reasonably occur as a result of the research.
4. I have the right to be told about the benefits, if any, I can reasonably expect from participating.
5. I have the right to be told about other choices I have and how they may be better or worse than being in the research. These choices may include other procedures, drugs or devices.
6. I have the right to be told what kind of treatment will be available if the research causes any complications.
7. I have the right to have a chance to ask any questions about the research or the procedure. I can ask these questions before the research begins or at any time during the research.
8. I have the right to refuse to be part of the research or to stop at any time. This decision will not affect my care or my relationship with my doctor or this institution in any other way.
9. I have the right to receive a copy of the signed and dated written consent form for the research.
10. I have the right to be free of any pressure as I decide whether I want to be in the research study.

If I have any questions or concerns I can ask the researcher or the research assistant. I can also contact the UCLA Office of the Human Research Protection Program (OHRPP) which helps protect research study participants. I can reach the OHRPP by calling [REDACTED] [REDACTED] from 8:00 AM to 5:00 PM, Monday to Friday. If I call this office and do not speak English or Spanish, I should have someone available who can interpret for me. I may also write OHRPP, 11000 Kinross Avenue, Suite 102, Box 951694, Los Angeles, CA 90095-1694.

Version: 04/10

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