PEDIATRIC HEAD TRAUMA: CEREBRAL PERFUSION PRESSURE AS AN INDICATOR OF OUTCOME

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This dissertation is dedicated to my parents who always believed.

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Brain injury is a common and devastating event in the United States impacting both the adult and the pediatric populations. In the pediatric population there are over 100,000 children under the age of 15 treated annually for neurological trauma with many suffering significant long-term disability and death. There are extensive data and research evaluating the impact of cerebral trauma in the adult population. Optimization of cerebral perfusion pressure (CPP) has gained recognition as a therapeutic endpoint in the management of brain-injured adults. This study evaluated the relationship between CPP and intracranial pressure (ICP) in children with severe traumatic brain injury. This study focused on the effectiveness of perfusion of injured neurons and the relationship to outcome.

Fifty-five children, aged 1.5 to 15 years, admitted for severe blunt head trauma (Glasgow Coma Score $\leq$ 8) were retrospectively studied looking at systolic blood pressure, heart rate, temperature, mean arterial pressure, intracranial pressure, and

cerebral perfusion pressure as an indicator of outcome as measured by the DELTA injury and disability score. Demographic data collected included age, sex, ethnicity, and admission Glasgow Coma Scale score. Data were analyzed using the SAS software. Results indicate that the first 48 hours after an injury is the critical period to influence outcome with mean arterial pressure, intracranial pressure, and cerebral perfusion pressure significant indicators of outcome ($p \leq 0.0005$).

When subjects were divided into two groups, children who died and children who survived, temperature was significant ($p \leq 0.0005$) for the first four days post injury. Temperature continued to maintain significance when subjects were divided into survivors with poor outcome and good outcome. The relationship between outcome and therapeutic interventions is unclear and requires further evaluation in a larger prospective study.

CHAPTER 1
INTRODUCTION

Background of the Problem

The management of traumatic brain injury (TBI) is a fairly new discipline. Until 40 years ago TBI was regarded as an untreatable insult. Since that time, treatment for TBI has improved significantly. The improvement in therapy is credited to emerging techniques and concepts in intracranial pressure control and cerebral perfusion management. However, there is little consensus regarding the management of these patients (Chestnut, 1997b). This problem is exacerbated when discussing the neurotrauma care of children. From research now available, there are strong supporting data from prospectively collected, observational studies that there is a biological advantage toward favorable outcome associated with younger age. There is also evidence that the path of physiological events underlying the brain's response to injury in children is somewhat different than seen in adults (Aldrich et al., 1992; Bruce et al., 1979; Bruce, Schut, Brumo, Wood, & Sutton, 1978; Luerssen, Klauber, & Marshall, 1988; Muizelaar et al., 1989; Obrist, Langfitt, Jaggi, Cruz, & Gennarelli, 1984).

Injury is the leading cause of death among children and adolescents in the United States. Death from unintentional injury for age groups 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years was 36%, 43%, 39%, and 46% respectively for the year 1998. This represents a total drop in the death rate of 38% between the years 1979 and 1998 (Guyer et al., 1999). The impact of childhood injury is immense in terms of direct costs to society and the tremendous emotional toll of death and disability. Brain injury is a

common and devastating event. In the pediatric population, there are over 100,000 children under the age of 15 treated annually for neurologic trauma with many suffering significant long-term disability and death (Guyer & Ellers, 1990; Lehr & Baethmann, 1997; Tepas, DiScala, Ramenofsky, & Barlow, 1990).

History of Pediatric Trauma Care

In 1917 a French munitions ship and a Norwegian freighter collided causing an enormous explosion at a narrow point in the harbor of Halifax, Nova Scotia, Canada. Two thousand were killed, 9,000 injured and over 31,000 left homeless. Pleas for medical help were issued throughout Canada and the United States. A health care team from Boston led by William E. Ladd responded. Dr. Ladd was moved by the special medical needs of the children and upon his return to Boston dedicated himself to the surgical care of infants and children. This is considered the birth of pediatric surgery as an independent surgical specialty. At this time infectious diseases were the most lethal childhood illnesses. But by 1947, with the advent of sulfa drugs, penicillin, and smallpox and polio vaccines, the death rate from these illnesses began to fall. During the l940s, trauma became the leading cause of death in children (Dietrich, 1954; Godfrey, 1937; Goldbloom, 1986; Press, 1947).

Epidemiology

In 1937 Edward Godfrey, M.D., commissioner of the New York State Department of Health, wrote of the failure of health care workers to give important consideration to childhood accidents. "What is the net gain if a child, through breast feeding and pasteurized milk, is prevented from dying of gastroenteritis if he pulls a stewpan of boiling water off the stove and is fatally scalded? What use to protect him against diphtheria to be killed by an automobile" (p. 153).

Today, trauma remains the major cause of death in children between the ages of 1 and 14, with head injury accounting for 40 % of fatal childhood injuries. Head injury accounts for 100,000 pediatric hospitalizations per year in the United States. The incidence of head injury is approximately 200 per 100,000, with an ensuing mortality rate of 10 %. For comparison, the next leading cause of death in the pediatric age group is leukemia, with a rate of death of approximately 2 deaths per 100,000 (Francel, Park, Shaffrey, & Jane, 1996). When the pediatric population is evaluated as a whole, the most common cause of head injury are falls at approximately 35% of patients and motor vehicle accidents at 25% of patients. When severe trauma is isolated from the above numbers, motor vehicle accidents account for about 75% to 80% of the injuries. Falls drop to 15% (Waxweiler, Thurman, Sniezek, Sosin, & O'Neil, 1995).

Bicycle accidents are a common cause of traumatic injury in children and young adolescents. Bicycle accidents resulted in more than 400,000 emergency department visits and 500 to 600 deaths in the United States in 1986. In 1982, 70% of all bicycle-related injuries occurred in children younger than 15 years of age. Most of these severe accidents involved a motor vehicle. Similar to bicycle accidents are pedestrian injuries to children between the ages of 1 to 14 years. Fatal pedestrian injuries are more common than fatal passenger injuries in preschool and school-aged children (Campbell, 1992; Pautler, Henning, & Buntain, 1995).

Safety Systems

Young people are at risk of head injury as pedestrians, as cyclists, and as occupants of motor vehicles. The risks and consequences vary with age and maturity (Simpson, Blumbergs, McLean, & Scott, 1992). Infant and child safety is an ongoing concern. The advent of seat belts with the subsequent addition of shoulder straps or the three point

restraints decreases the fatality rate of accidents by 40% to 50% and the severity of injury by 55% to 60% (Rivera, 1999). Car seats, when used properly with a five-point restraint system, make fatality 11% less likely. The use of bike helmets by children has significantly decreased severe head injury (DiGuiseppi, Rivara and Koepsell, 1990; Goldsmith, 1992). A study by Spaite, Murphy, Criss, Valenzuela, and Meisen (1991) showed that not wearing a helmet in a serious crash was strongly associated with major head injury in 22% of all patients evaluated, whereas, only 1 in 116 patients wearing helmets during a crash had major head trauma. A mandatory bicycle helmet law instituted in Victoria, Australia, reduced the number of cyclists admitted to the hospital with a marked reduction in the proportion with head injuries when compared with the same period in the year before (Ryan, 1992; Vulcan, Cameron, & Watson, 1992).

Pathophysiology of Pediatric Head Injury

One of the most striking differences between the pediatric and the adult brain is the size, both in terms of the absolute size of the brain and its size relative to the rest of the body. At birth the brain comprises 15% of total body weight decreasing to 3% of total body weight in an adult. The brain grows rapidly relative to the rest of the body during childhood, reaching 75% of adult size by the age of two and 90% of adult size by the age of six (Ward, 1995).

In the young child, the skull is also different from that of the older child and adult. Up until the age of three the skull has unfused sutures. The skull is thinner and more pliable. This pliable, thin skull can expand markedly to avoid compression or expansion of the brain. However this pliability of the immature skull makes the brain more vulnerable to injury. Direct blows to the skull tend to cause more focal deformation, and to a limited extent absorb more of the force of the impact and thus convey less force of

the blow to areas of the brain remote from the area of impact (Francel et al., 1996; McLaurin & Towbin, 1990).

The young brain has significantly less myelination than that of the adult. Recticular system myelination continues on into adult life. While there is limited research on the elastic properties of brain tissue in the young, it does appear that unmyelinated brain tissue of the infant and young child is more susceptible to shearing injuries than that of the older child or adult. An additional physiological difference that makes the young brain susceptible to head injury is the concept of plasticity of the central nervous system. This idea is based on the observation that young children are able to sustain injuries and recover function, whereas, their older counterparts are not (Ward, 1995).

At birth, cerebral perfusion appears to be fairly homogenous, but regional patterns later emerge that reflect the ongoing sequence of functional maturation that occurs in the brain. Cerebral blood blow changes are linked to maturation that occurs in the brain. Regional blood flow changes are linked to changes in metabolism. Regional variation in blood flow may explain altered susceptibility of certain areas of the developing brain to head trauma. However, the immature brain appears to tolerate anoxia and hypoxia better than the adult brain (Francel et al., 1996).

The immature brain has unique characteristics with regard to brain edema. The immature brain shows less edema than the mature brain after significant head trauma. Speculation of the reason for this difference ranges from differences in the blood brain barrier to the lower mean arterial pressure seen in younger animals. Brain edema fluid clears more rapidly in the immature brain (Ghajar & Hariri, 1992).

Cerebral perfusion pressure, which is the difference between the mean arterial pressure and the intracranial pressure, appears to be lower in the child than in the adult. Multiple studies on adults have indicated a minimal cerebral perfusion pressure of 50 mm Hg is required to maintain adequate perfusion with 70 mm Hg felt to be optimum to maintain adequate perfusion of the brain so that deleterious decompensation does not occur (Shapiro & Smith, 1993). The mean systemic blood pressure in children is lower; thus, the cerebral perfusion pressure in children may be normal below 50 mm Hg (Rosner, Prineas, Loggie, & Daniels, 1993). The actual minimum cerebral perfusion pressure for the immature brain has not been determined and may vary with the child's age.

When discussing the skull and brain of children, it is important to note that whenever a child suffers a head injury, there is damage done not only to the current structures but also to the process by which the immature nervous system progresses to a mature state. The central nervous system has a very difficult time regenerating itself. While there is evidence that some regeneration can take place, it is difficult for significant damage to be repaired. It is therefore more imperative to prevent damage than recoup lost function (Ward, 1995).

In general terms, the brain must have enough cerebral blood flow to meet its metabolic needs. Cerebral blood flow is felt to be between 50-100 mm Hg in the young child and adult. It is probably lower in the newborn (birth to 1 month) and infant (1 month to 12 months). Currently there is no definitive answer to what constitutes adequate cerebral blood flow. The answer appears to vary with age, metabolic demands, and other factors. Most researchers believe that ischemic damage can occur when

cerebral blood flow falls below 18 to 20 ml per 100 gm of brain tissue per minute. There are four variables that have a significant effect on cerebral blood flow: (1) systemic blood pressure, (2) arterial blood gases, (3) metabolic demands of the brain, and (4) intracranial pressure (ICP). Blood pressure and cerebral blood flow can be evaluated through the relationship of cerebral perfusion pressure (Mean arterial pressure (MAP) – Intracranial pressure (ICP) = Cerebral perfusion pressure (CPP) (Ward, 1995).

Mechanisms of Injury

As previously stated, motor vehicle accidents comprise the majority of severe head trauma seen in the pediatric population. A motor vehicle accident can be viewed as a series of four accidents, each with the capacity of causing serious injury. First, there is the initial collision event, which occurs when the vehicle strikes or is struck by an object. There is an abrupt change in velocity and direction in the movement of the vehicle. Deformation of the vehicle may lead to direct injury of the occupant. The second potential collision may occur as the occupant strikes the interior of the vehicle. This is the most common cause of injury in a motor vehicle accident and the target of belt restraint systems (Pautler et al., 1995).

The human body is triphasic, with solid, liquid, and gaseous systems combining to provide function and protection. The brain is continually bathed in cerebral spinal fluid. During a collision the head undergoes a sudden change in velocity. While the head strikes or is stuck by an object, the change in motion is not immediately transferred to the brain which continues forward until it strikes the anterior aspect of the cranial vault. This is the third potential collision, as solid organs strike the limits of their confining space. The most commonly seen phenomenon is the coup-contre-coup mechanism of injury. The brain strikes the occipital aspect of the skull as the head accelerates; when the head

then reflects in the opposite direction, the brain strikes the frontal aspects of the cranium (Pautler et al., 1995).

The fourth accident is when objects such as children's toys, automobile parts, or groceries are unrestrained within the vehicle. These items may become projectiles during a collision, striking an occupant and causing further injury (Pautler et al., 1995).

Mechanical Causes of Brain Injury

Traumatic brain injury may be classified into three mechanical causes: (1) an impact defined as the collision of the head with a solid object at an appreciable velocity, (2) an impulsive load which produces sudden motion of the head without significant physical contact, and (3) a static or quasistatic loading situation in which the consequences of speed of occurrence may be neglected. The first mechanism, impact loading, causes brain injury through a combination of contact forces and inertial forces. If the head is prevented from moving after it is struck, then the impact injury is imparted to the head as contact force. Inertial force occurs when the head is set in motion with or without a contact force and results in acceleration of the head. The second mechanism occurs through what is commonly referred to as the whiplash effect. The head is propelled forward rapidly and then just as quickly propelled backwards. While the cranium has not directly been struck, the brain within the cranial vault has suffered trauma. The third mechanism is rare but can occur if a slowly moving object traps the head against a rigid structure, slowly squeezing the skull to produce numerous comminuted fractures of the cranial vault (Halliday, 1999).

Injury to the brain results if contact of inertial forces strains the tissue beyond its structural tolerance. Strain is the amount of tissue deformation caused by an applied mechanical force and is either compressive, tensile, or shear in nature. Compressive

strain results from tissue compression, and tensile strain is produced by stretch of the tissue. Shear strain is the type of distortion that occurs when one tissue slides against another. Brain and vascular tissue, being virtually incompressible, typically sustains damage via tensile and shear strain (Halliday, 1999).

Pattern of Brain Injury

Traumatic brain injury may be divided into two primary patterns of injury, those that produce focal injury and those that produce diffuse injury. Focal brain injuries occur as the result of contact forces. Examples of contact force injuries are skull fractures, epidural hematoma, coup contusion, and subdural hematoma. Contracoup contusion, intracerebral hematoma, and subdural hematoma are examples of inertial forces (translational acceleration) that produce focal and diffuse injury. Intertial force injuries (rotational acceleration) are seen as concussion, diffuse axonal injury, subarachnoid hemorrhage, tissue tear hemorrhage, and gliding contusion (Halliday, 1999).

Mortality and Morbidity

The mortality rate after traumatic brain injury of all severities is lower for children as a group than for adults. Howeve,r for children with severe traumatic brain injury the mortality rate is as high as 59% in one series and does not include those children who died at the scene of their injury. Other studies show a mortality rate of 29% for victims of severe traumatic brain injury who are less than twenty years old and a case fatality rate of 33% for those 15 years of age or younger. The factors that contribute most to the outcomes of traumatic brain injury in children are the mechanisms of injury and the severity of the primary brain damage (Jennet, Teasdale, & Braakman, 1979; Kraus, Fife, & Conroy, 1987).

If one uses the Glasgow Coma Scale (GCS), children who suffer severe injuries (GCS scores < 8) often have better outcomes than those predicted for adults with the same score. The reported mortality from severe injury in children ranges from 9% to 53%, with the average at approximately 20%. This mortality is about half of that reported for adults admitted with the same degree of injury by GCS (Ghajar & Hariri, 1992; Luerssen et al., 1988; Nakayama, Copes, & Sacco, 1991; Tepas et al., 1990).

Children in different age groups clearly have different mortality rates and functional outcomes. Infants and preschool aged children appear to have the worst functional outcomes. Although the immaturity of the brain may protect against loss of more focal functions, it may result in a more significant decrease in overall cognitive function. For equivalent injuries, often the residual neuropsychological defects can be more profound in infants and young children than in adolescents and adults (Francel et al., 1996).

Clinical Presentation

An accurate neurological assessment, performed close to the time of trauma, is vital to formulating the plan of care. The most reliable marker for determining outcome in the brain damaged individual, whether adult or child, is the level of consciousness after resuscitation. The Glasgow Coma Scale, which will be discussed in detail later, was developed to provide clinicians with a rapid, standardized, easy-to-use system to assess patients with altered levels of consciousness. The use of the Glasgow Coma Scale in the assessment of patients after traumatic brain injury has become universally accepted and forms the foundation for communication among clinicians responsible for the care of these patients (Ghajar & Hariri, 1992).

Observation of a patient's eyes, speech, and motor responses to stimuli provide the care provider with a reliable estimate of level of neurologic function. The Glasgow Coma Scale is based on a score between 3 and 15 and represents the numerical sum of these three determinants. The cerebral metabolic rate of oxygen (CMRO2), which reflects mainly supratentorial brain metabolism, is considered the most accurate measurement of brain function and correlates closely to the Glowgow Coma Scale. Based on this relationship, care providers can predict mortality in this population of patients as a function of neurologic function and indirectly as a function of brain metabolic activity. Since infants and toddlers are unable to speak or follow commands appropriately, a children's coma score (CCS) was developed with a maximum score of 11 compared with 15 on the adult scale (Ghajar & Hariri, 1992).

Purpose of the Study

The purpose of this study is to investigate the relationship between cerebral perfusion pressure (CPP) and outcome in severely head injured children. This study seeks to determine if there is a definite threshold of CPP in the severely head injured child, and if there is, what that threshold is. Is there a predictable relationship between increased intracranial pressure (ICP) and CPP? Can this defined threshold be predictive of outcome? The answers to these questions will help determine the therapeutic range of CPP and ICP that allows for the best outcome in pediatric brain injured patients. This will permit development of standard protocols of care for severely head injured children and predict outcomes. The assumption of this study is that there does exist an ideal or threshold value for CPP for traumatic brain injured children regardless of the value of ICP and MAP.

Conceptual Framework

Disturbances of cerebral circulation and metabolism play an important role in the pathophysiology of severe head injury. Once inflicted, primary cerebral injury resulting from TBI is immutable and irreversible. A major concept is that secondary insults add to the primary damage inflicted by the trauma and impair neuronal healing. Secondary systemic insults exert their deleterious effects by impairing the transport of oxygen and nutrients. These secondary effects include raised intracranial pressure, arterial hypotension or hypoxia, acute anemia, and high blood viscosity. These factors have an adverse effect on cerebral blood flow and metabolism. These potentially viable cells should be the targets of clinical strategies (Chestnut et al., 1993; Ghajar, 2000; Ghajar & Hariri, 1992; Miller, Sweet, Narayan, & Becker, 1978; Robertson et al., 1999; Sullivan, 2000).

Significance of the Study

It is currently apparent that vigilant neurologic and cardiopulmonary monitoring combined with aggressive management of postinjury intracranial hypertension, cerebral perfusion pressure, uncontrolled seizure activity, hypoxia, and hypotension improves the functional survival after head injury. The major goal in management of traumatic brain injuries is the prevention of secondary brain damage by the avoidance of cerebral ischemia and maintenance of cerebral perfusion (Hilton, 2000).

A four year effort under the aegis of the Joint Section on Neurotrauma and Critical Care of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, supported by the Brain Trauma Foundation, resulted in an empirical, evidence-based analysis of the existing state of the literature for 14 topics integral to traumatic brain injury treatment. The overall summary demonstrated that the

present state of traumatic brain injury management is poorly founded in terms of well-performed, empirical, clinical outcome studies. With respect to the management of pediatric traumatic brain injury, the situation is even less secure. The overall conclusion of pediatric neurotraumatologists is that there are insufficient clinical data to make definite statements on any aspects of managing pediatric traumatic brain injury (Chestnut, 1997b).

Ghajar et al. (1995) show this inconsistency in a review of the management of patients with severe head injury in the United States. This point is further brought home by a similar study by Bulger et al. (2002). Thirty-four academic trauma centers show pronounced variation in all aspects of care of adult head trauma patients. This inconsistency of care is even more pronounced when management of children is evaluated. Tilford et al. (2001) examined therapies and outcome for pediatric head trauma patients in three pediatric intensive care units (PICU) showing marked variations in both variables. Research on pediatric head trauma patients has lagged far behind that of adults. As a result, large variations in practice styles and outcomes persist across centers that care for children with head injuries. The numerous studies in adults have led to evidence-based guidelines to support their management; whereas, therapies for children have been extrapolated from adult studies.

Data acquired and analyzed from this study will help identify trends that facilitate management of TBI in children that may be of prognostic value, both in assessing the effect of therapy as well as predicting outcomes in terms of mortality and morbidity. The potential financial benefits of this study are the development of a standard protocol leading to improved outcomes which will decrease the cost of hospitalization through a

reduction in length of stay, decrease the length and cost of rehabilitative care and reduce the emotional toll and expense to families.

Study Questions

The following hypotheses will be tested:

Children with non-penetrating traumatic brain injury with a cerebral perfusion pressure averaging 50 mmHg or higher will demonstrate better outcome, as measured by the DELTA disability and injury score (DS), than subjects with a cerebral perfusion pressure averaging less than 50 mmHg.

Children with non-penetrating traumatic brain injury will tolerate a lower average cerebral perfusion pressure than adults with non-penetrating traumatic brain injury as measured by DS.

There is an inverse relationship between intracranial pressure and cerebral perfusion pressure in children with traumatic brain injury.

Definition of Terms

Glasgow Coma Scale

One of the important concepts in evaluating neurologic injury is the Glasgow Coma Scale (GCS). In 1974 Teasdale and Jennet proposed a clinical scale for assessing the depth and duration of consciousness and coma. Three aspects of behavior are independently measured: motor responsiveness, verbal performance, and eye opening. The patient's best responses are recorded and a cumulative score is obtained. The lower the total score, the more severe the neurologic compromise (Appendix B). The Glasgow Coma Scale is modified for use with infants and small children with open fontanels (Appendix C) (James & Trauner, 1985).

DELTA Disability and Injury Score

The Delta disability and injury score (DS) is a means of evaluating the qualitative degree of disability and tracking rate and extent of injuries. It is based on a categorized assessment (Appendix D) of four components that describe autonomous function. The

basic premise of this assessment scheme is that injury-related disability produces a negative score that can be periodically reevaluated to document rate and extent of recovery (Tepas, 1989). Disability, as assessed at discharge, is considered mild if the DELTA score is -2 or less, moderate if -3 to -5 and severe for greater than -5 (Kisson, Tepas, Peterson, Pieper & Gayle, 1996).

Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) is designed to evaluate patient outcome following, among other things, traumatic brain injury. Similar to the Glasgow Coma Scale, the Glasgow Outcome Scale assigns numerical values based on clinical condition (Appendix E). The Glasgow Outcome Scale is appropriate for use from the time of hospital discharge until several years post injury. As with the Glasgow Coma Scale, a lower numerical total on the Glasgow Outcome Scale indicates a more severe outcome. Correlation between initial GCS and GOS is low; however, GCS scores six hours after presentation correlated better with eventual outcome (Waxman, Sundine, & Young, 1991).

Cerebral Blood Flow

Normal mean cerebral blood flow (CBF) in adults is 50ml per 100g brain tissue per minute at an arterial PCO2 of 40mg. In children and adolescents the CBF value is higher and probably inversely related to age, although normal values in the younger age groups have yet to be established (Obrist et al., 1984).

Cerebral Blood Volume

Cerebral blood volume (CBF) is the flow of blood through the brain, important for the delivery of oxygen and removal of waste products. In normal circumstances when CBF falls the physiological electrical function of the cell begins to fail. Further, an

increase or decrease in cerebral arterial blood volume will cause an increase or decrease in cerebral arterial blood volume because of arterial dilatation or constriction.

Cerebral Metabolic Rate of Oxygen

The cerebral metabolic rate of oxygen (CMRO2) is calculated by multiplying CBF and the arteriovenous difference of oxygen content (AVDO2). Normal CMRO2 is 3.2 ml/100 g min (Kennedy & Sokoloff, 1957). When CBF falls, CMRO2 is initially maintained because the brain extracts more oxygen from the blood. A lowering of CMRO2 of greater than 50% of normal causes disintegration of functional elements of the cell, eventually leading to neuronal death or infarction (Bouma & Muizelaar, 1992).

Arteriovenous Difference of Oxygen

The arteriovenous difference of oxygen content (AVDO2) is the amount of oxygen gas (in ml gas/100 g min) extracted from the brain. Normal AVDO2 is 6.3 ml/100 ml (Kennedy & Sokoloff, 1957).

Volume-Pressure Index

Pressure-volume index (PVI) is a measure of brain compliance and is the calculated volume (in milliliters) required to raise ICP by a factor of 10. It is thought to be a reflection of the vascular component of the intracranial compartment.

CHAPTER 2
REVIEW OF LITERATURE

Physiology of Cerebral Circulation and Metabolism

The brain, unlike other tissues, is enclosed in a rigid shell. This fact makes volume regulation of the brain more sophisticated. When the ability of the cerebrospinal fluid and intracerebral blood to adjust for volume is exhausted, the intracranial pressure will rise. A rise in intracranial pressure reduces cerebral perfusion pressure with a corresponding decrease in cerebral blood flow (CBF). Under normal circumstances, the volume-regulating mechanisms of the brain work to keep the brain volume within normal limits. One of the mechanisms controlling normal brain volume is the fluid exchange across the brain capillaries. The brain differs from most organs of the body in its highly sophisticated semipermeable capillary membrane function. The capillary is permeable for water but less permeable for other molecules and solutes. The interplay among water, solutes, and crystalloids effectively controls brain volume within allowable limits (Grande, Asgeirsson, & Nordstrom, 1997).

Under normal circumstances, energy requirements of the brain are high. Most of the energy is needed for restoration of ionic gradients across the cell membrane, for maintaining membrane integrity, and for molecular transport between central and peripheral sites. The oxidation of glucose is the single most important source of energy for the brain. The oxidation of glucose is much more efficient than anaerobic metabolism in the production of adenosine triphosphate (ATP). The end product of aerobic metabolism of glucose is carbon dioxide, which easily crosses the blood brain barrier.

The end product of anaerobic metabolism is lactic acid, which accumulates and is toxic to the brain. The main purpose of cerebral circulation is to provide sufficient glucose and oxygen to the brain. Since the brain itself has no storage capacity for either of these substrates, a tight coupling between CBF and cerebral metabolism is necessary for maintaining normal neuronal activity. The supply of glucose is usually sufficient, thus oxygen transport is the limiting factor in determining adequate cerebral circulation (Bouma & Muizelaar, 1992).

Cerebral metabolism can be assessed by the Fick principle as the product of cerebral blood flow and the arterio-venous differences (AVD) of metabolites consumed and produced by the brain. Under normal circumstances, CBF is closely coupled to cerebral metabolism, and changes in CBF are accompanied by reciprocal alterations in oxygen and glucose extractions, as calculated by AVD of oxygen (AVDO2) and glucose (AVD-Glu). In ischemic conditions, extractions of oxygen and glucose increase in order to compensate for the low CBF. Following severe head injury, cerebral metabolic rates of oxygen (CMRO2) and glucose (CMR-Glu) are reduced by as much as 50%. In these patients, as opposed to ischemic patients, metabolic dysfunction presumably occurs as a result of cellular injury, rather than by ischemia. If so, cellular demand for oxygen and glucose by the injured brain is low, and therefore, lower uptake is expected (Cruz, Jaggi, Hoffstad, 1995).

Shalmon, Caron, Martin, Hoyda, and Becker (1994) assessed the association between oxygen and glucose utilization in conjunction with CBF in severely head-injured patients. Also studied was the hypothesis that the cerebral supply of these metabolites is sufficient for metabolic demand. Fifteen severely head injured patients were

prospectively studied. Glasgow Coma Score ranged from 3-7. Conclusions reached were that traumatic brain injury alters the metabolic demands of neuronal cells and hence the uptake of oxygen and glucose. Low uptake of oxygen and glucose results in small AVDO2 and AVD-Glu regardless of their supply, and CMRO2 and CMR-Glu are often coupled to CBF in severely head-injured patients.

Cerebral Edema

The pathophysiology of ischemic brain edema depends primarily on the duration and severity of ischemia. Cerebrovascular permeability as well as hydraulic conductivity of capillaries, hydrostatic and osmotic pressure gradients, and tissue compliance and resistance are also associated with the ischemic edema process. A hydrostatic pressure gradient across the capillary develops soon after the ischemic onset and is the driving force for early accumulation of edema fluid. Hatashita, Hoff, and Salamat (1989) sought to clarify whether blood brain barrier and an osmotic gradient across the capillary are associated with the development of ischemic brain edema. Using adult male Sprague-Dawley rats that were subjected to occlusion of the middle cerebral artery (MCA), the researchers demonstrated that the accumulation of edema fluid was related to a hydrostatic pressure gradient. This developed soon after the onset of ischemia, and was followed by an osmotic pressure gradient as ischemic injury progressed.

Intracranial Pressure

Intracranial pressure is an estimate of the force required to displace blood and CSF from the intracranial space in order to accommodate the new volume. A thick layer of bone penetrated by several foramina bound the intracranial space. The tentorium divides it into two large compartments, and the compartments communicate through the tentorial incisura. Since the thick bone of the calvarium is essentially nondistensible, the volume

of the intracranial space is virtually constant, irrespective of the pressure generated within it. The tentorium itself can be displaced upward or downward but the total intracranial volume remains unchanged. The intracrainial space is occupied by fluid and solid material and these contents are nearly noncompressible. This noncompressability is the basis for the Monro-Kellie doctrine (Rosner, 1993).

The Monro-Kellie doctrine put forth in 1783 the concept that the intracranial space contains only two compartments that can change in volume, brain matter, and intravascular blood. In 1846 Burrows added the concept of cerebrospinal fluid. He maintained that the blood volume of the brain does change in volume under a variety of circumstances, and is accompanied by a reciprocal change in volume in one of the other intracranial components, either the brain, intravascular blood or brain tissue water, or the cerebrospinal fluid (Lang & Chestnut, 1994; Langfitt, 1969; Shackford, 1997).

The largest component of the brain is the parenchyma. It represents approximately 1100 to 1200 grams and should be considered constant under most conditions. The vascular component represents blood distributed between arteries, arterioles, capillaries, venules, and the larger venous system. This total volume is approximately 150 ml but varies widely. The cerebralspinal fluid compartment represents approximately 150 ml of volume and has tremendous therapeutic potential since a portion is usually available for removal. When combined, the total volume is approximately 1500 ml of which the majority (parenchyma) is fixed and 20 percent (CSF, blood and water) are variable. This concept continues to form the basis of cerebral intracranial pressure. One exception to this concept is infants since the skull is not yet rigid (Rosner, 1993).

Many pathological conditions affect the cerebral parenchyma, though rarely in absence of effect upon the vasculature or CSF components. Cerebral edema is the prototypical process capable of increasing the parenchymal component of the intracranial volume. Cerebral edema is an increase in the water content of the brain. Cerebral edema is further separated into two types of brain water accumulation. These two pathological types of cerebral edema are cytotoxic edema and vasogenic edema (Rosner, 1993).

Cytotoxic edema refers to the accumulation of primarily intracellular water. Vasogenic edema represents ultrafiltrate of plasma leaking at a greater than normal rate into the cerebral parenchyma. This is usually due to insults that affect primarily vasculature at the capillary endothelial level and the integrity of the blood-brain barrier (Rosner, 1993).

Cytotoxic edema is primarily intracellular and will respond to therapies aimed at cellular mechanisms for maintaining salt and water balance. This can be viewed as metabolic processes requiring therapies aimed at cellular metabolism. Vasogenic edema is more mechanical in nature and therapies aimed at vasogenic edema will be more mechanically based and directed at the blood-brain barrier (Rosner, 1993).

Some of the first research generated describing the behavior of ventricular fluid pressure in patients with intracranial hypertension was presented by Lundberg in 1960. Lundberg first described “A”-wave or “plateau wave”. This intracranial phenomenon is characterized by spontaneous and acute elevations in ICP rapidly rising above baseline levels (usually 15 to 25 mm Hg). These elevations may reach levels of 50 to 100 mm Hg and last anywhere from 2 or 3 minutes to as long as 20 or 30 minutes. These ICP spikes

usually abort as quickly as they begin. Lundberg concluded these spontaneous A-waves reflected vasodilation with subsequent increases in CBV (Rosner & Becker, 1984).

While CBV has been shown to increase during the plateau, CBF is slightly decreased. Matsuda, Yoneda, Handa, and Gotoh (1979) studied five patients with increased intracranial pressure and noted a marked decrease in cerebralvascular resistance during the plateau waves. The researchers proposed that plateau waves indicate a period of marked cerebral vasodilation followed by an increase in CBV. Rosner and Becker (1984) in a study of cats with fluid percussion head injuries concluded that plateau waves occur when there is intact autoregulation responding to changes in CPP.

Changes in ICP waveforms occur under various physiologic and pathophysiologic conditions and may provide valuable information about intracranial adaptive capacity. Intracanial waveform analysis provides information about intracranial dynamics that can help identify individuals who have decreased adaptive capacity and are at risk for increases in ICP and decreases in CPP, which may contribute to secondary brain injury and have a negative impact on neurologic outcome (Kirkness, Mitchell, Burr, March & Newell, 2000).

Intracranial hypertension is defined as a persistent elevation of intracranial pressure with an intracranial pressure over 20 mm Hg. During the expansion of intracranial space-occupying lesions, such as subdural and epidural hematomas, the mechanisms for spatial compensation fail. The brain becomes less compliant so that small increases in volume cause increasing rises in intracranial pressure. As intracranial pressure increases, the decreasing difference between arterial and intracranial pressure becomes equivalent to the cerebral perfusion pressure. Leech and Miller (1974) looked at eight anaesthetized,

ventilated adult baboons. The intracranaial volume-pressure response was examined during different levels of raised intracranial pressure during induced changes in systemic arterial pressure and cerebral blood flow. At normal intracranial pressure, the volume-pressure response was unchanged by alterations in systemic arterial pressure and cerebral blood flow. At raised intracranial pressure the systemic arterial hypertension rendered the intracranial contents more sensitive to the effects of an addition to the ventricular volume as shown by an increased volume-pressure response. As intracranial pressure is increased there is a linear correlation between the volume-pressure response and both arterial pressure and cerebral blood flow. The clinical implication of this phenomenon is that arterial hypertension in patients with increased intracranial pressure is likely to have a deleterious effect by increasing brain tightness.

A retrospective study of 245 patients with TBI evaluated the contribution of CPP and ICP to neurological deterioration. It was found for this study that the most powerful predictors of neurological deterioration was the presence of intracranial hypertension (ICP > 30 mm Hg). The CPP also had a prognostic power on neurological deterioration when its level was less than 60 mm Hg (Feng, Huang, Gao, Tan, & Liao, 2000).

Robertson et al. (1999) compared two management protocols with long-term outcome in patients with severe head injury. One protocol was targeted at intracranial pressure management and the second was targeted at cerebral blood flow management. One hundred eighty-nine adults admitted with severe head injury at a Level 1 trauma center were studied prospectively in a randomized clinical trial. Mean arterial pressure, cerebral perfusion pressure, and PaCO2 were seen as the primary differences between the

two protocols. The CBF-targeted management protocol was found more successful in reducing secondary ischemic insults.

This CBF-targeted management protocol is known as the Lund therapy and aims to reduce ICP. It is based purely on physiologic principles for cerebral tissue and blood volume regulation in a tissue with disrupted blood-brain barrier and allows for both the risks of increased ICP and the risks of compromised microcirculation. The Lund therapy emphasizes reduction in microvascular pressures to minimize edema formation in the brain. The goal of the therapy is to preserve a normal osmotic pressure, to reduce capillary hydrostatic pressure by reducing systemic blood pressures, and to reduce CBV by vasoconstricting precapillary resistance vessels (Eker, Asgeirsson, Grande, Schalen, & Nordstrom, 1998; Grande, Asgeirsson, & Nordstom, 2002; Robertson, 2001).

A study to evaluate the Lund therapy by the developers of the protocol involved a prospective, nonrandomized outcome study over a five year period on severely head injured patients with increased ICP. Results were compared with a historical control group with the same selection criteria for patients who were treated according to conventional principles. The results showed the clinical outcome in the Lund therapy group of patients considerably better compared with the outcomes of patients treated with conventional, CPP, based therapies (Eker, Asgeirsson, Grande, Schalen, & Nordstrom, 1998).

Naredi et al. (2001) conducted a prospective non-random study of patients with severe head trauma using the Lund therapy. One of the two purposes of the study was to determine whether the good outcome obtained with the Lund therapy in two previous

outcome studies could be reproduced. The outcome results from the two previous studies were successfully reproduced.

The effect of hypothermia on ICP, systemic and intracranial dynamics, and metabolism in patients with severe traumatic head injury was studied to clarify optimal temperature. Thirty-one patients were studied. Data results showed that ICP decreased significantly at brain temperatures below 37 degrees Celsius and decreased more sharply at temperatures 35 to 36 degrees Celsius. There was no difference observed at temperatures below 35 degrees Celsius. The author concluded that decreasing body temperature, after traumatic head injury, can reduce intracranial hypertension while maintaining sufficient CPP without cardiac dysfunction or oxygen debt. Temperatures of 35 to 35.5 degrees Celsius seemed to be optimal (Tokutomi, Morimoto, Miyagi, Yamaguchi, Ishikawa, & Shigemori, 2003).

Cerebral Perfusion Pressure

Cerebral perfusion pressure is the pressure gradient across the vasculature tree. When systemic arterial pressure is normal and the ICP is normal, the difference between CPP and systemic arterial pressure is minimal and probably unimportant under most circumstances. These conditions fail to hold in the damaged brain and/or in the face of hypertension. While ICP and mean systolic arterial blood pressure may vary independently of one another, neither can be affected without altering CPP. Cerebral perfusion pressure correlates with cerebral blood flow when either blood pressure or ICP is altered (Rosner, 1995).

Cerebral ischemia dominates traumatic brain injury as the single most important event-determining outcome. The primary role of CPP maintenance is the preservation of cerebral blood flow through early and accurate monitoring. Cerebral perfusion pressure

is amenable to physician manipulation. Monitoring of cerebral perfusion pressure is achieved by measuring intracranial pressure via subdural or intraventricular access Bouma, Muizelaar, Choi, Newlon, & Young, 1991).

In 1986 Kontos and Wei studied the appearance of superoxide anion radicals in cerebral extracellular space during and after experimental fluid-percussion brain injury. Experiments were carried out on cats. The results supported the following conclusions: 1) Fluid-percussion injury causes the generation of superoxide which continues for at least one hour after injury. 2) Superoxide generated by brain injury and/or radicals derived from it are responsible for the sustained vasodilatation and reduced responsiveness of cerebral arterioles to arterial hypocapnia.

Rosner and Coley (1986) examined CPP as a function of head elevation. Eighteen patients with intracranial hypertension were strictly monitored with head elevations of 0 degrees to 50 degrees in 10 degree increments. The results indicated that for CPP to be maximized, patients with increased intracranial pressure should remain flat in bed. There was no case in which CPP improved with head elevation even though ICP was usually at its highest point. Conversely, Feldman et al. (1992) and Gopinath, Robertson, Narayan, and Grossman (1994) looked at the effect of head elevation on ICP and CPP. Both studies concluded that head elevation of 30 degrees significantly reduced ICP without significantly changing CPP.

Changaris et al. (1987) monitored cerebral perfusion pressure and Glasgow Coma Scale scores to guide the management of 136 consecutive patients admitted to a trauma service. Cerebral perfusion pressure was chosen as the single determinant to correlate with GCS because it represents the net effects of mean arterial pressure (MAP) and ICP.

The authors found that cerebral perfusion pressure has the greatest impact on potential human survivorship.

A study of 50 patients with severe head injury (GCS of 8 or lower) was undertaken by Shigemori et al. (1989) to ascertain thresholds of ICP and CPP for CBF and brain function. Extra- and intracranial blood velocities, determined by transcranial ultrasonography, were found decreased when ICP increased to 20-30 mm Hg and when CPP decreased to 40-50 mm Hg.

McGraw (1989) looked at the issue of determining the most beneficial CPP. A review of data collected over a nine-year period at the University of Louisville Trauma Center showed that a CCP of 80 mm Hg is a critical point at which mortality and morbidity change. Graphing GOS versus CPP derived this figure. A look at mortality showed a semi-linear relationship between GOS and GCS. There appeared to be a natural break in the data at a CPP of 80 mm Hg. Outcomes were observed to be more favorable when the CPP was kept above 80 mmHg. There was a decrease in percent mortality, and increase of good outcomes and a decrease in the number of GCS deteriorations. When CPP remained below 60 mmHg for six hours, death could be predicted with the highest accuracy. This retrospective study further determined that patients could withstand acute drops in CPP to levels below 60 mm Hg, however, a sustained drop in CPP for six hours is less tolerable. The critical time is five hours or under for depressions in CPP below 60 mm Hg.

Rosner and Daughton (1990) used CPP as a method of management for ICP. Thirty-four consecutive patients with GCS $\leq$ 7 were clinically managed to an CPP of 84 $\pm$ 11 mm Hg, ICP of 23 $\pm$ 9.8 mm Hg, and SABP of 106 $\pm$ 11 mm Hg. All patients were

nursed with the head of the bed at 0 degrees. The results indicated that CPP can be artificially elevated by clinical manipulation without deleterious ICP or systemic effects.

Marmarou et al. (1994) studied 386 severely brain injured patients (GCS $\leq$ 8) obtained from the combined data banks of the Traumatic Coma Data Bank (TCDB) and the Medical College of Virginia Neurocore. The objective was to determine which factor, raised ICP or hypotension, was most responsible for the reductions in CPP during the course of therapy. The amount of time CPP was less than 60 mm Hg during the first 72 hours of monitoring as a function of GCS and GOS was determined. The data obtained suggests that for a CPP threshold of 60 mm Hg, arterial pressure should not be allowed to fall below a mean of 80 mm Hg that corresponds to a systolic level of 114 mm Hg.

Rosner and Rosner (1994) looked at 158 patients (GCS $\leq$ 7) with traumatic brain injury. These patients were managed using volume expansion, CSF drainage via ventriculostomy, systemic vasopressors, and normocapnia to maintain a minimal CPP $\geq$ 70 mm Hg. This data led to the conclusion that CPP management yields favorable clinical results up to six-fold better than traditional techniques directed at ICP. When causes of mortality were examined, CPP management alone reduced death rates by 33-50%.

Conversely, a 1994 study by Shalmon et al. purposed to correlate simultaneous measurements of CPP and CBF in severely head-injured patients and to assess the ability of predicting CBF from CPP. Fifty-two consecutive head-injured patients were prospectively evaluated for this study. The data indicated that CPP and CBF are poorly correlated in head injured patients. The maintenance of MABP above 90 mm Hg and

preventing intracranial hypertension above 20 mm Hg does not insure adequate CBF in severely head injured patients.

The use of CPP management as the primary goal of therapy was thought to yield a lower mortality than with the more traditional ICP-based techniques. Rosner, Rosner, and Johnson (1995) studied 158 patients with GCS scores of 7 or lower. The patients were clinically managed to maintain CPP at 70 mm Hg or higher. The mortality results obtained were significantly better than other reported series across GCS. The researchers surmised that cerebral perfusion pressure management can serve as the primary goal in the treatment of TBI with substantially improved mortality and morbidity.

Cruz, Jaggi, and Hoffstad (1995) emphasized exploring the relationship of cerebral perfusion pressure and vascular resistance to cerebral blood flow, as well as to cerebral oxygen metabolism. These researchers felt that cerebral vascular resistance, more than cerebral perfusion pressure, determined important cerebral hemodynamics. To that end, 66 adults with severe acute brain trauma were prospectively evaluated. All patients had GCS of between 4 and 8, coma for at least 12 hours and intracranial pressure monitoring. Cerebral vascular resistance was calculated as equal to cerebral perfusion pressure divided by cerebral blood flow. Data analysis did not demonstrate any correlation between cerebral perfusion pressure and cerebral blood flow, between cerebral perfusion pressure and arterio-jugular oxygen content difference, and between cerebral perfusion pressure and cerebral metabolic rate of oxygen consumption, over a broad range of perfusion pressures ranging from 60 – 130 mm Hg. In contrast, a significant correlation was found between cerebral vascular resistance and cerebral blood flow, where higher values of cerebral vascular resistance were associated with lower blood flow levels, and

vice versa. Thus cerebral vascular resistance (not perfusion pressure) was more closely correlated with different patterns of cerebral blood flow and metabolism.

Giulioni and Urino (1996) used a mathematical model to study the possible effect of CPP changes on ICP. The model mimicked intracranial hemodynamics and CSF dynamics. Specifically, the study aimed to clarify how a sudden CPP decrease, caused by arterial hypotension, can affect CBV, ICP, and CBF. The model showed the relevant role of CPP changes elicited by acute arterial hypotension on intracranial dynamics. To achieve intracranial stability, CPP should be maintained above 80 to 90 mm Hg.

The goal of fluid resuscitation in a patient with TBI is restoration of CPP. Shackford (1997) used a porcine model to determine if a hypotonic saline solution or Ringers Lactate provided the best protection against secondary brain ischemia. The ideal fluid must be effective in restoring CBF and CPP with small volumes and have little effect on either ICP or cortical water content in the uninjured areas of the brain. Shackford concluded cerebral perfusion pressure was elevated and CBF increased after brain injury following infusion of hypertonic saline thus decreasing or limiting secondary brain injury.

Elevated CPP and decreased ICP is seen in a similar study by Simma, Burger, Falk, Sacher, and Fanconi (1998). Hypertonic saline verus Ringer's Lactate was studied in a randomized prospective study of 35 consecutive children with head injury (GCS $\leq$ 8). All children received continuous infusions of 3% saline to raise serum osmalarity to the level required to reduce intracranial pressure to < 20 mm Hg and < 15 mm Hg in patients with an open fontanel. Cerebral perfusion pressure was maintained at 60-70 mm Hg for older children and 50 mm Hg in infants. The children receiving hypertonic saline

showed decreased ICP and significantly improved CPP. An evaluation of outcome showed hypertonic saline to be efficacious and safe.

The Traumatic Coma Data Bank (TCDB) was evaluated by Chestnut (1997a) to delineate the influence of hypotensive episodes occurring during the early (time of injury through resuscitation) and the late (in intensive care units) posttraumatic periods. The analysis consisted of 493 patients who survived nine or more hours into their ICU course. It was determined that the occurrence of hypotension during either the early or the late period was statistically significant, and an independent predictor of outcome. Chestnut determined the estimated reduction in unfavorable outcome (death or vegetative state) for each of these occurrences independently and found that the elimination of early hypotension was predictive of a 15-fold reduction and elimination of late hypotension was predictive of an 11-fold reduction in relative risk.

Juul et al. (2000) examined the relationship and relative importance of ICP and CPP in severely head injured (GCS 4 to 8) patients. The study of 407 patients was prospective and involved more than 50 treatment centers in Europe, Australia, Canada, and Argentina. Evaluation of patient outcome using the GOS failed to demonstrate any significant benefit of a CPP greater than 60 mm Hg. Conversely an ICP greater than 20 mm Hg is associated with increased mortality rates compared to ICPs of less than 20 mm Hg. The aim of increasing CPP to levels greater than 70 – 80 mm Hg in patients with severe head injury, while not attempting to reduce the ICP if it is greater than 20 mm Hg, was found unacceptable.

The retrospective analysis of prospectively collected data on 114 head-injured patients between January 1997 and August 2000 evaluated optimal CPP. Mean arterial

pressure, ICP, CPP were continuously recorded and pressure reactivity index (PRx) was calculated. Pressure reactivity index is defined as the ability of vascular smooth muscle to respond to changes in transmural pressure, one of the key mechanisms responsible for autoregulation in CBF. The CPP-oriented treatment strategy was used with a target CPP of at least 70 mm Hg. Patient outcome was assessed using the GOS six months after discharge. The researchers determined that the correlation between PRx and outcome was significant, a higher PRx the less favorable the outcome. Pressure reactivity index reacted dynamically to changes in CPP with breakpoints for a decline in cerebrovascular pressure reactivity at approximately 60 and 85 mm Hg. It was concluded that patients with a mean CPP close to optimal were more likely to have a favorable outcome than those whose mean CPP was more different than optimal CPP, optimal CPP individually defined for each patient (Steiner et al., 2002).

In a prospective study, 124 adult head injured patients were studied during their stay in intensive care unit. A continuous computerized data collection system recording minute by minute values for physiological variables was initiated. Monitored variables included heart rate, systolic blood pressure, mean arterial pressure, intracranial pressure, oxygen saturation, and peripheral and core temperatures. Cerebral perfusion pressure was calculated on-line. Patient outcome was evaluated using the Glasgow Outcome Scale score. Data obtained confirmed hypotension and papillary response as major predictors of poor outcome. Therefore management of BP was found to be important in the treatment of patients after head injury. Cerebral perfusion insults were found to be more important than ICP insults. Hypotension and a low CPP were indicated as the best predictors of death. Hypotension was a significant predictor of poor outcome. Low CPP,

patient age, hypocarbia, and papillary response were good predictors of good/poor outcome. This study validates the premise that secondary insults play a significant role in determining patient outcome and occur commonly with current clinical management (Andrews et al., 2002)

The use of a CPP driven protocol was challenged by Oertel, Kelly, Lee, Glenn, Vespa, and Martin (2002). This study tested the hypothesis that increasing MAP decreases ICP after TBI. A total of 23 patients were continuously monitored for MAP, ICP and jugular-venous oxygen saturation. The data indicated that in the majority of cases ICP increased due to an increase in MAP. The authors suggested that the vasoconstrictory cascade is not functioning in these patients. The authors proposed that CPP therapy has an indication in patients with a high GCS and low jugular-venous oxygen saturation. They further concluded that in the majority of subjects ICP increased with increasing MAP and did not recommend CPP therapy as a general concept for treating increased ICP.

A restrospective analysis of critical thresholds for ICP, MAP, CPP, and fluid balance was associated with outcome after TBI. A total of 392 adult patients were studied. The control group consisted of 193 randomly assigned patients. The study group received standard treatment plus hypothermia for 48 hours. Intracranial pressure measurements of 20, 25, and 30 mm Hg; MAP of 70 and 80 mm Hg; CPP levels of 50, 60, and 70 mm Hg; and fluid balance levels in quartiles were examined for their effect on outcome as measured by the GOS six months after injury. Glasgow Coma Scale score at admission, age, MAP < 70 mm Hg, fluid balance lower than -594 mL, and ICP > 25 mm Hg, in that order, were the most powerful variables in determining outcome. The authors

recommended maintaining CPP of > 60 mm Hg. They also maintained that driving CPP levels > 80 mm Hg risks increasing the possibility of medical complications (Clifton, Miller, Choi, & Levin, 2002).

The driving pressure gradient for CPP is the difference between MAP and critical closing pressure (CPP – zero flow pressure). Therefore, determination of the difference between MAP and CCP should provide an appropriate monitoring of effective CPP. Based on this concept, the authors compared conventional measurements of CPP by MAP and ICP with effective CPP, measured by blood flow velocities of the middle cerebral artery. Seventy consecutive head trauma patients who received invasive ICP pressure monitoring were included in the study. It was determined that the indirect measurement of CPP (MAP – ICP) is an equally, but less invasive method, of measuring CPP (Thees et al., 2002).

In another study Thees et al. (2003) investigated whether CPP is a reliable parameter of sufficient cerebral perfusion and oxygenation. In an animal model of controlled ICP, the effect of decreasing CPP, due to increasing ICP, on cerebral tissue oxygenation was studied. Reduced CPP due to increased ICP led to a continuous decrease in cerebral oxygen saturation of hemoglobin and a decreased CPP in all animals. The experimental findings further suggested that CPP thresholds may be misleading. In some animals a CPP of 45 mm Hg was sufficient to provide adequate cerebral tissue oxygenation while in other animals a cerebral perfusion pressure of 42 mm Hg was associated with a severe reduction in cerebral blood flow. Furthermore, after severe brain injury CPP shows a poor correlation with CBF. The authors concluded that perhaps an

individual determination of CPP thresholds with respect to cerebral oxygenation and cerebral function is required for therapeutic management of intracranial hypertension.

Cerebral Autoregulation

Cerebral autoregulation is the ability to maintain a constant cerebral blood flow despite a changing cerebral perfusion pressure. Cerebral perfusion pressure is the stimulus to cerebral autoregulation, not the absolute systemic arterial pressure. Cerebral vasculature maintains cerebral blood flow relatively constant across a wide range of pressure gradients through vasodilation and vasoconstriction. Within the vascular compartment, CBF remains relatively constant despite changes in CPP over the 50- to 170-mm Hg range (Lang & Chestnut, 1994). Autoregulation of CPP is accomplished by changes in the cerebrovascular resistance achieved by alterations in the caliber e.g., constriction when the pressure rises and dilation when the pressure decreases, of the vessels. The consequence of constant flow and changing vessel size is a change in the CBV (Gray & Rosner, 1987). It is well established that CBF, over a wide range of arterial blood pressure, changes proportionally less than associated changes in pressures (Harper, 1966; Lassen, 1959).

Vasconstriction and vasodilatation occur by changes primarily in the cerebral arteries, primarily the arterioles. The varying diameter changes cerebral vascular resistance. A reduction in systemic pressure leads to a reduction in CCP. Cerebral vascular resistance is reduced in a manner that compensates for the reduction in pressure gradient and CBF is maintained (Giulioni & Ursino, 1996; Rosner, 1995).

Under normal conditions, most vasoconstriction occurrs by the time the CPP is 110-120 mmHg. At this level of CPP, cerebral vascular resistance is nearly maximal, with little vasoconstriction left to be attained. As CPP is reduced, the vasculature begins

to dilate but only slowly. A study by Kontos et al. (1978) on anesthetized cats studied the response of cerebral precapillary vessels to changes in arterial blood pressure. Vessel responses were found to be size dependent. Between mean arterial pressures of 110 and 160 mm Hg autoregulatory adjustments in caliber occurred only in vessels larger than 200 microns in diameter. Small arterioles, less than 100 microns in diameter, dilated only at pressures equal to or less than 90 mm Hg; below 70 mm Hg their dilation exceeded that of the larger vessels. When pressure rose to 170-200 mm Hg, small vessels dilated while the larger ones remained constricted. At very high pressures (greater than 200 mm Hg), forced dilation was frequently irreversible. Measurement of the pressure differences across various segments of the cerebral vasculartur showed that the larger surface cerebral vessels (over 200 microns) were primarily responsible for the adjustments in flow over most of the pressure range. Kontos et al. further determined in animal studies that the amount of vasodilatation that occured between 80-100 mm Hg CPP is on the order of 10% to 15% of the total range. The remaining 80% to 85% of vasodilatation occurs from a CPP of 70 to 80 mm Hg to 50 to 60 mm Hg. The researchers concluded that the rate of radius change is logarithmic and not linear within the autoregulatory range.

Below the lower limits of autoregulation of cerebral autoregulation, the vasculature is passive. Vessels, once maximally dilated, cannot dilate further and must collapse as the pressure gradient within them is further reduced. Once the CPP drops below the lower limits of autoregulation, vessels collapse and blood flow declines rapidly (Weinstein & Langfitt, 1967).

The active range of cerebral autoregulation is 50 to 160 mm Hg CPP. Within this range blood flow is relatively constant across a wide range of CPP, and the vasculature constricts as CPP is increased. Vasculature constriction causes a slight increase in blood flow but a decrease in blood volume. Therefore as CPP increases, vasculature constricts and ICP decreases. Thus within the active range of cerebral autoregulation, ICP is expected to vary indirectly with CPP (DeWitt et al., 1986; Kontos et al., 1978).

At the upper limits of cerebral autoregulation, the vasculature is maximally or nearly maximally constricted. Any changes in CPP near the upper limits or slightly above the upper limits of cerebral autoregulation results in a net increase in cerebral blood flow but little change in ICP. If the pressure increases dramatically above this level, the vasculature passively dilates, blood flow increases markedly, and ICP increases. While this phenomena is often seen in cerebral pathology such as cerebral encephalopathy it rarely, if ever, occurs after cerebral trauma (Kontos et al., 1978).

This series of events assumes that cerebral metabolic rate and metabolism are constant. This is not always the case as a reduction in CPP may be accompanied by reductions in level of consciousness and reductions in metabolism. These reductions will shift the blood flow curve to lower levels, similar to the Starling curve of the heart being shifted upward or downward by sympathetic influences (Rosner, 1995).

When there is a cerebral insult, such as occurs by mechanical trauma, the ability of the vasculature to respond is altered. Lewelt, Jenkins, and Miller (1980) tested the hypothesis that concussive brain injury impairs autoregulation of CBV by studying 24 cats subjected to hemorrhagic hypotension. The authors observed an increase in cerebral vascular resistance. The cerebral autoregulatory curve is depressed and shifted to the

right. This phenomenon of cerebral injury occured as a result of severe trauma although it was also observed in chronic hypertensive disease. The authors concluded the primary result is the need for supranormal levels of CPP to achieve and maintain normal levels of CBV. Thus, because cerebral vascular resistance was increased, the pressure gradient across the vasculature must be increased to achieve relatively normal CBV.

Cerebral injury alters the critical closing pressure of the cerebral vasculature. The cerebral critical closing pressure is the CPP pressure at which blood flow begins. This CPP is usually between 0 and 5 to 10 mm Hg. Cerebral injury increases the critical closing pressure of the cerebral vasculature and may raise it to 30 to 35 mm Hg or more. This increase further shifts the cerebral autoregulatory curve to the right (Nelson et al., 1992).

Bauer et al., (1999) developed a model using piglets to evaluate the effect of cerebral volume expansion on CPP. Mild CPP reduction (30% of baseline values) was completely compensated for by blood flow and oxygen update of the cerebrum. This finding correlated with the autoregulatory threshold in piglets. Additional CPP reduction, which surpassed the autoregulatory threshold, resulted in a decreased blood flow to the cerebrum with a reduction in cerebral oxygen delivery and cerebral oxygen uptake.

The use of catecholamine infusion is commonly used to increase MAP in order to preserve blood flow when increased ICP compromises CPP. This CPP protocol is based on the premise that a high CPP can help stabilize ICP and prevent the vasodilatory cascade when the CPP is close to the lower limits of the autoregulation plateau. A prospective study of 42 patients examined the influence of autoregulation on the amplitude and direction of changes in intracranial pressure in patients with severe head

injuries during the management of CPP. Continuous recordings of CBF velocity, ICP, and MAP during the start or change of continuous norepinephrine infusion concluded that cerebral perfusion pressure-oriented therapy can be a safe way to reduce ICP, whatever the status of autoregulation (Ter Minassian et al., 2002).

In a prospective study involving 122 patients with severe head trauma Hilatky et al. (2002) evaluated the extent and timing of impairment of cerebral pressure autoregulation. An autoregulatory index (ARI) was used as the independent variable. A normal ARI value is 5 ± 1.1. The changes in ARI value over time were examined against other physiological values. The authors concluded that inability of cerebral vessels to autoregulate CBF may play a role in the vulnerability of the injured brain to secondary insults. Further, the results indicated that this vulnerability increased beyond the first 24 hours postinjury.

Lang, Czosnyka, and Mehdorn (2003) studied the relationship between arterial blood pressure, ICP, directly measured brain tissue oxygenation, and middle cerebral artery blood flow veloscity in severely head injured adults. This prospective study involved a total of 14 patients to whom blood pressure was pharmacologically (norepinehrine) manipulated to achieve CPP ranging from 50 to 100 mm Hg. The authors demonstrated that cerebral autoregulation and tissue oxygen reactivity were mutually correlated. The better the cerebral autoregulation was preserved, the smaller were the brain tissue oxygenation changes when CPP changed. There was a close link between cerebral blood flow and oxygenation.

Poiseuille's Law

Poiseuille's Law relates flow through a tube directly to the pressure gradient across the tube, the radius of the tube to the fourth power, and inversely to the viscosity of the fluid.

$$Q = \frac{\pi \Delta P r^4}{8 \eta l}$$

For the above equation Q, is the rate of blood flow, ΔP is the pressure difference between the ends of the vessel, r is the radius of the vessel, l is length of the vessel, and η is viscosity of the blood. Since the rate of blood flow is directly proportional to the fourth power of the radius of the vessel, this demonstrates that the diameter of a blood vessel (which is equal to twice the radius) plays the greatest role of all factors in determining the rate of blood flow through a vessel (Guyton & Hall, 2000).

Adjusting the equation for cerebral perfusion pressure, we derive the following equation.

$$\text{Flow} = \frac{\pi (CPP) r^4}{8 \eta l}$$

It can be seen that only the vascular radius is altered during cerebral autoregulation. Under conditions of high CPP, the radius of the vessels is maximally small with relatively little additional vasoconstriction available. Under these conditions, the radius remains constant. Therefore, when CPP is high, any additional increase in perfusion pressure must increase blood flow. Any decrease in viscosity must also increase blood flow.

When CPP is 70 to 80, the vasculature is believed to be in the midrange of its diameter. The cerebral vascular is, therefore, capable of vasoconstriction and

vasodilation. Changes in CPP around this normal range result in very little change in CBF. There is, however, significant change in the radius of the vasculature. The change in vascular radius size results in change in CBV, which manifest in ICP changes. A smaller radius translates into a reduction in CBV and a reduction in ICP. Below the lower limits of autoregulation, any increase in CPP is associated with not only an increase in blood flow, but also expansion of the vasculature, tending to increase ICP (Rosner, 1995).

Traumatic brain injury increases the resistance of the cerebral vasculature. This increased resistance is through alterations in the vascular endothelium. When the injury is severe, the level of CPP required to move into the active range of the cerebral vasculature is higher and probably narrower. The CPP must be higher and the range in which ICP varies directly with CPP increases (El-Adawy & Rosner, 1988).

Cerebral Compliance

Brain compliance is the ability of the cranial contents to accommodate an extra amount of volume without an increase in ICP. This additional volume may be in the form of a hematoma, cerebral spinal fluid, or increased cerebral blood volume. Changes in blood pressure or CPP have a major influence upon the intracranial blood vessels, particularly the arterioles when autoregulation is intact. Outside the range of autoregulation, brain compliance or pressure-volume index (PVI) become inversely related to changes in CPP (Bouma, Muizelaar, Bandoh, & Marmarou, 1992). Muizelaar, Marmarou, and Ward (1989) obtained measurements of ICP and PVI in comatose patients with severe head injuries ranging in age from 4 to 50 years. The authors determined that within the range of cerebral autoregulation PVI is not dependent on CPP changes. When cerebral autoregulation is not intact, the higher pressure in the arterial

system is transmitted to the arterioles, capillaries, and veins. This leads to increased transmural pressure transfer into brain parenchyma. This effect is magnified by passive dilation of these vessels. This makes the walls thinner, thereby, decreasing the barrier to pressure transfer.

Bishop, Bishop, and Rosner (1994) tested the hypothesis that the volume tolerance of the brain as measured by PVI would decrease as the head was elevated from zero to 45 degrees. This hypothesis was based on the concept of a linear relationship of PVI and CPP above the lower limits of autoregulation. Pressure volume index was measured in 15 adult neurosurgical intensive care patients at head elevations of zero, 15, 30, and 45 degrees. Pressure volume index decreased in all patients with increasing head elevation. Intracranial pressure and CPP both decreased with increasing head elevation. The elevated head position decreased ICP by increasing venous drainage with a secondary increase in CBV. This study suggested that CBV may actually be increased with head elevation. A flat position was determined to be superior to a raised head position in the management of head injured patients. Improved outcome in patients treated in the flat position suggested that ICP was less important than CPP in the brain injured patient.

Mannitol and Fluid Balance

Poiseuille effects are extremely important when understanding the effect of mannitol and other osmotic agents. Administration of mannitol increases cerebral blood flow when CPP is relatively high, and it also lowers ICP and helps maintain CBF when CPP is in the midrange. Mannitol does not withdraw fluid from the edematous brain. It does not act through cerebral dehydration. Kaufman and Cordoso (1992) studied cerebral edema in cats and observed the administration of mannitol (0.33 gm/kg q4h) did not reduce brain water.

Mannitol potentates blood flow and oxygen delivery through Poiseuille effects rather than through cerebral dehydration in the adequately hydrated patient. Mannitol exhibits its effect by decreasing the viscosity of blood. The viscosity of blood increases as the hematocrit increases. The viscosity of blood at a normal hematocrit of 40 is about three. This means that three times as much pressure is required to force blood through vessels as would be necessary for water (Guyton & Hall, 2000). Research on patients undergoing surgery for intracranial aneurysms by Burke, Quest, Shien, and Cerri (1981) studied the effect of mannitol on cerebral edema. Mannitol reduced erythrocyte rigidity and decreased whole-blood viscosity, thereby, enhancing tissue perfusion in the cerebral circulation.

Muizelaar, Lutz, and Becker (1984) described changes in ICP and CBF in a group of severely head-injured patients with intact and defective autoregulation after mannitol administration. For patients with intact autoregulation the decrease in resistance to flow from decreased blood viscosity and increased resistance from vasoconstriction balanced so that CBF remained the same. The authors termed this blood viscosity autoregulation of CBF, analogous to pressure autoregulation. When autoregulation was not intact, there was no vasoconstriction, CBF increased with decreased viscosity.

The effect of fluid resuscitation in pediatric head injury was evaluated in a prospective, clinical study using Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) compared with hypertonic saline (sodium 268 mmol/L, 598 mOsm/L). A total of 35 consecutive children were studied. The findings showed that treatment of severe head injury with hypertonic saline is superior to treatment with lactated Ringer's solution. An increase in serum sodium concentrations significantly correlated with lower ICP and

higher CPP. Children treated with hypertonic saline required fewer interventions, had fewer complications, and stayed a shorter time in the ICU (Simma et al., 1998).

A similar study by Peterson, Khanna, Fisher, and Marshall (2000) showed that administration of hypertonic saline solution to children with closed head injury appeared to be a promising therapy for control of cerebral edema. A retrospective chart review of 68 children with closed head injury used 3% hypertonic saline to increase serum sodium to levels necessary to reduce ICP $\leq$ 20 mm Hg.

In a follow-up, Khanna et al. (2000) conducted a prospective study to evaluate the effect of prolonged infusion of 3% hypertonic saline (514 mEq/L) and sustained hypernatremia on refractory intracranial hypertension in pediatric traumatic brain injury patients. Ten patients with increased intracranial pressure resistant to conventional therapy (head elevation at 30 degrees, normothermia, sedation, paralysis and analgesia, osmolar therapy with mannitol, loop diuretic, external ventricular drainage in five patients) showed decreases in ICP and increases in CPP with increases in serum sodium.

Hypercapnia

It is generally well accepted that hyperventilation reduces ICP by reducing cerebral blood volume through constriction of the pial and cerebral arterioles. As CO2 readily crosses the blood brain barrier, a decreased PaCO2 is immediately reflected in a reduced PCO2 in the interstitial brain fluid. This then leads to a reduction in hydrogen ion (H+) concentration in the vicinity of the cerebral blood vessels. Because the H+ ion is one of the most potent relaxants of smooth muscles of cerebral arterioles, a reduction in its concentration will lead to rapid vasoconstriction. Vasoconstriction is not dependent on low CO2 and can be maintained only if the increased perivascular pH can be maintained.

Studies have shown that pH in blood and cerebrospinal fluid returns to normal during prolonged hyperventilation, despite sustained hypocapnia (Christensen, 1974).

Muizelaar and van der Poel (1989) studied New Zealand white rabbits to examine whether the return to normal pH during prolonged hyperventilation would be accompanied by vasorelaxation. Pial arteriolar vasoconstriction was maintained with prolonged hyperventilation. They concluded that hyperventilation is effective in reducing cerebral blood volume for less than 24 hours and that it should be used only during actual ICP elevations.

Cruz demonstrated improved outcome associated with TBI management based on optimized hyperventilation. A 1995 study using hyperventilation as a primary therapy showed improved outcomes secondary to improved glucose uptake. A 1998 study design compared hyperventilation therapy to CPP therapy, in a group of TBI patients. The hyperventilation therapy group showed a 12% mortality. For the patients treated with the CPP therapy the mortality was 32%.

In an editorial to the 1998 Cruz study, Chestnut (1998) presented the study as another "salvo in the vociferous and occasionally vitriolic interchange between two preeminent groups in head injury management: the CPP camp and the optimized hyperventilation camp" (p.210). Chestnut calls for the elimination of the continuing polarization of management strategies. He believes the future of head injury management lies in targeting therapy to the underlying brain pathophysiology based on injury type and evolution over time. Furthe,r Chestnut sees that only by considering therapeutic modalities as complimentary will there be a successful transition to a targeted approach.

Physiology of Pediatric Cerebral Circulation and Metabolism

As discussed, cerebral vasculature is regulated by metabolism (metabolic autoregulation), CPP (pressure autoregulation), blood viscosity (viscosity autoregulation), and PaCO2 (CO2 reactivity). Cerebrovascular reactivity and regulation of CBF are disturbed after severe traumatic brain injury (Bourma & Muizelaar, 1992). These principles also form the template for the management of pediatric TBI.

In 1957, Kennedy and Sokoloff studied cerebral circulation in children using the nitrous oxide method first described by Kety and Schmidt in 1948. Modifications to the procedure included a reduction in the amount of blood drawn and achieving active cooperation with the child. The results were some of the first to systematically quantify the physiological differences between children and adults. The comparison of the results found notable differences in pulse rate, blood pressure, hemoglobin concentration, blood gas concentrations, and blood pH. The mean cerebral blood flow in children, 106 milliliters per 100 grams per minute, was found to be considerably greater than the mean value, 60 milliliters per 100 grams per minute, observed in the young adults. Also significantly higher in children, was the cerebral oxygen consumption, the mean value being 5.2 milliliters per 100 grams per minute as compared to 4.2 milliliters per 100 grams per minute in the adults. The cerebral vascular resistance in the children was 0.8 mm Hg per 100 gram per minute, which is lower than the 1.4 mm Hg per 100 gram per minute observed in adults. No difference in the cerebral respiratory quotient between the two groups was observed.

Pediatric Traumatic Brain Injury

Pediatric head trauma is common and is the leading cause of death and disability in childhood. Children are more likely to suffer increased intracranial pressure and diffuse

cerebral injury than adults, who tend to develop focal intracranial lesions (Graneto & Soglin, 1993). Multiple studies have put forth the proposal that there is a relationship of patients' age to mortality from head injury. This relationship applies to all levels of severity.

A series of 8,814 head-injured patients admitted to 41 hospitals was prospectively studied. Of the total patients studied 1,906 (21.6%) were 14 years of age or less. Except for patients experiencing profound hypotension or subdural hematoma, the pediatric patients exhibited a significantly lower mortality rate compared to the adults (Luerssen et al., 1988)

The Glasgow Coma Score is the accepted method of evaluating patients suffering from traumatic brain injury. Lieh-Lai et al. (1992) observed a significant portion of children with severe TBI and relatively low GCS scores who seemed to have a better functional outcome than expected. They conducted a study to determine the validity of the GCS score alone in predicting the outcome of severe TBI in children. Seventy-nine children were studied retrospectively. The researchers concluded that a low GCS score is not a sole predictor of poor outcome in children with TBI.

Pigula, Wald, Shackford, and Vane (1993) hypothesized that hypertension and/or hypoxia occurring in children suffering from traumatic head injury (GCS < 8) would have significantly higher mortality than normotensive children with normal blood gases. Over a five year period, 58 children were prospectively evaluated on the basis of systolic blood pressure and arterial blood gases. Children in the normotensive and normal blood gas group had a significantly improved survival. These results were validated by a retrospective review of 509 children from the National Pediatric Trauma Registry.

A study by Mendelow et al. (1994) identified children hospitalized for traumatic brain injury during a six-year period (1988-1993). All children had a GCS of $\leq$ 8 and required ICP monitoring. The GOS was used to determine outcome at six months. Twenty-nine children were studied of which eight children died. In the survivors four were severely disabled; five moderately disabled; and 12 had good recoveries. There were no vegetative survivors. For this study, the minimum CPP associated with better outcomes was found to lie between 41 and 57 mm Hg. Further analysis showed that improved outcome for children was an average minimum CPP greater than 50 mm Hg. The authors proposed that this lower minimum CPP value reflects fundamental differences in cerebral physiology between adults and children.

As previously stated, adult brain injury studies recommend maintaining CPP above 70 mm Hg. Downard et al. (2000) retrospectively evaluated CPP and outcome in 118 brain-injured children. No patient with mean CPP less than 40 mm Hg survived. Among patients with mean CPP in deciles of 40-49, 50-59, 60-69, or 70 mm Hg, no significant differences in GOS distribution existed. Thus low mean CPP was lethal. In children with survivable brain injury (mean > 40 mm Hg), CPP did not stratify patients for risk of adverse outcomes. The authors interpreted these data to suggest that there may be a threshold for cerebral hypoperfusion, above which a CPP must be maintained with no marginal benefit from additional CPP elevation. It was further suggested that it may be more efficacious to concentrate on minimizing the variation of the CPP around the clinically targeted level rather than elevating the level.

Intracranial pressure and cerebral perfusion pressure were monitored to establish which one is more predictive of outcome and to examine whether there are significant

threshold levels. Data were obtained from 291 severely head injured patient (207 adults and 84 children). A CPP of 55 mm Hg and ICP of 35 mm Hg appeared to be the best predictors in adults. For the children, the levels were a CPP of 43 to 45 mmHg and an ICP of 35 mm Hg. The CCP thresholds of 45 mmHg for children and 55 mmHg for adults show that children have lower thresholds. This correlates with blood pressure, which is normally lower in children than adults (Chambers, Treadwell, & Mendelow, 2001).

A retrospective chart review of 320 consecutive pediatric patients with TBI from 1992 through 1996 was undertaken to evaluate the relationship of patient care variables to survival and functional outcomes. The review concluded that the ability to maintain a CPP of $\geq$ 50 mm Hg was the single most important predictor of TBI survival. Thus, these authors concluded monitoring and optimizing CPP is critical to the management of pediatric patients (Hackbarth et al., 2002).

Forty-five acutely comatose children who sustained severe, non-missile brain trauma were prospectively evaluated and treated to a protocol to maintain normalized values for ICP, CPP, and arteriojugular oxyhemoglobin saturation difference (CEO2). Six-month clinical outcomes were assessed in relation to physiological abnormalities observed during the acute phase of injury. At six months, 37 children were in the favorable outcome (GOS) category, whereas six children exhibited unfavorable outcomes. Two children died, and six exhibited severe disability. No children were in a prolonged vegetative state. The children with unfavorable clinical outcome were significantly related to more pronounced intracranial hypertension and more profound

concomitant decreases in CEO2 (Cruz, Nakayama, Imamura, Rosenfeld, de Souza, & Giorgetti, 2002).

Diffuse Brain Swelling

One area felt to be different in the pediatric patient is the higher frequency of diffuse brain swelling after trauma. This is believed to be due primarily to increased cerebral blood volume and has been attributed to partial or complete disruption of cerebral autoregulatory mechanisms, allowing vasodilation (Aldrich et al., 1992; Bruce et al., 1978; Bruce et al., 1981). Aldrich et al. collected data prospectively on 753 patients, 111 children, and 642 adults. Diffuse brain swelling occurred twice as often in children as with adults. Children diagnosed with diffuse brain swelling had a mortality rate three times as great as children without diffuse brain swelling. Adults with and without diffuse brain swelling had similar mortality rates. This data support the concept that children with TBI respond differently.

In 1994, Lang, Teasdale, MacPherson, and Lawrence reported a study involving a series of 118 patients with traumatic brain swelling. This retrospective review compared clinical findings in children with adults to determine the occurrence of neurological deterioration and outcome. Adults were more likely to have evidence of severe initial injury than children. The level of consciousness was similar in both groups at admission; although, adults showed secondary deterioration more often, and thus, had a poor outcome twice as often. The authors concluded that a child's brain may more readily respond to injury by developing diffuse swelling. A child has a proportionately greater intracranial CSF volume available for displacement. Therefore, the swelling appears to be benign in children in more than 75% of the cases; whereas, in adults its appearance signifies a poor outcome in two-thirds of the cases.

During a 15 year period (1968-1982), 434 non missile head injured patients were retrospectively studied by necropsy (Teasdale, Graham, & Lawrence, 1989). The researchers sought to discover the incidence of brain swelling and to relate its occurrence to features of primary damage and to other secondary complications such as hypoxia and raised intracranial pressure. In 40% of the cases dying within the first week of injury death occurred without evidence of brain swelling. Raised intracranial pressure and hypoxia were common findings. Teasdale et al. concluded that brain swelling per se was rarely the primary mechanism of brain damage in the fatally head injured patients. They did, however, observe a small number of fatal cases, one or two per year in a population of 2.7 million in whom brain swelling appeared to be the major intracranial lesions. Most of these cases were children.

Evaluation of the broad range of developmental, psychological, demographic, and social variables, as well as medical variables, on the neurobehavioral status of children who were more than a year post traumatic head injury was undertaken. Two variables, CPP and premorbid learning problem, were statistically significant predictors of outcome (Woodward et al., 1999).

Hyperemia

Hyperemia and vasodilation are a ubiquitous response of the pediatric brain to trauma (Piper, 1994). Cerebral hyperemia is commonly related to high ICP, caused mainly by increased CBV (Muizelaar et al., 1989). Bruce et al. (1979), in a study of 85 children suffering from severe head trauma (GCS 5-8), found that when hyperemia occurred in isolation, with minimal parenchymal damage, control of hyperemia with maintenance of a normal ICP should prevent death with a permanent recovery. When hyperemia congestion occurred, hyperventilation seemed to control hyperemia and ICP

for the first 24-48 hours. After this time frame multifocal brain edema seemed to occur and secondary increases in ICP were found. If these ICP increases were controlled, useful recovery occurred in 80% of the children. Bruce et al. suggested that cerebrovascular dilatation was a primary response of the pediatric brain to trauma and the rapid, early clinical deterioration seen is associated with acute brain swelling caused by increased cerebral blood flow, increased cerebral blood volume, and decreased incracranial compliance.

Muizelaar et al. (1989) in a sample of 32 children studied the relationship between hyperemia, CBF, ICP, and PVI in severe head injury. These researchers were unable to establish a correlation between hyperemia and high ICP or low PVI in head injured children. They concluded that real hyperemia is uncommon. Secondly, they found no linear relationship between CBF and CBV.

A retrospective review of children admitted to a Level 1 pediatric trauma center with severe traumatic brain injury sought to determine variables in the acute care period associated with survival (White et al., 2001). Children (0 – 17 years) admitted from 1991 to 1995 with nonpenetrating traumatic brain injury and an admission GCS of ≤ 8 were included in the study. The first 72 hours of hospitalization were analyzed in detail for 136 patients. The primary end point was survival. The data suggested that patients with a higher six hour GCS score were more likely to survive. Adjusting for severity of injury, survival was associated with maximum systolic blood pressure ≥ 135, suggesting that supranormal blood pressures are associated with improved outcome. Thus, actual elevation of blood pressures may be required in children suffering from traumatic brain injury.

Sharples, Matthews, and Eyre (1995) participated in a two- part study to understand the pathophysiology of pediatric head trauma. They sought to test the hypothesis that children with TBI differ from adults with TBI with increased cerebral blood flow (cerebral hyperemia). Cerebral blood flow, arteriojugular venous oxygen difference, and cerebral metabolic rate for oxygen were performed on 21 children with severe head trauma (GCS $\leq$ 8, mean age 8). The data from this study do not support the proposal that children have raised cerebral blood flow after severe injury. The study determined there is no fundamental difference between adults and children in the pathophysiological response of cerebral blood flow to severe head injury.

The objective of the second phase of the study by Sharples, Stuart, Matthews, Aynsley-Green, and Eyre (1995) was to explore whether cerebrovascular resistance is responsive to normal physiological mechanisms in children with severe head injuries, and to determine if the overall level of cerebrovascular resistance is abnormally low in these patients. Data indicate cerebrovascular resistance values were normal or raised in most cases and there was significant correlation between cerebral perfusion pressure and cerebrovascular resistance, suggesting preservation of autoregulation. They concluded that normal cerebrovascular reactivity was often preserved in children with severe head injury. Further, despite evidence that cerebral hyperemia is more common in the youngest children, there was no correlation between cerbrovascular resistance and age. No data were found to support the premise that the pathophysiology of traumatic encephalopathy in children was essentially different from that in adults.

A study undertaken to determine the role of acute CBF alterations in the pathophysiology of clinical head injury placed emphasis on the occurrence of hyperemia,

its time course and relationship to ICP, and its response to hyperventilation (Obrist et al., 1984). Seventy-five adult patients with closed head injury (mean GCS score 6.2) were studied within 96 hours of trauma. Fifty-five percent of patients developed acute hyperemia while 45% had subnormal flows. There was a correlation between hyperemia and the occurrence of intracranial hypertension. Their findings suggested that cerebral circulatory factors exerted an important influence on ICP, particularly in the presence or absence of acute hyperemia.

Hyperventilation

The use of hyperventilation is widely debated for use in the care of patients with TBI. Cerebral metabolic and vascular responses to head injury in children are less predictable than previously claimed and have raised concerns about the safety of routine hyperventilation. A prospective study assessed the effect of hyperventilation on regional cerebral blood flow in children. Twenty-three children with TBI were treated by altering minute ventilation to PaCO2 levels of >35, 25 – 35, and <25 toor. Measurements taken showed a clear relationship between the frequency of cerebral ischemia and hypocarbia suggesting that hyperventilation should be used with caution in children with TBI (Skippen et al., 1997).

Summary

The review of literature for both the adult and pediatric population suffering TBI clearly shows the lack of definite protocols for treating these patients. Past efforts to develop guidelines for the management of patients with TBI relied on author's expert opinion and practice experience, and thus, had the element of subjectivity. There is a lack of class I evidence available for many current management practices. A task force developed guidelines for the management of severe head injury using a meticulous

process relying on scientific evidence rather than expert opinion (Bullock et al., 1996; Chestnut, 1997b; Prough & Lang, 1997). The Brain Trauma Foundation (1996) was only able to issue three standards based on class I evidence (prospective randomized controlled trials) and only eight guidelines based on class II evidence (data collected prospectively with retrospective analyses based on clearly reliable data).

The recommendations issued by The Brain Trauma Foundation (1996) had a positive influence in establishing consistent treatment therapies for severe traumatic brain injury. Marion and Spiegel (2000) conducted a survey to determine management of head-injured patients in 1997 and to identify differences compared with a survey done in 1991. A forty percent response rate, from a total of 3,156 neurosurgeons contacted, showed a significant increase in the proportions of neurosurgeons who felt these patients should have ICP monitoring (28% vs. 83%), and a decrease in the proportion who used prophylactic hyperventilation therapy (83% vs. 36%) and steroid therapy (64% vs. 19%). Ninety-seven percent of respondents felt that the CPP should be maintained at >70 mm Hg, and 44% felt patients with severe head trauma should be treated at Level I trauma centers.

There are three most commonly used treatment approaches. One is the traditional approach, which has been to emphasize early surgical treatment of intracranial mass lesions, meticulous critical care treatment to avoid secondary injury to the brain, and to minimize intracranial hypertension (including the use of hyperventilation) (Robertson, 2001).

The second protocol is the CPP management, based on the vasodilatory cascade. According to this hypothesis, a reduction in CPP- either a decrease in arterial blood

pressure, an increase in ICP or both- stimulates the cerebral vessels to dilate in an attempt to maintain CBF. This is the normal pressure autoregulatory response to a decrease in CPP. Because the increase in CBV that accompanies the vasodilation further reduces CPP by increasing ICP, this sets up the cycle that leads to ever reducing CPP. An increase in arterial blood pressure has been observed to break this cycle and reduce ICP. Thus management is focused on maintaining CPP (Robertson, 2001).

The third approach is the Lund therapy, which emphasizes reduction in microvascular pressure to minimize edema formation in the brain. The goals of this approach are to preserve normal colloid osmotic pressure, to reduce capillary hydrostatic pressures by reducing systemic blood pressures, and to reduce CBV by vasoconstricting precapillary resistance vessels (Grande, Asgeirsson, & Norstrom, 2002; Robertson, 2001).

CHAPTER 3
METHODS

Research Design

This study was conducted in a retrospective fashion. Medical records of children diagnosed with traumatic brain injury that met study criteria were reviewed and data were collected. Data were collected on a Data Collection Form (see appendix A).

Research Setting

This was a single center study at a large medical center in Northeast Florida. This facility is an urban tertiary teaching hospital with a Level 1 adult and pediatric trauma center with immediately available neurosurgical services and is affiliated with a State University.

Sample Size

A statistically determined sample size of 43 subjects provided the desired sensitivity for a level of significance of $p < 0.05$ and a power of 0.95. Medical records of subjects who met study criteria were identified until the sample size was reached.

Sample Criteria

The inclusion criteria were as follows:

1. Children less than 15 years of age at the time of injury
2. Diagnosis of non-penetrating traumatic brain injury
3. Traumatic brain injury as a result of non-penetrating blunt head trauma.
4. Glasgow Coma Scale score equal to or less than 8 upon arrival in the Pediatric Intensive Care Unit.

5. Children with intracranial pressure monitor placement within 24 hours of traumatic brain injury
6. Children of both sexes
7. All social, economic, ethnic groupings

The exclusion criteria were as follows:

1. Infants and toddlers with unfused fontanels, i.e. those less than 18 months of age.
2. Children whose cerebral compromise was not the result of traumatic brain injury
3. Children whose cerebral compromise was the result of penetrating traumatic brain injury
4. Children with secondary medical diagnosis of encephalitis, Reyes syndrome, near drowning, diabetes, cerebral palsy, or other diagnosis that affect cerebral performance.
5. Children who did not undergo intracranial pressure monitor placement within 24 hours of the traumatic brain injury or if the invasive neurological procedure was performed at a referring hospital.
6. Other subjects in the opinion of the investigator who were not appropriate for the study.

Measures

Vital signs (BP, P, T), ICP, and CPP measurements were recorded at least hourly on the intensive care unit flow sheet. These were abstracted for the first 7 days after admission or until the patient died.

Pediatric Blood Pressure

The major determinant of a normal blood pressure in children was maturation, not chronological age. Increasing body size as a factor apart from age was needed to judge the relationship of a child's blood pressure from that of the normal population. It was therefore important that baseline blood pressure for each child be individually determined. Blood pressure monitoring occurred by noninvasive cuff pressure and by invasive arterial cannulation. Noninvasive and invasive blood pressure were measured

using Component Monitoring System (CMS M1176A, Phillips Medical Systems, Healthcare Solutions Group, Andover, Massachusetts, U.S.A.).

Mean Arterial Pressure (MAP)

Mean arterial blood pressure was determined by the cardiac output (CO), systemic vascular resistance (SVR), and central venous pressure (CVP) which was based upon the relationship between flow, pressure and resistance: MAP – (CO – SVR) + CVP. Because CVP is usually at or near 0 mm Hg, this relationship is often simplified to: MAP = CO – SVR. In practice, however, MAP is not determined by knowing the CO and the SVR, but rather by direct or indirect measurements of arterial pressure. At normal resting heart rates, MAP can be approximated by the following equation: $MAP = P_{diastolic} + 1/3\ (P_{systolic} – P_{diastolic})$ where P is equal to pressure. For example, if systolic pressure is 120 mmHg and diastolic pressure is 80 mmHg, then the mean arterial pressure will be approximately 93 mmHg. At high heart rates, however, MAP is more closely approximated by the arithmetic average of systolic and diastolic pressure because of the change in shape of the arterial pulse pressure (it becomes narrower) (Klabunde, 2001). Mean arterial pressure was determined by continuous monitoring of blood pressure using Component Monitoring System (CMS M1176A, Phillips Medical Systems, Healthcare Solutions Group, Andover, Massachusetts, U.S.A.).

Intracranial Pressure

Intracranial pressure (ICP) is a function of the relative space occupied by the brain, the cerebrospinal fluid, and the cerebral blood volume. An increase in the volume of one must be accompanied by a reduction in one or more of the other volumes or there will be an increase in the intracranial pressure (Shackford, 1997). Intracranial pressure monitoring was obtained using the Camino fiber optic catheter-tip transducer (Camino

Laboratories, San Diego, California, U.S.A.). Placement of the Camino monitoring device was accomplished in the operating room or at the bedside under sterile conditions by a qualified neurosurgeon. The monitoring device was placed in the subdural space with the transducer mounted on the side of the head at the level of the foramen of Monro.

Cerebral Perfusion Pressure

An intimate interdependence exists between the intracranial pressure and systemic arterial blood pressure (SABP). The link between ICP and SABP is cerebral perfusion pressure. Cerebral perfusion pressure is calculated as the arithmetic difference of the mean arterial pressure and the mean intracranial pressure with both referenced to the level of the external auditory meatus and with the patient in the flat position (Ghajar & Hariri, 1992). Cerebral perfusion pressure was calculated manually from MAP obtained through Component Monitoring Systems and ICP obtained through the use of the Camino intracranial transducer (MAP – ICP = CCP).

Heart Rate (Pulse)

Heart rate (pulse) was documented from readings obtained from Component Monitoring System (CMS M1176A, Phillips Medical Systems, Healthcare Group, Andover, Massachusetts, U.S.A.).

Temperature

Body temperature was documented from readings obtained from IVAC thermometers (CNA Medical, Rockwall, Texas, U.S.A.).

Data Collection Procedure

The Medical Center for data collection is a Level 1 pediatric trauma center. As such the Division of Pediatric Surgery and Trauma participates in the National Pediatric Trauma Registry (NPTR). The NPTR accepts data on injured children. On March 1,

2002, because of a lack of funding, the NPTR stopped accepting data. However, the pediatric trauma program continued to use the NPTR data collection form to track patients and the data were entered into a Division of Pediatric Surgery and Trauma computerized data base. It was from this data base that subjects meeting research criteria were identified. The beginning date was September 30, 2002 working backward in time.

Data collection were transcribed from the patient intensive care flow sheet located in closed medical record. All data collected were part of the normal and routine care of children with traumatic brain injury. Data were collected by the principal investigator, the co-investigators, or by surgical research assistants. Data collected included post injury day, time clinical values obtained, heart rate (pulse), temperature, cuff blood pressure, arterial line blood pressure, mean arterial pressure, intracranial pressure, and cerebral perfusion pressure. Demographic information, which included sex, age, and ethnicity, GCS and DELTA scores were included in data collection.

Data Collection

All subjects had cerebral pressure devices placed with measurements taken. Subjects had either an intracranial pressure monitor or an external ventricular drain (EVD). Several subjects had both. For those subjects with both ICP and EVD monitoring, the ICP value was used for data evaluation. Additionally several subjects had blood pressure recorded by cuff, arterial-line or both. For subjects with both cuff and arterial-line blood pressures, the arterial line blood pressure was used for data evaluation.

Data collected for each subject, systolic blood pressure, pulse, temperature, mean arterial pressure, intracranial pressure, and cerebral perfusion pressure, were averaged to a single value for each 24 day. Thus BP1 represents the average systolic blood pressure for a single subject for a 24 hour period. Data were entered for each subject for each day

the intracranial monitor remained in place. Thus subject data ranged from two days up to 15 days. For purposes of data analysis, a maximum seven days data were evaluated. This decision was based two factors, one that maximum cerebral edema peaked at 2-4 days and less than half of the subjects had intracranial pressure monitors in place for longer than 7 days. It was felt this decrease in subject data would present biased results.

Procedure for the Protection of Human Subjects

All patients who met criteria were included for data gathering. As no clinical interventions were proposed and data collection was by medical record review, a request was made and accepted by the Medical Center Institutional Review Board (IRB) to wave the informed consent requirement. Patient confidentially was maintained at all times. Subjects were identified numerically within the context of discussions within the Division of Pediatric Surgery and Trauma, Department of Surgery, University of Florida and the context of a doctoral dissertation.

Data Analysis

Descriptive analysis was used to clarify the structure of the demographic data, obtain a simple descriptive summary, and possibly lead to a more sophisticated analysis. Analysis of variance (ANOVA) was used to determine the relationship between cerebral perfusion pressure and outcome in children diagnosed with traumatic brain injury. Regression analysis was used to determine inverse linear relationship between cerebral perfusion pressure and intracranial pressure.

CHAPTER 4
ANALYSIS AND RESULTS

The purpose of this retrospective study was to evaluate CPP on outcome in children experiencing severe blunt head trauma. Subjects were identified through the pediatric trauma registry. Measurements included systolic blood pressure, heart rate, temperature, mean arterial pressure, intracranial pressure, and cerebral perfusion pressure. Outcome was measured using The DELTA disability and injury score.

Subject Demographics

Fifty-nine pediatric trauma patients were identified via the pediatric trauma registry who met study inclusion criteria. The timeframe for the injuries spanned November 1995 through September 2002. Of the 59 subjects, one was omitted because the medical record could not be produced by the Medical Center Medical Records Department. Three additional subjects were eliminated after a review of their medical record indicated they died within twenty-four hours of injury and hospitalization. A cerebral pressure catheter was not placed prior to the child's death or the monitor was in place for less than six hours. It was apparent from the record review these children suffered injuries so severe that medical intervention was not a factor in their outcome.

Subject Age, Sex and Ethnicity

The mean age of the subjects was 8.4 years (SD = 4.2), with a range from 1.5 years to 15.0 years (see figure 4.1). Four subjects were Hispanic (7.3%), thirteen were black (23.7%) and thirty-eight were white (69%). Thirty-five of the subjects were male (63.6%) and twenty female (36.4%). The mean DELTA score was -4.7 (SD = 3.1) with

a minimum score of -9 for those children who survived (see figure 4.2). The mean GCS score was 5.5 (SD = 2.4) with a minimum value of 3 and a maximum value of 13 (see figure 4.3).

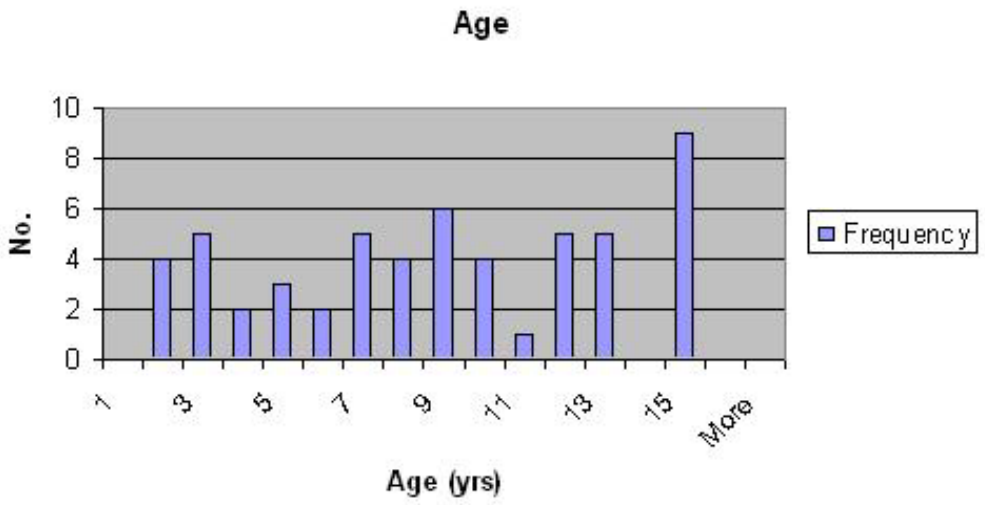

Figure 4-1. Age Distribution

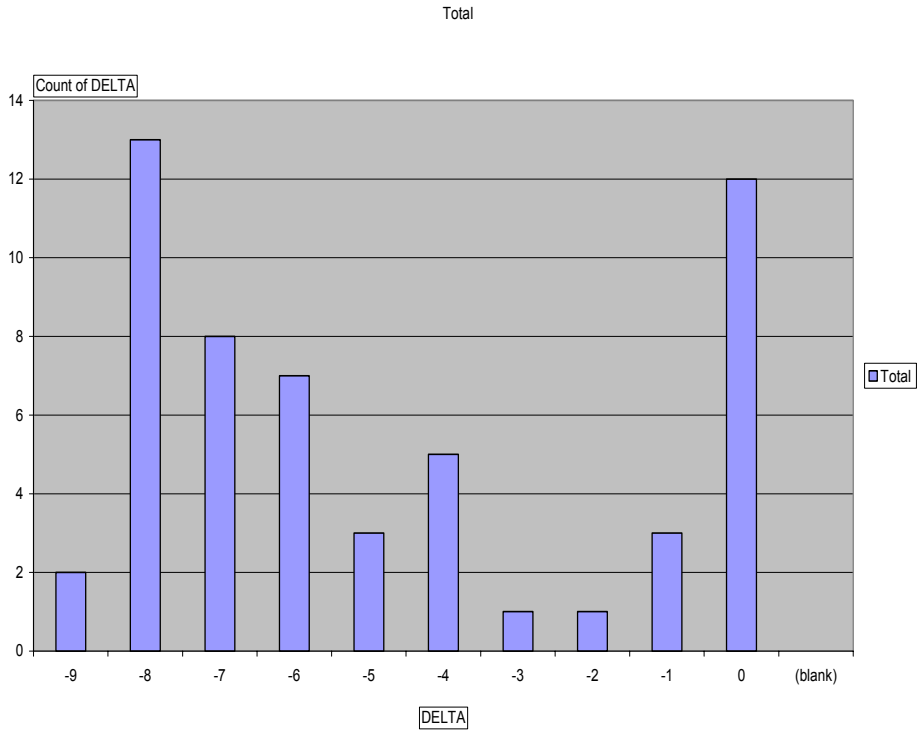

Figure 4-2. Distribution of DELTA severity and outcome score

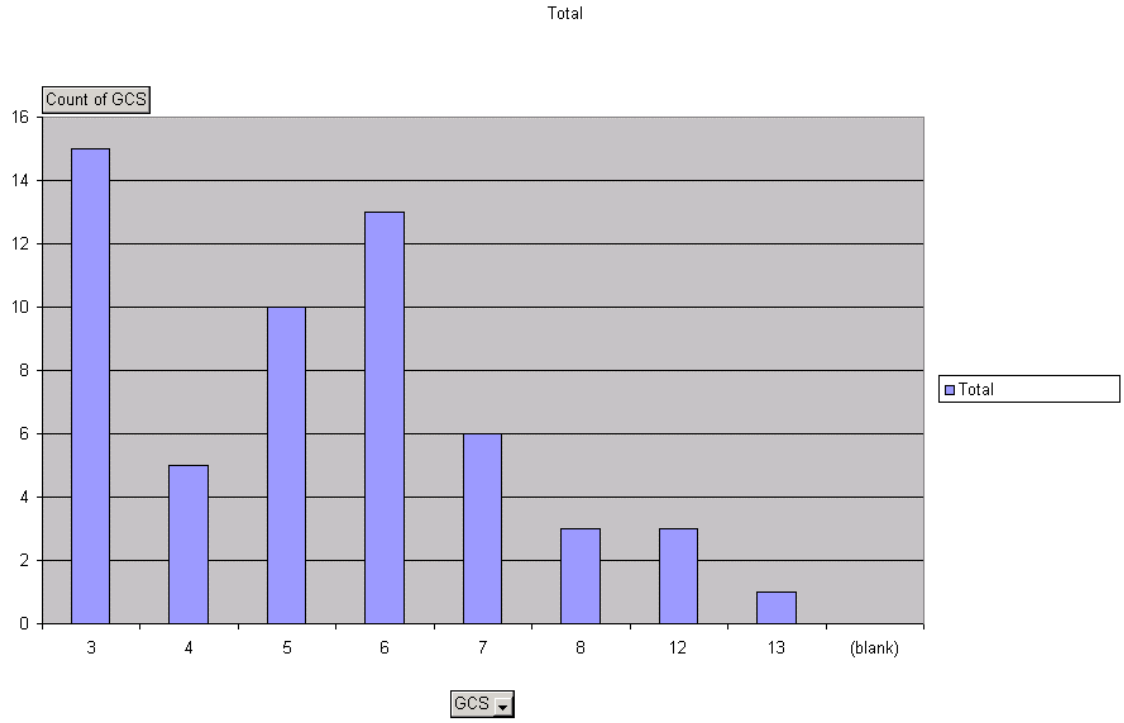

Figure 4-3. Distribution of Admission GCS Score

Mechanism of Injury

The majority of children (76.3%,42) suffered injuries from a motor vehicle (see figure 4.4). Twenty children (36.6%) were passengers in an automobile involved in a collision, either with another car or an object such as a tree or post. Twenty-two (40%) children were hit by motor vehicles, either as pedestrians or while riding bicycles, skateboards, all terrain vehicles (ATV), and dirt bikes. Three (5.3%) children were hit by objects, such as a baseball or brick, two (3.6%) children were victims of child abuse, and six (10.9%) children suffered falls. Two children were classified in the other category (3.6%). One was injured by falling off a horse and one a near hanging. It is apparent from this small sample that motor vehicles continue to be the greatest cause of severe head trauma in children.

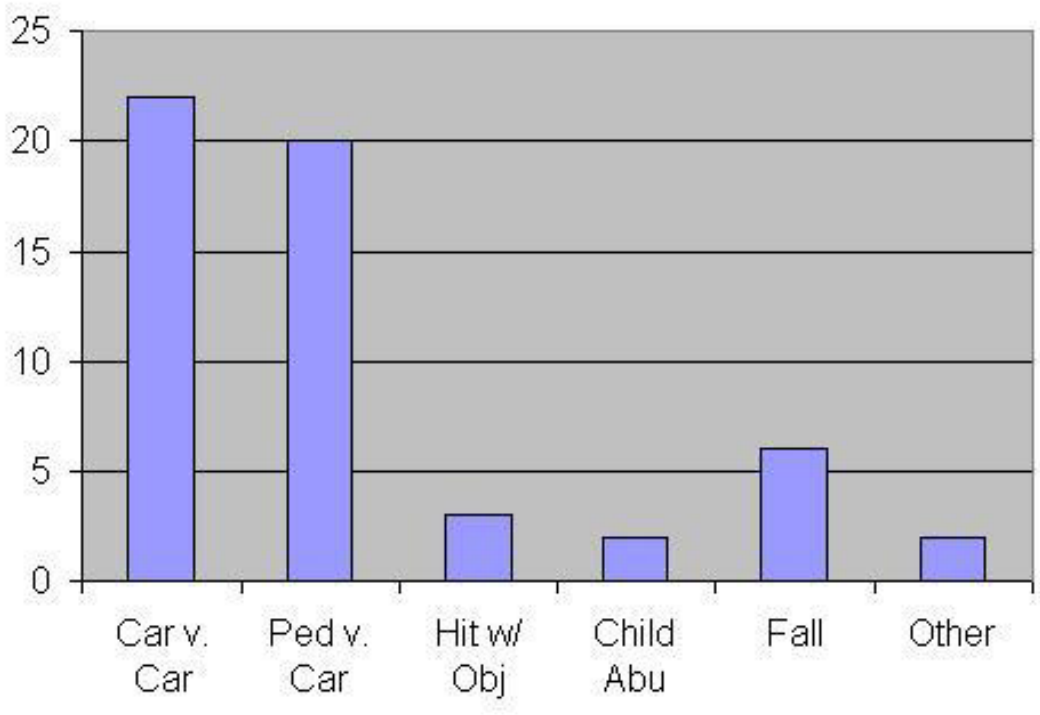

Figure 4-4. Mechanism of Injury

Research Findings

Data were analyzed using SAS (SAS Institute Inc., Cary, North Carolina). Descriptive statistics were used to obtain the summary measures for the data. The t-test procedure, analysis of frequency, multiple regression, logistic regression, and Pearson's correlation analysis were used to address the research questions.

Research Questions

Question 1. Children with non-penetrating traumatic brain injury with a cerebral perfusion pressure averaging 50 mm Hg or higher will demonstrate better outcome, as measured by the DELTA disability and injury score (DS), than subjects with a cerebral perfusion pressure averaging less than 50 mm Hg.

Data were analyzed by separating subjects into two groups, those with CPP at or above 50 mm Hg and those with CPP below 50 mm Hg. The purpose was to evaluate

outcome, as measured by DELTA scores, of the two groups. The mean DELTA score of the group with a CPP at or below 50 mm Hg was -4.1 (SD = 3.84). The mean DELTA score of the group with a CPP above 50 mm Hg was -4.8 (SD = 3.12). The mean age for the group with a CPP at or below 50 mm Hg was 8.0 years (SD = 5.37). The mean age for the group with a CPP above 70 mm Hg was 8.5 (SD = 4.15). Using stepwise regression the data were evaluated for 7 days. On day of injury, blood pressure ($p = 0.0163$), temperature ($p = 0.00011$), MAP ($p = 0.0338$), ICP ($p = 0.0256$), and CPP ($p = 0.0147$) were significant in predicting CPP. On post injury day (PID) 1, MAP ($p = 0.0238$), ICP ($p = 0.0470$), and CPP ($p = 0.0487$) were significant predictors of outcome. On PID 2, blood pressure ($p = 0.0009$) and ICP were significant ($p = 0.0029$). Post injury day 3 ($p = 0.0149$) and PID 4 ($p = 0.0003$) showed only temperature as significant for outcome. For PID 5, temperature was no longer significant, but MAP ($p = 0.0334$), ICP ($p = 0.0154$), and CPP ($p = 0.0183$) again became significant. By PID 6, only blood pressure was significant ($p = 0.0028$).

Question 2. Children with non-penetrating traumatic brain injury will tolerate a lower average cerebral perfusion pressure than adults with non-penetrating traumatic brain injury as measured by DS.

The subjects were again separated into two groups, those with CPP at or above 70 mm Hg and those with CPP less than 70 mm Hg. The mean DELTA for the group with a CPP at or below 70 mm Hg was -4.1 (SD = 3.34). The mean DELTA for the group with a CPP above 70 mm Hg was -5.52 (SD = 2.90). The mean age for children at or below 70 mm Hg was 7.7 years (SD = 4.44). The mean age for children above 70 mm Hg was 9.3 years (SD = 3.97). Using t-test to measure outcome, BP ($p = 0.0001$), pulse ($p =$

0.0292), MAP (p = 0.0001), ICP (p = 0.0064), and CPP (p = 0.0001) were significant on the day of injury. For PID 1, BP (p = 0.0001), pulse (p = 0.0083), MAP (p = 0.0001) and CPP (p = 0.0001), were significant. For PID 2, BP (p = 0.0001), MAP (p = 0.0001), CPP (p = 0.0001) and temperature (p = 0.0003) were significant. On PID 3, BP (p = 0.0088), MAP (p = 0.0001), ICP (p = 0.0230), CPP (p = 0.001,) and temperature (p = 0.0342) continued to be significant. These data indicated that those children with a CPP above 70 mm Hg had a greater window of opportunity for therapeutic interventions which may have positively impacted outcome. While these data were significant, one cannot make the conclusion that children tolerate lower CPP pressure than adults. To answer this question a similar retrospective data review of adults with nonpenetrating traumatic brain injury needs to be conducted.

Question 3. There is an inverse relationship between intracranial pressure and cerebral perfusion pressure in children with traumatic brain injury.

Using Pearson's correlation analysis it was determined that there was an inverse relationship between ICP and CPP (R = 0.45, p = 0.0007).

Additional Findings

A second statistical model was utilized with the following parameters. Subjects were separated into two groups, children who died (DELTA = 0) and children who survived (DELTA = -1 to -12). All previous variables, with the addition of GCS score, were compared for these two groups for 4 days. These same variables were then compared to only those children who survived. The goal was to determine which variables impact survival and outcome.

Linear logistic regression was used to compare children who died with the children who survived. The day of injury shows temperature ($p = 0.0152$) as the only significant variable. The odds ratio of temperature for children who survived was 11.666 times higher than children who died. For PID 1, temperature was again significant ($p = 0.0167$) with an odds ratio of 6.133. On PID 2, temperature ($p = 0.0398$) and CPP ($p = 0.0356$) were significant variables in determining survival with the odds ratio of 6.470 and 1.125 respectively. For PID 3, only temperature was significant ($p = 0.0220$) with an odds ratio of 6.696. The mean temperature of children who died was 37.1 degrees Celsius with a minimum temperature of 34.6 degrees Celsius and a maximum temperature of 38.9 degrees Celsius. The mean temperature of the children who survived was 38.1 degrees Celsius with a minimum temperature of 37.0 degrees Celsius and a maximum temperature of 39.7 degrees Celsius.

Children who died were then excluded from the model. The survivors were separated into two groups, those with long term sequelae or disability (DELTA $\leq$-5) and those with injuries that will resolve (DELTA $\geq$- 4). On the day of injury age ($p = 0.0287$), CPP ($p = 0.0596$), and GCS ($p = 0.0246$) were significant in determining outcome with the odds ratio of 1.295, 1.060, and 0.619 respectively. On PID 1, ICP was significant ($p = 0.0124$) with the odds ratio of ICP for those with improved outcome 1.411 higher than those with poor outcome. Post injury day 2 showed age ($p = 0.0400$) and ICP ($p = 0.0370$) significant with an odds ratio of 2.088 and 1.891. By PID 3, no variables were significant with relationship to outcome.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

Most serious childhood injuries are the result of motor vehicle accidents. With the increased use of skateboards, in-line skates, all terrain vehicles, dirt bikes, etc. children are at increasing risk for accidents resulting in serious injuries and permanent disability. While parent teaching and diligent supervision continue to be the best way to decrease childhood accidents, they will continue to occur. It thus becomes imperative for health care providers, specializing in the care of injured children, to seek optimum clinical management.

The purpose of this retrospective design study was to evaluate the variables of systolic blood pressure, pulse, temperature, mean arterial pressure, intracranial pressure, cerebral perfusion pressure along with age, Glasgow Coma Scale score, ethnicity, and sex on outcome, as measured by DELTA disability and severity score, on children with nonpenetrating traumatic brain injury. Fifty-five children who met criteria were evaluated by medical record chart review.

Discussion of Findings

Cerebral Perfusion Pressure

Subjects were separated into two groups for data evaluation. One group consisted of subjects with a CPP at or below 50 mm Hg and a second group with CPP above 50 mm Hg. The mean DELTA score for the group with CPP at or below 50 mm Hg was -4.1 with the mean DELTA score for the group above 50 mm Hg -4.8. This indicated that children with a CPP at or below 50 mm Hg had a slightly better outcome than

children with CPP above 50 mm Hg. This value difference in the two mean DELTA outcome scores is very small and functionally insignificant. This data analysis indicates the outcome value for both groups is essentially equal indicating a CPP of 50 mm Hg may not be the benchmark value for predicting improved outcome as measured by DELTA score.

When subjects were divided by a CPP at or below 70 mm Hg and a group above 70 mm Hg the results were similar. The mean DELTA score for the group at or below a CPP of 70 mm Hg was -4.1. The mean DELTA score for the group above a CPP of 70 mm Hg was -5.5. This result indicates children at a higher CPP exhibited worse outcome as measured by DELTA score. While the difference in the two DELTA outcome scores was minimal it is still significant that the children with a higher CPP value showed a worse outcome.

Evaluation of these results indicate concern regarding the value of the DELTA score with both the 50 mm Hg and the 70 mm Hg models. Children who did not survive their injuries were assigned a DELTA score of zero. It is probable with this statistical model that children who died contaminated the DELTA score. Zero is a higher value than any of the negative DELTA score values assigned to the children who survived. Based on the statistical model used, children who died were included in the summary data. These children were likely assigned to the good outcome range.

Both models showed variables affecting cerebral health, BP, MAP, ICP, and CPP significant towards outcome on PID 0 and PID 1. The values of BP, pulse, and MAP were significant for the first three days. In addition, intracranial pressure was significant the first day. These data results continue to show the importance of early intervention

and appropriate resuscitation of the pediatric trauma patient immediately post injury. The window of opportunity continues to remain within the first 48 hours post injury.

Temperature was significant on PID 0. Temperature was also found to be significant by PID 3 and PID 4. This may represent physiological response to open wounds. Since the majority of subjects were involved in motor vehicle accidents it is speculated they suffered multiple injuries. The presence of injury to the abdomen or extremities and the impact of surgical intervention is the most likely explanation for the significance of temperature. By PID 5 temperature droped off as a significant variable which coincides with effective antibiotic therapy.

Survival versus Nonsurvival

Subjects were separated into two groups, those subjects who survived their injuries and those subjects who died as the result of their injuries. Evaluation of these data indicated age and GCS score to be significant. The mean age for children who died was 7.1 years and for children who survived was 8.3 years. Review of the literature regarding childhood accidents indicates younger children at higher risk, especially regarding pedestrian versus motor vehicle and as passengers in motor vehicles. As this cohort of subjects suffered the majority of their traumatic brain injury from motor vehicles the data are consistent with existing literature.

These same groups showed a mean GCS score of 6.1 for children who died and a mean GCS score of 5.3 for children who survived. The result was unexpected since the lower the GCS score at admission suggested a more seriously injured patient. The data indicate that children with lower GCS scores have a higher probability of survival than those children with higher GCS scores. The GCS score recorded in this retrospective

chart review was the admission GCS score. Brain injured patients often present to Trauma Centers with compromised neurological values but show significant improvement within hours of admission. This may have been a factor in these data results. For future research, it might be advantageous to record GCS score values at eight hours and 24 hours post injury. Glasgow Coma Scale score values recorded at these times might represent more accurately the extent of the brain injury and neurological deficit.

The data analysis results for this model indicated the single most important factor for survival is temperature. The mean temperature of children who died was 37.1 degrees Celsius. The mean temperature of children who survived was 38.1 degrees Celsius. This result was unexpected. There is much in the traumatic brain injury literature, some of it covered in the literature review for this study, promoting the benefits of lower core body temperature in patients suffering from TBI (Tokutomi et al., 2003). Conversely, a study by Andrew et al. (2002) evaluating multiple variables did not show temperature as significant in determining outcome, either for mortality or morbidity.

The importance of temperature in determining outcome is a significant finding from this study. The data indicate improved survival for subjects with a higher body temperature. This is consistent with the normal and usual care of hospitalized children. The exception to this demand for warmth has been pediatric traumatic brain injured patients. They have often been artificially maintained at lower than normal body temperatures. The rationale for lowering core body temperature was to decrease the demand for oxygen by the injured brain. The data obtained in this study bring this therapy into question and provides an avenue for further research.

Good Outcome versus Poor Outcome

The subjects from the previously identified group of children who survived their TBI were separated into two groups. One group was classified as the good outcome group. This group was defined by a DELTA score of -1 to -4. The second group was classified as the poor outcome group. This group was defined by a DELTA score of -5 to -12. Evaluation of data for these two groups indicates age, admission GCS score, and CPP on the day of injury as significant prognosticators of outcome.

The mean age of the poor outcome group of children was 9.6 years. The mean admission GCS score was 4.9. Children with good outcome had a mean age of 6.2 years and a mean admission GCS score of 6.6. It is not surprising that age and GCS score have an inverse relationship as older children engage in more risk taking behavior and suffer more severe injuries. The mean CPP on PID 0 of the good outcome group was 72 mm Hg while the mean CPP on PID 0 for the poor outcome group was 62.93 mm Hg. This 10 mm Hg variance in mean values of PID 0 CPP is significant. The mean value of 72 mm HG for the good outcome subjects is consistent with the research findings conducted primarily on adults. The findings of this study indicate that children and adults have the same threshold of CPP on the day of injury relative to improved long term outcome. It is thereby concluded from the data obtained in this study that children do not tolerate a lower CPP value than adults with comparable injuries.

The results of this study differ with the results obtained in a similar retrospective study conducted by Clifton et al. (2002). The Clifton et al. study concluded that GCS at admission, age, MAP, fluid balance, and ICP were the most powerful variables in

determining outcome. While both studies concluded admission GCS score and age to be significant indicators of outcome, the Clifton et al. study did not list CPP as a significant outcome and this current study only lists CPP as a physiological variable with significance towards outcome. What is particularly interesting regarding the Clifton et al. study is omission of CPP form the list of significant physiological variables. Both MAP and ICP are listed as physiological variables of significance. Since CPP is a function of both MAP and ICP, it is surprising that CPP did not present as significant. Along this same thought is the absence of MAP and ICP from the current study. With CPP a significant physiological variable, one might expect MAP and ICP to also be significant. These results involving MAP, ICP, and CPP might indicate there is less interdependence among the three physiological variables than previously thought.

Compounding Factors

The majority of subjects were injured secondary to motor vehicle accidents. There was initial concern during evaluation of data that the variables and outcome were impacted by other injuries to the subjects. The concern was the possibility of hemodynamic compromise which may influence data. However a careful review of the raw data show that all subjects remained hemodynamically stable. Fluid resuscitation in the field, the trauma center, and pediatric intensive care unit was sufficient to maintain vital signs, with the exception of temperature, within normal physiological range specific to the age of each subject.

Conclusions

Clear implications for clinical practice cannot be drawn from this study. Continuing research to clarify data obtained from this study is necessary. Data obtained from this research study show that temperature plays a greater role in the outcome of

children with traumatic brain injury then previously thought. While the need to keep patients warm is widely known and universally practiced by health care providers, the dramatic impact of temperature seen in this study group of pediatric head trauma patients is unexpected. This is in contrast to some published protocols which seek to maintain patients suffering from TBI at a lower than normal core body temperature to decrease oxygen demands. These conflicting therapies need further evaluation.

The finding that the first 48 hours post TBI is critical to outcome is consistent with current practice. The framework of trauma care is based on the value of immediate interventions to stabilize patients. Continued diligence is critical to maintain physiological variables within acceptable range. What continues to remain unclear is the definition of acceptable range.

Limitations of the Study

Study Design Limitations

While accepted clinical treatment for traumatic brain injury was used for all subjects there was no standardized treatment protocol used in this retrospective study. Specific management of children with intracranial injuries varied slightly according to the preference of the treating physician. Numerous modalities, including sedation, administration of mannitol, hyperventilation, vasopressors, ventriculosotomy, and decompressive craniectomy were used with varied frequencies.

A second concern was the time frame of the subject injuries. The fifty-five children were injured in the time period from November 1995 to September 2002. During this eight year study period it is possible and likely probable that treatment protocols changed. It is difficult to assess whether outcome was the result of the variables studied or subtle changes in treatment.

Retrospective studies always suffer limitations with biases such as the following: varying degrees of doctor and nurse engagement, and varying quality of general intensive care at different times. Further, the presence of pre-existing medical conditions or co-morbidities for each subject was unknown. These factors may have played a significant role in the clinical outcome of the subjects.

Statistical Analysis Limitations

A major conceptual limitation of regression techniques is they can only ascertain relationships. Regression analysis can never address underlying causal mechanisms. Multiple regression is most effective as a statistical model with 10 to 20 times as many observations (subjects) as one has variables. Using this formula, the number of subjects should be 60-120. The number of actual subjects was 55. Therefore, the small sample size is a limitation of the study.

Strengths of the Study

A strength of the study includes location, a Level I pediatric trauma center in a large metropolitan area. A further strength of the study was the reliability associated with the assignment of the DELTA outcome score. The pediatric trauma program is coordinated by a masters prepared clinical nurse specialist who is concurrently an associate clinical professor in the College of Nursing at the associated University. All DELTA scores were assigned by this single individual, guaranteeing consistency of subject outcome evaluation.

Recommendations for Further Research

There has been a lack of research on a standardized treatment protocol for children suffering traumatic head injury. The majority of research is conducted on adult patients with the results of these studies extrapolated for care of children.

There is need for a prospective study which clearly evaluates the optimal range of blood pressure, temperature, intracranial pressure, and cerebral perfusion pressure that will provide for optimal outcome by decreasing the occurrence of secondary cerebral injury. The involvement of nursing staff in the development and implementation of treatment protocols is critical. As observed from this retrospective study, the window of opportunity for interventions which may affect outcome is small and nursing participation is essential.

The relationship of specific therapeutic interventions that link physiological variables such as BP, temperature, MAP, ICP, and CPP to survival and functional outcome is yet to be clarified. Further investigation is warranted and may require a multiple center study to recruit a large enough patient population for a meaningful analysis of the problem.

Children, as with adults, are at increased risk for infection from the invasive devices that are placed to monitor essential physiological parameters. Recently a study by Schmidt et al. (2003) has proposed mathematical models to estimate noninvasively ICP and cerebral autoregulation. Once these mathematical models are validated for use with adults there must be similar studies on children and infants. This highly fragile group will benefit tremendously from increased ability to closely monitor critical physiological variables with limited stress to the child.

Implications for Clinical Practice

The major implications for nursing practice is continued appreciation for the value of diligent clinical assessment and the recording of accurate vital signs, especially within the first 48 hours after injury. The prevention of secondary ischemic injury to the brain is one of the key components in determining outcome. As seen with data from this study

the window of opportunity to positively impact outcome in pediatric head trauma patients is narrow, with each fluctuation in physiological value critical. Aggressive observation and assessment followed by appropriate intervention to maintain blood pressure, pulse, temperature, intracranial pressure, and cerebral perfusion pressure within normal range are imperative.

Of surprise in the data analysis was the importance of temperature in determining outcome in the subjects evaluated. Keeping patients warm is a function of nursing care. Nurses can assure that patients are kept warm. Nursing must take responsibility for maintaining normal body temperatures for the pediatric patients in their care. Further, it is imperative that nursing impress upon ancillary services that participate in care the importance of keeping children warm. Nursing is the gatekeeper and must continue to exercise its authority to promote optimal care for patients.

APPENDIX A
DATA COLLECTION TOOL

PatNum	Date	PID	Time	BP-A-line	BP-cuff	Pulse	Temp	MAP	EVD-ICP	EVD-CCP	Camino-ICP	CaminoCPP
			0700									
			0800									
			0900									
			1000									
			1100									
			1200									
			1300									
			1400									
			1500									
			1600									
			1700									
			1800									
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			2000									
			2100									
			2200									
			2300									
			2400									
			0100									
			0200									
			0300									
			0400									
			0500									
			0600									

Demographic Information:

Age –

Sex –

Ethnicity –

Delta Score -

APPENDIX B
GLASGOW COMA SCALE (GCS)

Best motor response			Best verbal response			Eye Opening	
Obeying	5		Oriented	5		Spontaneous	4
Localizing	4		Confused	4		To speech	3
Flexing	3		Inappropriate	3		To pain	2
Extending	2		Incomprehensible	2		None	1
None	1		None	1			

APPENDIX C
MODIFIED GLASGOW COMA SCORE FOR INFANTS

Best motor response			Best verbal response			Eye Opening	
Spontaneous	6		Coos, babbles	5		Spontaneous	4
movement							
Withdraws to	5		Irritable cry	4		To speech	3
touch							
Withdraws to	4		Cries to pain	3		To pain	2
pain							
Abnormal	3		Moans to pain	2		No Response	1
flexion							
Abnormal	2		No response	1			
extension							
No response	1						

APPENDIX D
DELTA DISABILITY AND INJURY SCORE

Function, Central Nervous System (CNS)

-1 Attention deficit, nightmares, fixation and distraction despite otherwise normal function

-2 Reading, speaking learning deficit

-3 Objective CNS deficit: obtundation, paresis, seizure, etc.

Function, Musculoskeletal (M/S)

-1 Temporary deficit – cast, bandage, etc.

-2 Long-term defect – loss of muscle group, scarring dysfunction, limb, etc.

-3 Permanent disability – limb loss, wheelchair, walker, dependent, etc.

Lifestyle, Medication

-1 Finite, short-term drug dose – antibiotics, etc.

-2 Lifelong as needed (PRN) medication – antibiotics for aspienia, seizure, medications, etc.

-3 Lifelong, ongoing medication

Lifestyle Care

-1 Temporary finite help from cast, dressing, etc.

-2 Special education, care

-3 Custodial care

APPENDIX E
GLASGOW OUTCOME SCALE

Death	1
Persistent vegetative state	2
Severe disability	3
Self-care	4
Independent	5

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BIOGRAPHICAL SKETCH

Lesley Morgan received a Bachelor of Arts degree in biology from Randolph-Macon Woman's College in 1975 and a Bachelor of Science in Nursing from Vanderbilt University in 1977. Her professional experience began as a pediatric nurse on a medical-surgical floor.

She earned a Master of Science in Nursing from the University of Florida in 1983 and a Master of Business Administration from the University of Miami in 1986. She then followed an administrative track in nursing first as the Nurse Manager of a School-Age/Adolescent Unit and then an Infant/Toddler Unit at Jackson Memorial Medical Center, Miami, Florida. This was followed by promotion to Director of Pediatric Nursing, Shands Jacksonville Medical Center (formerly University Medical Center), Jacksonville, Florida.

At this time she joined the United States Naval Reserve, as a Nurse Corps Officer with the rank of Lieutenant junior grade. In the course of her navy career she became proficient in perioperative nursing and subsequently became Director of Perioperative Services at Shands Jacksonville Medical Center.

She has continued active participation in the Navy Reserve currently holding the rank of Commander. Her military honors include the Navy Achievement Medal with star for second award and the Navy Commendation Medal with star for second award. She is an active member of the Naval Reserve Association (NRA) and the Association for Military Surgeons of the United States (AMSUS).

Her nursing awards include induction into the Sigma Theta Tau International Society for Nurses. Lesley holds membership in the Association of periOperating Room Nurses and holds certification as an Operating Room Nurse.