

Impact of secondary insults on the outcome of paediatric traumatic brain injury

**A Retrospective cross sectional study at the Red Cross
Children's Hospital, Cape Town**

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Chief Investigator.....
Signature **Date**

Supervisor.....
Signature **Date**

Abstract

Introduction:

Secondary insults in severe traumatic brain injury (TBI) may worsen outcome; however, these are poorly characterized in children. For example, despite the known association between intracranial pressure (ICP) and poor outcome, there are few large paediatric series on the subject, definitions vary, functional outcome is often not assessed, and the best measures to assess ICP for statistical analysis are unknown. We aimed to document the frequency of secondary insults, and the association of various ICP measures, with outcome in a large cohort of paediatric patients with severe TBI.

Materials and Methods:

A retrospective analysis of 5-year prospectively collected data was examined for the frequency of hypoxia, hypotension, raised ICP, and low cerebral perfusion pressure (CPP). ICP parameters included initial ICP, mean ICP in the first 24 hours, mean ICP overall, peak ICP, mean ICP over 20 mmHg, and episodes of ICP over 20 mmHg. Hypotension was defined by age- and height-adjusted mean arterial pressure ranges, and hypoxia was defined as arterial partial pressure of oxygen (PaO₂) less than 8kPa or pulse oximetry less than 90%. We examined for univariate and multivariate associations with mortality and the Extended Paediatric Glasgow Outcome Score.

Results:

The study comprised 141 patients with a median age of 6 years. Mean follow up was 2 yrs (Range 0.5-6yrs). Overall mortality was 9.9% and 22.8% of patients had an unfavorable outcome on the dichotomized EGOS. Frequencies of pre-hospital hypotension and hypoxia were 19.1% and 26.2% respectively; in-hospital frequencies of the same were 9.1% and 22.7% respectively. In-hospital hypotension was associated with mortality (p=0.01) and functional outcome (p=0.04). All of the ICP and CPP measures were associated with outcome in univariate analysis, in multivariate analysis, mean ICP overall and mean ICP in first 24hrs were independently associated with mortality and functional outcome; CPP <40 and highest ICP were independently associated with mortality.

Conclusions:

Secondary insults in paediatric severe TBI are common and represent potentially treatable factors. Hypotension appears to be of greater influence than hypoxia. Mean ICP, mean ICP in the first 24 hours, and peak ICP were the most useful parameters of ICP to examine in association with outcome.

Dedication

To my ailing Father, Watson.

"I am, because you were".

Thank you for being my dad.

To my mum, Josephine.

Words fail me.

You are an anchor that never waivers.

To my wife, Patricia.

I cherish you.

Thank you for listening and most of all, for the laughter.

To the Almighty God, thank you.

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To my wife and friend Patricia, thank you for your steadfast support, and for being my biased umpire in the game of life.

The almighty God, thank you.

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List of Abbreviations

| | |
|-----------------|---------------------------------|
| ATP | Adenosine Triphosphate |
| ATPase | Adenosine Triphosphatase |
| BBB | Blood Brain Barrier |
| CBF | Cerebral Blood Flow |
| CNS | Central Nervous System |
| CO ₂ | Carbon Dioxide |
| CPP | Cerebral Perfusion Pressure |
| CSF | Cerebrospinal fluid |
| CT | Computerise Tomography |
| DAI | Diffuse Axonal Injury |
| DRC | Departmental Research Committee |
| EDH | Extradural Hematoma |
| GCS | Glasgow Coma Score |
| EGOS | Extended Glasgow Outcome Score |
| ICH | Intracranial Hypertension |
| ICP | Intracranial Pressure |
| K | Potassium |
| LSES | Low Social Economic Status |
| MAP | Mean Arterial Pressure |
| MRI | Magnetic Resonance Imaging |
| MVA | Motor Vehicle Accident |
| Na | Sodium |
| PIM | Paediatric Index of Mortality |
| PTS | Paediatric Trauma score |
| PVI | Pressure Volume Index |
| RXH | Red Cross Children's Hospital |
| SDH | Subdural Hematoma |
| TBI | Traumatic Brain Injury |
| UCT | University of Cape Town |
| USD | United States Dollar |

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1. Introduction

The central nervous system (CNS) is a highly specialised information processing and adaptation organ system with high-energy demands and a negligible capacity for nutrient storage, vulnerable to mechanical and chemical stresses. Mechanisms have evolved to protect the brain from mechanical stresses (cranial vault/CSF cushion), chemical stresses (blood- brain barrier), and to provide constant nutrient supply (rich blood supply) and maintain suitable homeostasis (constant interstitial fluid and CSF turnover). However, these are clearly insufficient to protect the brain against all forms of injury, and so brain trauma is a major cause of mortality and neurological morbidity in the developed and developing worlds. Much of what we know about head trauma, though, has emerged from adult studies; few studies have been conducted in childhood populations.

Given the anatomical, physiological, developmental, epidemiological, and pathological differences between adults and children, paediatric-specific data are urgently needed. Secondary insults in TBI are important because they represent avoidable or treatable factors that may influence outcome. Little data on the subject exists for the paediatric community. In 1990, Sharples et al reported that potentially avoidable factors contributed to as much as 32% of avoidable deaths¹. Ten years later, Chambers et al examined the cause and incidence of secondary insults in adults and children and found differences between the 2 groups, suggesting for both that vigilance for potential secondary insults is critical². To date though, there have been no large cohort paediatric studies that have examined these secondary insults in detail, in particular in association with functional outcome. The following sections review important aspects of pathology and pathophysiology of TBI, clinical data that have been published to guide decision-making, and an overview of the clinical imperatives in managing TBI. This is followed by an analysis of data at our hospital, with an emphasis on selected potential secondary insults.

2 Literature review

2.1 Epidemiology of paediatric traumatic brain injury

Trauma is the leading cause of death in children and young adults, causing between 50 to 60% of deaths in patients between 5 and 19 years of age in industrialised western nations, and a major

contributor to the mortality in developing countries³⁻⁷. It is the leading cause of death in children over the age of one in developed countries as well as children over the age of 4 in developing countries.

Population based surveys show that overall incidence rates follow a trimodal pattern, with peaks in early childhood, late adolescence/early adulthood and the elderly (Fig 1), with mechanisms of injury correlating with age groups. For children under the age of 17, hospital based incidence rates of 70 per 100,000 populations per year are reported⁸.

Patients who sustain traumatic brain injury (TBI) have the highest mortality and permanent disability of all trauma patients; TBI has been implicated in as much as 70-80% of accidental deaths following trauma in children^{9,10}.

The direct costs associated with TBI are staggering: 2.56 billion US Dollars were spent in total hospital charges for 58,600 admissions in the continental US in the year 2006¹¹. A further cost of up to 7 billion USD was incurred for rehabilitation, disability support and loss of productivity. For each injury death, there are more than 200 emergency department visits¹.

Fig 1 Annual mortality rate by age for severe TBI in the United States 1997-2007

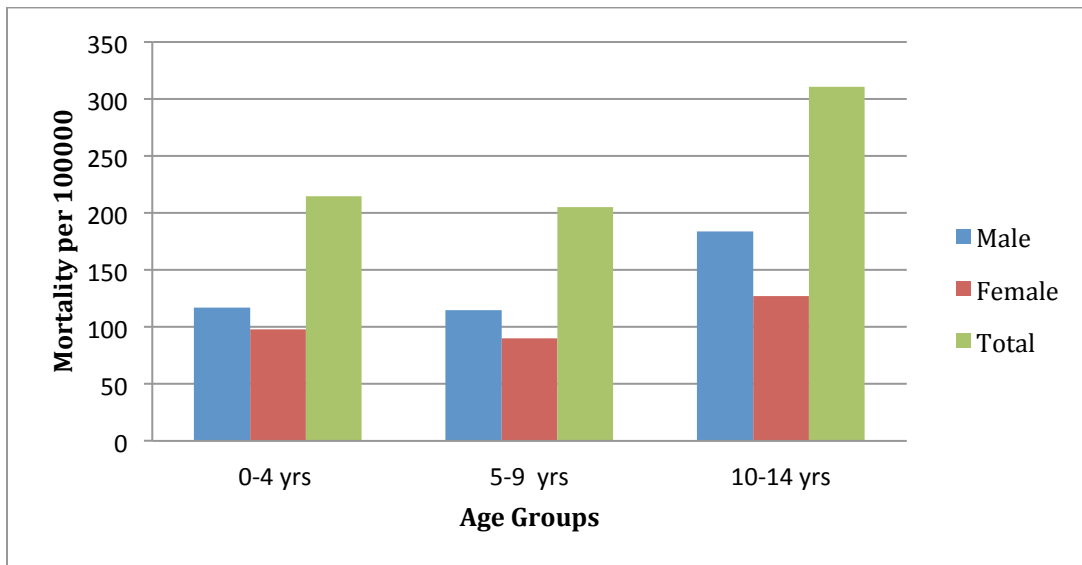


Fig 1: Victor G. Coronado et al, Surveillance for Traumatic Brain Injury Related Deaths United States, 1997-2007 Surveillance Summaries May 6, 2011 / 60(SS05);1-32

2.2 Physiological considerations in TBI

2.2.1 Brain metabolism and circulation

The brain is the most metabolically active organ in the body, accounting for 1-2% of body weight but receiving at least 10% of the glucose and oxygen supply of the body, with 10% of the cardiac output perfusing the brain in an awake and resting state. Oxidative metabolism of glucose in turn provides 99.5% of the brain's energy via production of ATP under normal resting circumstances that is partly used to maintain cell membrane ionic pump functions, such as the Na⁺/K⁺ ATPase. In special circumstances (e.g., lactation, diabetes, starvation), oxidative metabolism of the monocarboxylic acids and ketones may be utilized for energy provision.

2.2.2 Regulation of cerebral blood flow

The brain has very limited innate capacity for oxygen and glucose storage, and hence depends on continuous blood flow to meet these needs. Availability of these substances depends on blood substrate concentration, volume of blood flow, and the rate at which the substrate crosses the blood-brain barrier. Cerebral blood flow (CBF) is regulated to provide an adequate substrate supply to the brain, mainly through changes in diameter of resistance vessels and therefore vessel caliber¹². This regulation responds to metabolic signals, blood pressure, viscosity, and changes in the arterial partial pressure of CO₂. In metabolic autoregulation, cerebral blood flow is coupled to metabolic demand, i.e. alterations in metabolic needs lead to proportional changes in CBF.

As regards pressure autoregulation, principles underlying Poiseuille's equation of laminar flow apply to arterial flow:

$$CBF = k (CPP \times d^4) / (8 \times l \times \nu)$$

(k is constant, CPP is cerebral perfusion pressure, d is vessel diameter, l is vessel length and ν is blood viscosity)

All other factors remaining constant, alterations in CPP are compensated by dynamic changes in vessel diameter to maintain near constant CBF¹³. Briefly, increased CPP results in arteriolar constriction and decreased CPP results in arteriolar dilation. Normally, pressure autoregulation maintains relatively constant CBF in the CPP range of 50 to 150 mm Hg (Fig. 2). CPP beyond these

ranges result in loss of capacity to autoregulate, as the vessel calibers are maximally dilated or constricted, resulting in pressure passive blood flow.

In considering viscosity autoregulation, Poiseuille's equation (above) is useful to predict the influence of viscosity on CBF. The viscosity of blood varies according to the levels of plasma proteins as well as the haematocrit. Higher viscosity equals raised cerebral vascular resistance [$CVR = 8 \times 1 \times \text{viscosity} / \pi \cdot r^4$] that leads to compensatory vascular changes by either vasodilatation or constriction, as appropriate to maintain near constant CBF^{14,15}.

Various theories have been advanced to explain the coupling of CBF to regional metabolism, as well as the mechanisms of pressure and viscosity autoregulation, but these remain poorly understood. Metabolic coupling is suggested to be a result of vasoactive metabolites from neurons. One such putative metabolite is adenosine. Other suggested chemicals include oxygen (O₂) and carbon dioxide (CO₂) as well as electrolytes H⁺, K⁺ and Ca²⁺^{16,17,18}. Some literature supports the role of vascular endothelium in cerebral autoregulation. The endothelium has important vasoactive mediators, with nitric oxide (NO) as the main factor effecting relaxation¹⁹. Transmural pressure rise triggers vasoconstriction (Bayliss effect) in the presence of endothelium^{20,21}. Endothelial substances mediating vasoconstriction include thromboxane A₂ and endothelin²².

Arterial CO₂ also exerts effects on vessel caliber and CBF. In the range of 20 to 60mmHg, 1 mm Hg change in P_{aco2} results in a 2% to 3% change in CBF under physiological conditions. Hypercarbia causes vasodilation and increased CBF, and hypocarbia results in vasoconstriction and decreased CBF. Whilst autoregulation is responsive to metabolism in adjusting CBF, CO₂ reactivity affects vessel caliber independent of any metabolic coupling. The effects of hypocarbia and hypercarbia are mediated by pH changes in the perivascular space. These effects last for less than 24 hours, after which the pH usually normalizes and vessel caliber reverts to normal dimensions²³.

2.2.3 The blood brain barrier and cerebral oedema

The blood brain barrier (BBB) is created by tight apposition of endothelial cells to separate the vascular system and the brain parenchyma. It is reinforced by numerous pericytes. A thin basement membrane surrounds endothelial cells providing support and a physical barrier between the circulation and the CNS environment. Astrocytes extend cellular processes covering the basement

membrane, enhancing the BBB by limiting cellular or macromolecular substances accessing the central nervous system (Figure 3).

Tight junctions in the brain endothelial cells within the brain prevent paracellular transport of most molecules. Oxygen, carbon dioxide and small lipophilic molecules such as ethanol can diffuse through the lipid membranes that constitute the BBB, but larger hydrophilic molecules require active transcellular transport mechanisms to enter the CNS^{24,25,26}.

Figure 2: Regulation of cerebral blood flow

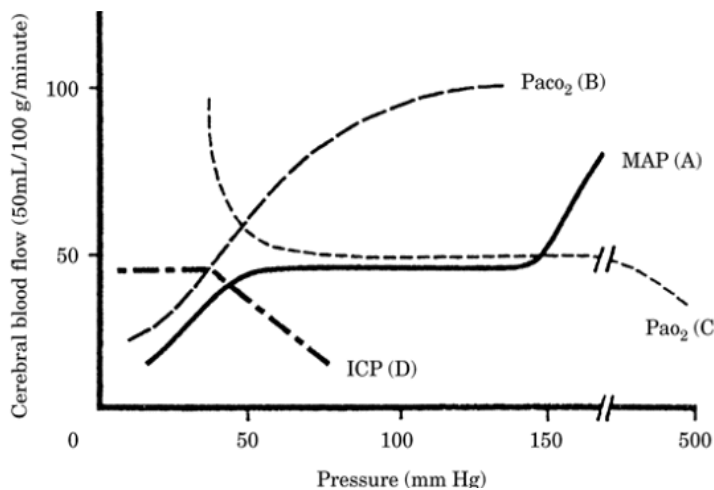


Fig 2: (A) Cerebral blood flow (CBF) autoregulation. CBF is maintained at 50 mL/100 g/minute for mean arterial pressure (MAP)/cerebral perfusion pressure = 50 to 150 mm Hg. (B) Linear relationship between partial pressure of arterial carbon dioxide (Paco₂) and CBF for Paco₂ = 20 to 80 mm Hg. (C) Pao₂ and CBF. (D) Intracranial pressure (ICP) and CBF. Adapted from www.neuroicu.info

Cerebral oedema is defined as increased brain water content. It is classified as *cytotoxic* when due to cellular swelling, *vasogenic* when leakage through a disrupted BBB increases extracellular fluid; *interstitial* when resulting from transependymal flow of CSF in patients with hydrocephalus; and *osmotic* when the brain is hyperosmolar relative to plasma, allowing water to flow along its concentration gradient through the BBB. Vasogenic and cytotoxic oedema are the most common forms in trauma.

Figure 3: The neurovascular unit (BBB)

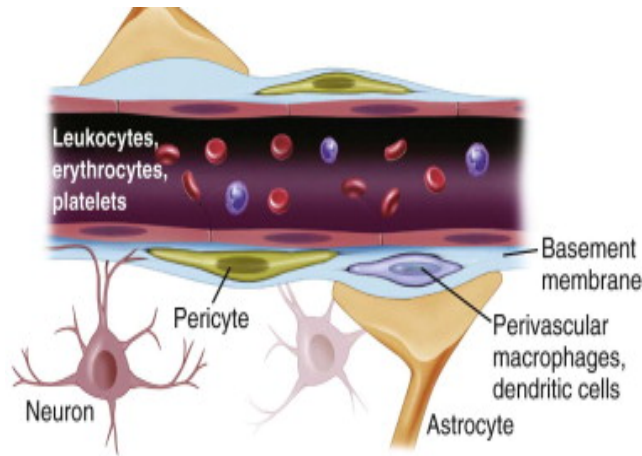


Fig 3: The blood brain barrier
Adapted from Youman's Neurological surgery 5th Edition

2.3 Intracranial pressure (ICP)

2.3.1 Dynamics

The cranial compartment is unyielding in volume in older children and adults. In health, the cranial volumetric contents consisting of brain (87%), cerebrospinal fluid (9%) and blood (4%) exist in a steady state dynamic, such that these incompressible fluids exert pressure in an enclosed cavity (filling pressure) influenced by the elastance of the enclosure. Along with contribution from atmospheric pressure (transmitted to the brain via the vasculature) and hydrostatic pressure (due to the fluid column of the contents) these three contribute to the ICP.

In older children and adults, ICP ranges from 5-15 mm Hg and on any Valsalva maneuver may reach as high as 40-50mm Hg but rapidly declines. In 2010, Avery *et al* conducted a study on lumbar CSF opening pressure in 197 children, in whom they had no evident reason to suspect raised ICP, and concluded that 28cm water was threshold for abnormally raised pressure (90th centile)²⁷. This approximates to about 20mmHg; however, it must be remembered that this was a study of predominantly older children (age range up to 8 to 18 years old), and ICP dynamics in health may be very different from that of the diseased state.

In a fixed volume environment, a rise in the content of one of the cranial components must be accompanied by a reduction in the other two as described by Monroe and Kellie.

²⁸²⁹. It may be expressed by the equation:

$$V_{\text{brain}} + V_{\text{CSF}} + V_{\text{blood}} + V_{\text{other}} = V_{\text{intracranial space}} = V_{\text{constant}}$$

The pressure-volume relationship is non-linear and hyperbolic at first in adults (sigmoid if completed): during the initial flat phase ICP rises slowly as compensation occurs (spatial compensation period) and further rises in volume then lead to a rapid increase in ICP (spatial decomposition period). A logarithmic scale of ICP versus volume yields a straight line, giving the pressure-volume index (PVI), understood to be the calculated volume in milliliters to raise ICP by a factor of 10. The PVI is age dependent, with infants having values of less than 10mls and adult values of 25mls reached by the age of 14, underlining important physiological differences in paediatric patients.

Figure 4: Pressure Volume Index

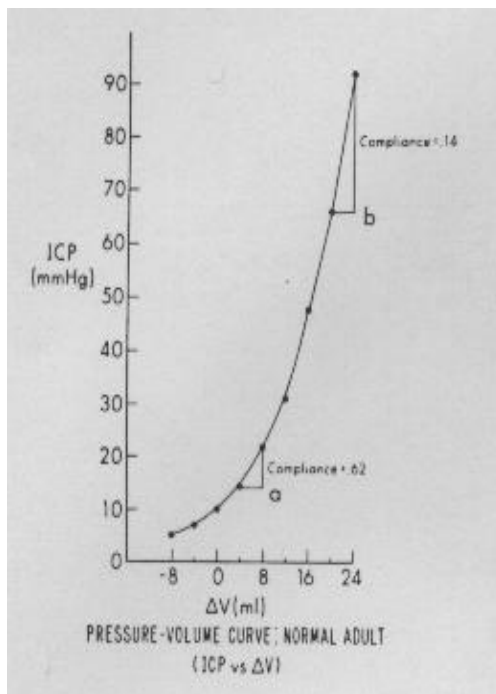


Fig 4: Pressure Volume Index curve, adopted from Marmarou A, Shulman K, Rosende R: A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. J Neurosurg 48: 530-537, 1978.

The normal ICP in younger children is not well known, and the optimal CPP is also unclear. The relationship between peak ICP values and duration of time above a clinical threshold of 20mmHg (widely accepted as a treatment threshold) versus outcome is equally unclear. Much of what we know about ICP in normal and pathological situations, and treatment protocols that arise from this knowledge, comes from adult studies, which are then extrapolated to children ³⁰.

2.3.2 Effects of high ICP

Failure to compensate for increased volume eventually leads to a rise in ICP; this pressure is transmitted to the compliant venous system. As cerebral perfusion relies on an arteriovenous pressure gradient, a rise in ICP leads to a reduction in cerebral perfusion pressure and a consequent reduction of cerebral blood flow if the lower limit of autoregulation reserve is reached.

CPP= Arterial in flow (MAP) – Venous pressure (Intracranial pressure)

A reduction in blood flow curtails nutrient supply, leading to bioenergetics failure, with membrane pump dysfunction and cytotoxic oedema leading to increasing ICP with further reduction in blood flow and onset of a vicious cycle. Hypoxia and hypotension similarly further contribute to this vicious cycle by impairing substrate supply.

2.3.3 Monitoring ICP

As much as it is clear that patients deteriorate with markedly elevated ICP, there are no clinical features that reliably estimate ICP values in trauma. Radiological features such as basal cistern obliteration may suggest raised ICP, but open cisterns do not exclude raised ICP³¹. Lundberg, in his landmark work in 1960 on ventriculostomy, demonstrated the potential value of ICP monitoring³². To date, a ventriculostomy catheter remains the gold standard in ICP monitoring; it can be reset to zero and recalibrated against an external standard³³. It also has therapeutic applications, allowing CSF drainage to reduce ICP³⁴. On the other hand, it carries the highest risks of infection and intracranial hemorrhage³⁵. It may be challenging to place a ventriculostomy in patients with compressed ventricles.

Other ICP monitoring methods include the subarachnoid bolt, which has been largely replaced with microsensor and fiberoptic transducers^{36,37}. These catheters may be inserted in the epidural space, subdural space or intraparenchymally, although the latter remains the most reliable. They are easy to insert and are reliable in measuring ICP; however, they cannot be reset to zero and exhibit drift over time³⁸.

ICP monitoring is only indicated in patients at risk of intracranial hypertension as it is associated with a small but present risk^{41,42}. The indications for ICP monitoring in children are largely extrapolated from data of adult studies; little paediatric-specific data is available, so indications for ICP monitoring in trauma vary between institutions. In adult guidelines, ICP monitoring has been given a level II recommendation for patients with severe TBI and normal CT findings if they are older than 40 years, have unilateral or bilateral motor posturing, or systolic BP lower than 90 mm Hg. In paediatrics, it is still considered only at the level of an option. Patients with moderate TBI are sometimes considered for ICP monitoring if undergoing treatment that would not allow serial neurological examinations such as prolonged anesthesia for surgery or pharmacologic paralysis for ventilatory management, or require treatment that might raise ICP, such as positive end-expiratory pressure (PEEP). A severe coagulopathy is a contraindication to ICP monitoring. Several potential noninvasive methods of assessing ICP to date; however, none have been reliable enough to be widely adopted in clinical use.

2.4 Pathophysiology of Traumatic Brain Injury

2.4.1 Biomechanics of Brain Injury

The basic common mechanisms causing TBI are contact or inertial (acceleration) loading. Contact injuries occur when the head strikes or is struck by an object, whilst inertial injuries (acceleration injuries) result from violent head movements. In practice, most traumatic brain injuries occur with a combination of the two basic mechanisms. Contact injuries cause local injuries as well as remote injuries. Local impact with various degrees of strain and stress result in linear or depressed skull fractures, as well as epidural hematomas and contusions when associated vascular structures are torn.

Remote effects occur as a result of either skull distortion or stress waves propagation. These may lead to injury patterns that include basilar skull fractures and countercoup contusions. Inertial loading on the other hand occurs from impact or from impulsive loading causing varied injuries. Three types of acceleration can occur: translational, rotational, and angular. Upon impact, the brain moves relative to the rigid calvarium, causing the bridging vessels between the brain and the dura to tear. Secondly, the force delivered to the soft brain causes it to deform.

Definition of Brain Injury Processes

Various combinations of the main mechanism of contact or inertial forces transmit destructive energy to the skull and hence its contents, with resultant variable degrees of injury to neurons, glial cells, axons and blood vessels at the moment of impact. This is termed **Primary brain injury**. A delayed phase of injury follows as a consequence of intracellular and extracellular pathways that occur over minutes to hours, and may last for weeks after the injury. Superimposed on these events are secondary insults such as hypoxia, hypotension, cerebral swelling, and the consequences of increased ICP and reduced CPP. These later events are termed **Secondary Brain Injury**.

2.4.2 Primary Brain Injury processes

Skull Fractures

Linear fractures occur because of impact, with little role for head motion and acceleration. Hard impacting objects cause a linear fracture, with most of the energy from the object being used to deform the skull locally and less energy dissipated to move or accelerate the skull. Acceleration injuries may occur in parallel with an impact that will cause a fracture because most impact situations will set the head in motion and therefore cause acceleration of the head, superimposed on the contact loading effects. Small hard impacting objects may cause *depressed fractures*. Because of focused loading, little or no propagation of the fracture occurs.

Basilar fractures occur by either direct impact or propagation of stress waves through the skull as a result of remote impact. Basilar fractures may also occur as a consequence of impact to facial bones. Common impact points producing a basilar skull fracture include the skull base, facial or mandibular bones, and remote skull impact points.

Focal Brain Injury

Epidural hematoma

Epidural hematomas occur because of tearing of dural vessels during the fracture initiation or propagation period, with bleeding into the epidural space. Epidural bleeding may occur without associated skull fracture because the local skull bending caused by an impact are sufficient to tear dural vessels without causing bone failure.

Coup Contusions

They occur at the impact point with skull bending or fracturing, causing the underlying cortical and pial vascular network to tear under strain. Damage is more likely to occur when the skull is “rebounding” from the impact and the vessels are experiencing tensile strain.

Contrecoup Contusions

Contrecoup contusions have been attributed to the phenomena of cavitation effects and inertial loading. Of the two, the more likely mechanism of contrecoup damage is translational or angular head motion. Cavitation results from brain movement towards the impact site, and creates negative pressure directly opposite the loading point, with strain to these areas. Alternately, vascular disruption and cortical damage in contrecoup regions are due primarily to acceleration effects and can result from either translation or angular head motions.

Intracerebral Hematoma

Large traumatic intracerebral hematomas are considered contusions in which larger, deeper vessels have been disrupted. Smaller single hematomas that are not associated with contusion probably occur because of stress concentrations resulting from impact or because of acceleration-induced tissue strains deep within the brain.

Tissue Tear Hemorrhages (Microhemorrhages)

These hemorrhages are considered to be due to inertial or head motion effects distinct from the intracerebral hemorrhages, which classically occur parasagittally, and in the central third of the brain (“gliding contusions”).

Subdural Hematoma

These occur chiefly either in relation to contusion and laceration, or as a form of vascular disruption involving tearing of parasagittal bridging veins located along the interhemispheric fissure and sagittal sinus.

Diffuse Brain Injury

Cerebral Concussion

All gradations of concussions (transient reversible neurological dysfunction as a result of trauma) are produced entirely by inertial loading^{43,44}. For a concussive injury, most of the strain is insufficient to cause structural damage. Instead, damage to the structures may be either partially or completely reversible, depending on the severity of the inertial loading.

Diffuse Axonal Injury

Axonal damage appears to be caused by angular rotational acceleration and not by contact phenomena, but that the magnitude of rotational acceleration needed to produce DAI requires the head to strike an object or surface, raising the likelihood of superimposed contact injuries^{45,46}. Critical factors in estimating the amount and extent of axonal damage include the magnitude, duration and onset rate of the angular acceleration, in addition to the direction of motion and the role of the intracranial membranes^{47,48,49}.

2.4.3 Secondary Brain Injury processes

Delayed secondary neurological damage after TBI is seen in the clinical finding of a “lucid interval”. Approximately one third of severely head-injured patients who demise will have demonstrated a period of lucidity sufficient to obey commands or speak^{50,51}. The inference drawn is that the primary events were insufficient to damage the brain beyond functioning, highlighting the importance of the secondary damage⁵². The mechanism of secondary injury here is clear, other mechanisms can be more difficult to understand, predict, or monitor.

Common to many of these pathomechanisms are the release of excitatory neurotransmitters

(glutamate) and oxygen free radicals, hypoxia-ischemia, and cerebral oedema, shifting brain metabolism toward anaerobic processes and dysregulated intracellular ion concentrations (calcium) that result in activation of both apoptotic/ necrotic cell death pathways with neuroinflammation^{53,54,55}. Associated systemic clinical 'secondary insults' (e.g. hypoxia, hypotension) also contribute synergistically to the complex biochemical fallout and pathophysiology. Given the vulnerability of the injured brain, a reduction of substrate delivery, whether via hypoxic or ischemic mechanisms, tend to aggravate the underlying pathophysiology.

Excitotoxicity

Following the primary injury, there is a direct release of excessive excitatory amino acids (EAA) chiefly glutamate & aspartate, into the extracellular space from presynaptic nerve terminals and astrocytes. These EAAs bind postsynaptic receptors (NMDA, AMPA) and activate ionic channels that cause influx of Ca^{2+} and Na^+ with passive secondary influx of water and anions such as Cl^- . The resultant cellular swelling coupled high levels of Ca^{2+} trigger necrosis and apoptosis, with activation of destructive enzymes including phospholipases, calpain/caspase as well as nitric oxide synthase (NOS)^{56,57,58}. Glutamate also depolarizes cellular membranes triggering voltage activated Ca^{2+} channels causing positive feedback loop⁵⁹.

Calcium Dysregulation

High intracellular Calcium in TBI arises from three principle sources: voltage gated channels triggered by mechanical membrane deformation, EAA triggered opening of channels and other pathways. Calcium is linked to many destructive effects including activation of proteases with cytoskeleton proteolysis, mitochondrial permeability transition, free radical toxicity, and mechanical perturbation of neuronal membranes^{60,61,62}. The final common pathway is widespread enzymatic activation with increased mitochondrial permeability causing cellular death via necrosis or apoptosis⁶³. Enzymatic induction has been confirmed in focal and diffuse models of TBI^{64,65}.

Disordered Brain Metabolism

The global or focal metabolic changes in TBI are demonstrated in various studies using the jugular/arterial differences in oxygen and lactate, 2-deoxyglucose technique assessing glucose metabolism, positron emission tomography studies with fluorodeoxyglucose, magnetic resonance spectroscopy as well as measurements of extracellular indices with microdialysis and brain oxygenation monitors. Aggregate data from these studies confirm that TBI triggers massive ion

fluxes across neuronal membranes with loss of resting membrane potential, and triggers the release of neurotransmitters into the extracellular space. The brain responds by increasing reuptake of neurotransmitters and ionic pumping to restore homeostatic balance. These energy dependent processes result in an abrupt increase in glucose utilization that is brief and maximal in areas most deformed by the injury⁶⁶. Focal lesions similarly trigger increased glucose metabolism in the penumbral border zone^{67,68}. PET studies demonstrate maximal glucose metabolism in the penumbra of contusions as well as the hemisphere underlying hematomas⁶⁹. The increased metabolism may persist for 5 to 7 days in humans^{70,71}. Animal and human data demonstrate glucose utilisation is then depressed for weeks after impact, in keeping with reduced metabolic requirements of the comatose brain.⁷²

Mitochondrial Permeability Transition

Mitochondrial Permeability Transition (MPT) a term coined by Kroemer and others, occurs as consequence of calcium-induced process of increased mitochondrial membrane permeability⁷³. Opening of mitochondrial membrane pores (MPTP) causes loss of transmembrane potential, swelling and eventual rupture of the outer mitochondrial membrane. This functional loss greatly influences neuronal ionic balance and metabolism. There is evidence that the molecule Cyclophilin D (CyD) that is normally involved in protein folding and found in the mitochondrial matrix, migrates to the inner membrane during MPT. Experimental data utilising cyclosporine to block CyD showed MPT activity was reduced, thereby implicating CyD as important in the pathway. MPT is an important mediator of necrotic cell death but its role in apoptosis is less clear with evidence for and against its influence^{74,75,76}. In vitro studies and TBI animal models suggest neuroprotective properties of cyclosporine, a subject of ongoing testing^{77,78}.

DNA Damage

The pathways resulting in DNA damage are chiefly via apoptosis and oxidative stress (nitric oxide [NO]). DNA damage is linked to apoptosis but apoptosis can occur without DNA fragmentation⁷⁹. Other mechanisms of DNA damage involve tumour suppressor gene *p53* which has varied roles in growth and apoptosis. Increased expression of *p53* with increase in DNA fragmentation and neuronal apoptosis has been shown after focal and diffuse TBI^{80,81}. Other delayed mechanisms include raised endonuclease activity with DNA fragmentation⁸².

Free Radical Formation

Molecular particles with unpaired electrons in their outer electron shells have a high chemical reactivity, and these free radicals are found in normal health as part of the mitochondrion respiratory chain. They also have immunological use as part of leukocyte bacterial killing^{83,84}. In TBI, these free radicals mainly form reactive oxygen species (ROSs) such as superoxide (O_2^-), which are injurious to cellular components including proteins, nucleic acids and lipids⁸⁵. The high concentrations of polyunsaturated fatty acids in the brain coupled with low levels of neuronal glutathione (anti-oxidant) make it particularly vulnerable to this ROSs^{86,87}.

Coupled Lactate Metabolism

Although traditionally glucose has been assumed to be the sole energy substrate for neurons, recent evidence suggests a synergistic coupled lactate metabolism between astrocytes and neurons, with astrocytes anaerobically metabolising glucose crossing the BBB and releasing lactate to the extracellular space, and neurons taking up lactate and metabolizing it aerobically via oxidative phosphorylation, generating 36 ATP molecules. Active neurons release glutamate into the extracellular space that is then taken up actively by astrocytes, triggering further astrocytic glucose breakdown. Experimental rodent TBI models suggest that there is an age-dependent ability of the brain to use alternative energy substrates after injury. The brain demonstrated reduced cortical contusion volume in younger rodents provided with a ketogenic diet⁸⁸.

2.4.4 Unique aspects in Paediatric patients

Anatomic and physiologic differences in children influencing the pathobiology of TBI

TBI physically affects the paediatric population differently from adults, due in part to differences in body size, proportion and physiology.

Anatomical considerations

Children generally have greater head to body surface area ratio and thinner skull bones, leading to increased susceptibility to the forces generated during impact events. The underdeveloped neck muscles and spinous processes, with associated ligament laxity and increased physiological mobility, all increase vulnerability to rotational impulsive stresses and strain.

Pathophysiological considerations

Brain constitution

The paediatric brain has higher water content (88%) compared with adults (77%) which is inversely related to the myelination process⁸⁹. The paediatric brain is thus softer and more prone to acceleration-deceleration injury. The unmyelinated brain is also more susceptible to shear injuries.

ICP dynamics

It is often considered that infants and young children may tolerate ICP increases better because of open sutures; however, how true this is in acutely raised ICP is not known, especially given the lower blood pressure norms and different cerebrophysiology of infants. Generally, the paediatric brain has a lower PVI with faster rise in intracranial pressure (10 mls in children versus 25 mls in adults)⁹⁰. What constitutes normal or a 'safe' ICP in children is unknown. Even in adults, there is some discussion still about what threshold of ICP requires treatment. In children, this is further complicated by the wide range of physiological change across the age range: an infant is hardly comparable to a 5-year old, who in turn is quite different from an adolescent. Furthermore, the dynamics between ICP and the adequacy of blood flow in physiological situations may be very different from that of a pathological situation, where underlying cellular stress, dysregulation of cerebral blood flow dynamics, microvascular injury and ischemia may be occurring. How this affects clinical decisions about ICP monitoring in children is discussed below.

Cerebral swelling

Diffuse cerebral swelling occurs more frequently in children with severe TBI as compared to adults^{91,92}. The age related mechanisms influencing this swelling are unclear but putative pathways include hyperemia,^{93,94,95} relatively compliant skulls with larger cranial changes and more diffuse distortions of the brain at injury, early oedema, either due to more diffusion of excitotoxic neurotransmitters in the immature brain, enhanced inflammatory response or enhanced BBB permeability^{96,97,98,99,100}. Other mechanisms common to all age groups such as DAI, intracranial hematomas and subarachnoid hemorrhage also play a role.

Neuroplasticity

Although children have higher neuroplasticity as compared to adults, there is evidence suggesting the developing brain is more susceptible to apoptotic neuronal cell death after TBI^{101,102,103}. This may partly contribute to our understating of why outcomes in infants with severe TBI is noticeably worse as compared to other age groups¹⁰⁴.

Hypotension and cerebral perfusion pressure

Systemic mean arterial pressure (MAP) is defined as the mean perfusion pressure throughout the cardiac cycle. MAP sensed by baroreceptors located in the carotid sinuses and the arch of the aorta is the basis for receptor control of arterial pressure, mainly by adjusting heart rate and arteriolar vessel radius. MAP is also the basis for autoregulation by organ systems such as the kidney, heart, and brain.^{7,20} MAP is the product of SVR and cardiac output (MAP= SVR × cardiac output).^{7,10}

MAP is generally closer to diastolic pressure because diastole represents about two thirds of the cardiac cycle when the mean heart rate is close to 60/min. This relationship is expressed in the well-known formulae :

$$\text{MAP} = \text{DBP} + (\text{SBP} - \text{DBP})/3$$

and

$$\text{MAP} = [\text{SBP} + (\text{DBP} \times 2)]/3$$

However, the proportion of diastole in the cardiac cycle changes with changes in heart rate. In calculations of MAP for a manually obtained ABP, these formulas must be used with caution, because they provide a good estimate of MAP only when the heart rate is close to 60/min.¹⁰

The exact incidence and impact of hypotension in childhood TBI is difficult to determine due to differential definitions. Norms for blood pressure in children are different according to the age of the child, yet age-adjusted figures are seldom reported. In fact, norms should ideally be calculated not only as a function of age but should also take height into consideration¹⁰⁵. BP normograms for age between children who are on the 3rd versus the 97th centile for age differ considerably. Furthermore, several studies use systolic BP as a measurement, even though MAP would be of greater relevance in calculating CPP. Also, what is normal for a patient without a head injury may

not be adequate for patients with disturbed brain physiology due to trauma, there is substantial evidence that traditional systolic BP targets in trauma underestimates secondary brain injury due to hypotension¹⁰⁶.

A report from the Traumatic Coma Data Bank described high prevalence (32%) of children under 4 years having hypotension¹⁰⁷. There is evidence suggesting that hypotension less than 75% of the age appropriate systolic blood pressure is associated with a poor outcome. Another author has evidenced the importance of maximal systolic BP of more than 135mmHg as a powerful predictor of survival (19 fold increase)^{108,109}. A study of 58 head-injured children used systolic BP of less than 90 mmHg to define hypotension and PaO₂ of less than 60 mmHg to define hypoxia¹¹⁰. They found that 67% of those who had hypotensive and/or hypoxic group died, versus 16% for children with neither insult. Vavilala et al¹¹¹ found a poor outcome in all children who had an admission systolic BP of less than 90 mmHg. In their study though, the 75th centile systolic BP for age was a better predictor for outcome than the 90mmHg threshold. The same group found that the association between hypotension and outcome was greatest in the early period after trauma¹¹².

Calculating optimal CPP in children is even more challenging. Given that ICP treatment thresholds in children are subject to debate, CPP is arguably even more difficult because it depends not only on the age-related variability in normal ICP but also that of blood pressure. A fuller discussion on the subject is continued below.

2.5 Management of paediatric severe TBI

2.5.1 Treatment rationale

The principle of current neurosurgical and neurocritical care interventions is to avoid or treat secondary injuries, most commonly intracranial mechanisms (e.g. hematoma and elevated intracranial pressure) and systemic mechanisms (e.g. hypotension and hypoxemia). There are several variations in the choices made at different centres in how to treat TBI, and several controversies exist. What follows is a summary of some of the basic principles of relevance.

2.5.2 Non-surgical interventions

Prehospital and emergency room care

Availability and quality of pre-hospital care services is a crucial link in TBI care¹¹³. Appropriate and rapid prehospital management may significantly reduce mortality¹¹⁴.

Basic ATLS® principles are a cornerstone of the initial contact care guidelines. Rapid removal of the accident victim to a trauma care facility is critical to improve the chances of survival. Care personnel aim to extricate the patient safely without causing injury either to the casualty or other personnel at the scene¹¹⁵. A target of less than 30 minutes for the extrication of entrapped victims is recommended¹¹⁶.

All patients with a GCS score equal to or less than 8 are intubated; ventilation is controlled with continuous monitoring of oxygenation by pulse oximetry and preferably end-tidal CO₂ monitoring. As soon as possible, ventilator parameters should be checked with arterial blood gases. Preventing hypoxemia as well as hypo- and hypercapnia is important. The spine is immobilized while achieving safe airway via use of rapid sequence intubation. Early intubation may decrease mortality. However hyperventilation may increase the rates of severe hypercapnia to as high as 18%. Patients with severe hypercapnia had higher Injury Severity Scores and were more likely hypotensive, hypoxic, and acidotic^{117,118}.

Emergency room care proceeds along the same ATLS protocols with Primary surveys (Airway, Breathing, Circulation, Disability and Exposure) and Secondary surveys including history taking and constant re-evaluation. A reassessment of the neurological status at this stage after the resuscitative manouvres is important in guiding care and determining patient prognosis.

Critical care management

Monitoring

Neurological intensive care for severe TBI proceeds with institution of close monitoring for neurological status and secondary injury processes arising from cerebral (raised ICP, cerebral ischaemia, seizures) or systemic processes (hypoxia, hypotension, anemia, hyper- and hypoglycemia, and fever).

Neurological status

Evaluation of mental status, cranial nerve, and pupillary and motor functions are conducted as part of regular neurological observations to detect clinical deterioration, and monitoring of relevant laboratory parameters.

ICP monitoring

There is no clinical or radiological feature that can reliably estimate ICP^{119, 120}. Monitoring ICP potentially provides a therapeutic end point and is also a clinical trigger for further interventions; however, debate continues about the role of ICP monitoring. Although ICP is often increased early after TBI, secondary rises in ICP may occur at day 3 to 10 post injury in up to 30% of patients with intracranial hypertension as a consequence of delayed intracerebral hematoma, cerebral vasospasm, brain oedema, or systemic hypoxia or hypotension¹²¹. Several reports have questioned the role of ICP monitoring over the years, but the strength of circumstantial evidence has always been considered strong enough to recommend ICP in published guidelines and so the ethics of a randomized controlled trial in the face of this evidence was always thought to render such a trial impossible. However, a recent trial in South America circumvented some of these issues by introducing ICP monitoring in a context where the practice was not standard. Therefore, funding was available for one arm of the trial and these were compared with conventional treatment. The trial has caused some controversy because ICP monitoring was not found to be beneficial. Generalisation of the data from the trial to more established centres has been questioned for several reasons: the centre was not experienced in ICP monitoring, the mortality for both groups was very high (40%), hyperventilation was used as a first tier therapy in as much as two thirds of both groups without any form of controlling for induced ischemia¹²².

Still, the trial does raise the point that even if these concerns are valid, the outcome at such institutions is still valid. It is true that as much as ICP monitoring may produce important information, what benefits or harms the patient is what the clinician does in response to the ICP number. All ICP-lowering therapies have potential to cause harm and the ICP number alone does not reveal its underlying aetiology, and therefore the appropriateness of treatment. Neither does it reveal whether the treatment is causing harm (such as the potential for hyperventilation to cause vasoconstriction). Data from children with ICP and brain oxygenation monitoring reveal substantial variability in the impact of different ICP values on brain oxygenation, which is not unexpected given that several different pathophysiological processes may be at work, including cerebral oedema,

hyperemia, subclinical seizures, spreading depolarizations, impaired autoregulation, vasospasm, etc.¹²³. Arguably, not only does there need to be sufficient clinical experience in ICP monitoring if there is to be any benefit, but also perhaps other monitors are needed to complement the information produced by the ICP monitor alone. These, and several other issues, remain unresolved.

The ICP threshold that should be targeted if ICP is monitored in paediatric TBI is subject to some debate. Although the threshold of 20mmHg is widely used, the foundation for this in children is weak, with the recommendation largely extrapolated from adult data. In the current guidelines there is no evidence to base a Level I or II guideline, and it is suggested that ‘treatment of intracranial pressure may be considered at a threshold of 20mmHg’. Although most clinicians feel that the ICP threshold of treatment should take into account the age of the patient, there are no firm data to support any specific thresholds based on age.

Sharples et al examined the 20mmHg threshold and found that CBF had an inverse relationship with ICP above 20mmHg¹²⁴. Similarly, the pressure volume index changes significantly when ICP is above 20mmHg¹²⁵.

The indications for ICP monitoring vary substantially between different institutions. In a study of practices in the United Kingdom, 60% of children underwent ICP monitoring but there was wide variation across centres, and many centres used ICP-lowering therapies without an ICP monitor *in situ*¹²⁶. From a recent survey across 32 centres in the US and Europe, the following was found: all centres used ICP monitoring and all used a 20 mmHg threshold in most patients; a quarter reported using a lower threshold for the youngest children¹²⁷. Perhaps even more variable are the choices made for interventions used to treat increased ICP. Again, most data are extrapolated from adult studies.

CPP and cerebral ischemia

There are no reliable clinical findings for impending cerebral ischemia; established infarction manifests as a clinical deterioration in consciousness, development of a new deficit, or a perfusion defect on CT or MRI. The ideal monitor for cerebral ischemia would give regional and global information about CBF because of the inherent marked variations in regional CBF after trauma, and would provide continuous information because of the dynamic CBF changes over time after the

injury. No such monitor exists. Techniques that are available fall under two general categories: those that detect cerebral perfusion or blood flow, and those that monitor CBF indirectly through cerebral oxygenation.

The simplest measure of brain perfusion is CPP, which is calculated by subtracting ICP from mean arterial blood pressure (MAP). CPP is widely available and convenient but limited in that only ischemia caused by increased ICP or by decreased BP is assessed. Furthermore, autoregulation may or may not be intact after trauma, or its relative strength may be limited, which adds another dynamic to determining the adequacy of a particular CPP for metabolic need. Therefore, for these and many other reasons, several lines of evidence show that the correlation between specific CPP values and perfusion appropriate for metabolic need is poor, except at very low CPP ranges.

As discussed above, calculating what is an adequate blood pressure for a child with TBI is further complicated by different definitions of hypotension, different age-related norms, the influence of height on blood pressure norms, etc. Therefore, it would be expected that determining an optimal CPP would be even more challenging because it takes these uncertainties and combines them with the uncertainty factor of normative ICP. So it is unsurprising that variable practices exist. A survey of 32 centres in North America and Europe found that the minimum threshold used across these centres varied from 35mmHg to 75mmHg¹²⁸; many centres used 3 different age-related CPP thresholds; one site did not target a CPP threshold at all. Current guidelines recommend that 'a minimum cerebral perfusion threshold of 40mmHg may be considered', but only at the level of an option. There was no good evidence platform to suggest anything more than that¹²⁹.

Several studies have reported CPP thresholds and outcome in paediatric TBI, using varying definitions. For Jones et al, a CPP threshold of 50 mmHg for children under 13 years old was appropriate¹³⁰. Chambers et al reported critical CPP thresholds of 48, 54 and 58 for age-groups 2-6, 7-10 and 11-15 years respectively and found a pressure-time index that had a high predictive value for outcome¹³¹. The same group previously used receiver-operating curves and found 45 mmHg to be the minimum CPP threshold for outcome prediction¹³². A study by Prabhakaran et al compared outcomes in 2 groups of severely head-injured children, one maintained at CPP > 50mmHg and the other at CPP > 70mmHg¹³³. Although this was a small study, there was a suggestion that patients maintained at a higher CPP fared better; however, there were more deaths in that group. Given the small numbers of the study, a definitive conclusion was impossible. Hackbarth et al also suggested

that maintaining a higher CPP is important: $\geq 80\%$ of their patients in whom CPP was maintained $>50\text{mmHg}$ survived, and $>90\%$ if CPP was $>60\text{mmHg}$ ¹³⁴. A study of very young children found that CPP was more associated with outcome than ICP, and that a minimum threshold of 45mmHg showed an outcome difference. However, 80% of their sample population had suffered non-accidental injury, the pathophysiology of which may be quite different to that of accidental TBI. On the other hand, Grinkeviciute et al found no statistical difference in minimum CPP between favourable and unfavourable outcome in 48 children, and Downard et al found that CPP elevation beyond 50mmHg was not associated with improved survival¹³⁵. The difficulty with all of these analyses though, is always that lower CPP may be a surrogate marker for increased severity of injury, which is associated with more frequent hypotension and increased ICP; therefore, CPP may be less an independent predictor of death rather than a measure of how severely the patient is injured.

Increasingly, the concept is growing of using other surrogate measures to determine the adequacy of CPP in individual patients with TBI, rather than presuming the same CPP would be appropriate for all patients^{136,137}. Most of these data are in adult patients, very few target the paediatric population¹³⁸. Confirming that CPP thresholds are not equivalent for all patients, Figaji et al found that maintaining CPP above 50mmHg did not completely prevent episodes of low brain oxygenation (unrelated to high ICP, hypoxia or anemia)¹³⁹. Exactly how best to assess this adequacy of perfusion remains an inexact science. No perfect method yet exists; however, several have been used to invasively or non-invasively, by imaging or monitoring strategies, to provide an assessment of the adequacy of perfusion to the brain, each of which has provide some insights but remains limited in its scope^{140,141}.

Transcranial Doppler ultrasonography (TCD) uses ultrasound waves through thin skull bone insonation windows (usually temporal bone) to determine blood flow velocity in the major cerebral vessels. Since flow volume is proportional to flow velocity, estimations of CBF may be made. Experiments assessing the relationship between peak flow velocity and changes in CBF have suggested that changes in MCA-flow velocity may be used as an indicator of relative changes in blood flow^{142,143}. The method is useful in the ICU because it can be used as a bedside tool and provides dynamic data, especially in response to interventions, such as autoregulation testing. However, the absolute values of TCD-based flow velocities are limited by inter-observer variability, vasospasm, the effect of CO_2 , anatomical constraints (to finding an optimal window), and the

difficulty in obtaining long term monitoring. TCD-based parameters such as the pulsatility index have been described as non-invasive measures of ICP; however, its reliability has been questioned¹⁴⁴.

Global blood flow can be estimated using the Kety-Schmidt technique, which uses NO as an indicator gas and allows bedside measurements. Stable xenon-CT and perfusion CT enable regional blood flow measurements and portable scanners make it possible to perform the measurements in the ICU. Of course, PET imaging remains the gold standard for assessing multiple inter-related variables in the brain, including regional and global CBF, oxygen extraction fraction and the cerebral metabolic rate of oxygen. The problem, though, remains that PET, like most imaging modalities, can only be done on stable patients, requires removal from the ICU, and only provides a snapshot of the brain at one point in time – it cannot predict or monitor how this will change over time. Data from bedside monitoring modalities suggest that the latter is a very important factor, because the pathophysiological state is highly dynamic.

Regional CBF may be estimated by locally implanted devices relying on two different methods, namely thermal diffusion or the laser Doppler method. These devices are invasive and estimate CBF in limited regions of the brain, with varied representation of the whole brain. They do, however, give a continuous assessment of cerebral hemodynamics and correlate well with values obtained by stable xenon-CT^{145,146}. Near-infrared spectroscopy appears to work reasonably well in elective cardiac surgery patients, and perhaps neonates with hypoxic-ischemic encephalopathy, but its role in trauma is limited by the several factors that impair the passage of the near-infrared beam through the skull, including a swollen scalp, skull fractures, subdural and subarachnoid blood and cerebral oedema.

Increasingly, measures of cerebral oxygenation have been used in neurocritical care. Jugular Venous Oxygen Saturation ($Sjvo_2$) measures the partial pressure of oxygen exiting the cranium by a conventional or fibreoptic catheter placed at the level of the jugular bulb. Although not a true measure of global flow, it approximates hemispheric oxygenation status and can measure the arterial-venous difference in oxygen and lactate. It is, however, less sensitive to detect regional ischemia and the time of good quality data is reduced by the frequent need for adjustment. Fewer institutions utilize $Sjvo_2$ as regularly as in the past. Brain tissue Po_2 ($Pbto_2$) has been increasingly used as a monitor of the partial pressure of interstitial oxygen. Although it is a focal monitor it

appears to be sensitive to dynamic changes on global perfusion or hypoxia¹⁴⁷. Increasing use of complementary monitors have highlighted some of the limitations of care that is solely based on ICP alone, and may explain some of the variability of results reported in different studies.

Critical care intervention

The classic treatment paradigm for severe TBI has been a stepwise escalation in treatment aimed at controlling ICP. Various therapies are added if ICP does not respond adequately, starting with those having the least perceived risk and escalating to more aggressive measures. Although this is a widely used paradigm, it does not take into account the different causes of increased ICP, or the variability in different patients' response to specific ICP interventions¹³⁰ (see discussion above).

Management of CPP remains contentious . Current pediatric guidelines are largely extrapolated from adult TBI studies¹⁴⁸.CPP management strategy based on the concept of a vasodilator cascade set off by reducing CPP ¹⁴⁹. Some advocate targeting higher CPP thresholds while others caution against this, citing the risks of increasing ICP and promoting vasogenic oedema. Therefore, there is little agreement in adult TBI on what constitutes an optimal CPP. There are risks of both high and low CPP¹⁵⁰. In paediatric TBI, even less data is available to guide such a decision, and it is further complicated by the changing thresholds for BP with age (See discussion above).

There also is the described “Lund therapy” that emphasizes pharmacological control of microvascular pressure to minimize oedema formation in the brain^{151,152}. An increasingly popular approach has been to tailor the treatment to the underlying pathophysiology taking into account patient variability and the dynamic nature of the injured brain over time, using various monitors in combination to identify patient-specific alterations .

All these strategies are based to a greater or lesser extent on physiological rationales and observation of patient characteristics; however, few interventions have been tested in randomised controlled trials and none has clear evidence of superiority. That said, it is also clear that not only are outcomes from TBI progressively improving, and the outcomes in more aggressive treatment centres are considerably better than those of less aggressive centres¹⁵³. Which aspects of care maximally lead to those improved outcomes though, are not quite clear.

General measures optimising cerebral perfusion

Universal measures taken to minimize systemic factors that lead to raised ICP and reduced perfusion include elevating the head of the bed 30 degrees (reduces aspiration as well), sedation, airway protection/controlled ventilation, seizure control and treatment of systemic hemodynamic disturbances as well as temperature control. Other general supportive care should be instituted, including appropriate fluid, electrolyte and nutritional support with attention to endocrine dysfunction that may occur.

2.5.3 Surgical interventions

The majority of patients with severe TBI are managed by nonsurgical means - less than 30 percent require operative interventions. The role for surgery is increasingly based on the best available evidence of effectiveness of intervention. Operative intervention is generally acceptable in the following situations: evacuation of mass lesions associated with deteriorating level of consciousness, finding of new focal signs, severe and worsening headache, nausea or vomiting.

In unconscious, sedated and ventilated patients surgical evacuation is prompted by decline in neurological status (brainstem signs) and a sustained increase in ICP (often >25 mm Hg). Re-evaluation by CT scan after clinical deterioration may reveal an increase in mass lesion size and trigger operative intervention¹⁵⁴. Guidelines have been written to harness the best available evidentiary basis for treatment decisions¹⁵⁵.

3. Study justification

There is a paucity of data as regards the frequency and the impact of secondary insults on the outcome of paediatric TBI. Those studies that have been done tend to have relatively small cohorts, the secondary insults are not examined in detail, and/or associations with outcome are either not made or are only made with mortality not functional outcome. The largest series to date is from Pople *et al*, who reviewed 303 patients who had ICP monitoring for varied aetiology, 132 of these were TBI cases¹⁵⁶. However, the analysis of outcome included all the patients irrespective of aetiology, there was less robust review of the various parameters of ICP and CPP, and functional outcome was not assessed in detail. The study also did not include insults such as

hypotension/hypoxia. Other series have fewer subjects or include older teenagers that are more suited to adult TBI studies, hence confounding any results that are obtained.

For this study we decided to focus on pre- and intra-hospital hypotension and hypoxia, CPP thresholds and ICP thresholds in a large cohort of children with severe TBI.

3.1 Study objectives

The specific objectives of the study were as follows:

- 1) To describe the frequency of secondary insults amongst a large paediatric TBI cohort of patients.
- 2) To describe the association between raised ICP and decreased CPP and outcome as measured by mortality and the Paediatric EGOS.
- 3) To examine associations between differing parameters of raised ICP and outcome as measured by mortality and the Paediatric EGOS.
- 4) To describe the frequency and effects of prehospital and inpatient hypoxia and hypotension on the outcome as measured by mortality and the Paediatric EGOS. We aimed also to examine inhospital hypotension in greater detail by adjusting for the effect of age- and height in selecting our norms.

4. Methodology

4.1 Study design and duration

A hospital-based, retrospective descriptive cross-sectional study was performed. The study focused on the 5-year period from January 2006 to December 2010.

4.2 Study site, population and ethical approval

The study was performed at the Red Cross Children Hospital in Cape Town. Ethical approval was obtained from the relevant institutional boards of the University of Cape Town.

4.3 Data collection & quality assurance

Patients were identified from the Neurosurgery TBI database in which data are prospectively collected. Demographic and physiological data not in the database but required for the study were retrieved from patient clinical records.

All data were entered into an electronic data collection sheet designed for the study and were reviewed during data collection and post-collection for systemic or individual errors

4.4 Inclusion and exclusion criteria

All patients with a diagnosis of TBI who had invasive monitoring with complete medical records were included in the study. The following were excluded: patients not requiring monitoring (thought to be extubatable within 24 hours), monitor malfunction, patients who had a Glasgow Coma Score of 3/15 with fixed and dilated pupils and diffusely hypodense brain on head CT, suggesting global infarction patients with cervical spinal cord injuries and moderate TBI.

A total of 216 subjects from the prospective neurosurgery TBI database were considered; 75 patients were excluded for the following reasons: 65 were not monitored, 4 had monitor malfunction, 3 brain dead on arrival, 2 high cervical spine injuries, 1 traumatic aneurysmal rupture 2 weeks post injury (Moderate TBI).

A total of 141 patients were hence selected for the study, representing the group that were actively treated with intracranial monitoring and for whom we had a full set of data.

4.5 Data elements and outcome measures

Demographic data collected included gender and age.

Clinical data collected included mechanism of injury, presenting clinical features, duration of symptoms and the severity of the injury.

Physiological data collected included a range of variables to determine blood pressure and systemic oxygenation, ICP, and CPP. These were formulated for analysis as follows:

1. The measures of ICP analyzed:

- Mean ICP for duration of monitoring (mICP)
- Mean ICP first 24 hours (mICP24)
- Highest ICP during monitoring (hICP)
- Episodes of ICP>20 mmHg (eICP>20)
- Mean of the episodes of ICP>20 mmHg (mICP>20)

2. The measures of CPP analyzed

- Episodes of CPP less than 40 mmHg (eCCP<40)
- Episodes of less than 50 mmHg (eCPP<50)
- Lowest CPP (lowCPP)
- Mean CPP for duration of monitoring (mCPP)

3. Measures of systemic hypoxia:

- Initial or pre-hospital saturations < 90%
- In-hospital hypoxia: PaO₂ < 8 kPa (60 mmHg)

4. Measures of hypotension

- Initial Systolic BP < 90 mmHg
- In-hospital: MAP < 5th percentile for age, adjusted for height

MAP, ICP, CPP, and pulse oximetry were analysed from hourly records. PaO₂ was recorded from ICU arterial blood gas data that were performed routinely several times during the course of a day or whenever required by adverse changes in pulse oximetry or end-tidal CO₂. ICP was assessed at

the 20mmHg threshold and CPP at the 40 mmHg and 50 mmHg thresholds. Hypoxia was defined as pulse oximetry less than 90% or PaO₂ less than 8kPa. Hypotension was defined as initial systolic BP less than 90mmHg and MAP less than the 5th percentile for age and adjusted for height during ICU stay (height was measured in all patients)

Interventions

All the patients in the study had severe head injuries, and were therefore all intubated, ventilated, and sedated. Additional interventions included hypertonic saline, mannitol, thiopentone, external ventricular drainage and decompressive craniectomy.

Follow up data

Patients were followed up for at least 6 months after admission for inclusion in the study. Clinical notes at follow-up in the neurosurgical, occupational therapy, rehabilitative (occupational therapy, physiotherapy, speech and language therapy), behaviour clinic, and neurodevelopmental clinic to assign a functional outcome score based on the Paediatric Extended Glasgow Outcome Score (Paediatric EGOS). The functional score was assigned by the same resident paediatric consultant Neurosurgeon.

Outcome measures

The Paediatric Extended Glasgow Outcome Score (Appendix 1) was used.

4.6 Statistical analysis

Data were analysed using SPSS version 20.

Univariate analysis (chi square) was used to assess the relationship between the above clinical variables and the outcome parameters as measured by the mortality and the Paediatric EGOS. The latter was dichotomized as favourable (EGOS 1-3) vs. unfavourable (EGOS 4-8) to assess functional outcome.

All significant variables in univariate analysis were subsequently examined with logistic regression models to assess the relationship between the various secondary insults and outcome.

5. Results

Demographics and timelines (table 1)

The median age of the patients was 6 yrs; males constituted 57% of the cohort. Motor vehicle accidents (MVA) were the most common mechanism of injury (78%). ICP was monitored for a median of 5 days, and patients spent a median of 7.5 days in the ICU. Mean follow-up duration was 2.05yrs (range 6 months to 6 yrs). Demographics and timelines are as summarized in table 1.

Table 1: Demographics and timelines (n=141 patients)

| Characteristic | Value |
|-------------------------------------|--|
| Age (median,IR) | 6 yrs (IQR 3.7-10) range 2 mths-13 yrs |
| Gender (M/F) | 81/60 (57%/43%) |
| Mechanisms of Injury | |
| MVA-Pedestrian | 90 (63.8%) |
| MVA- Passenger | 20 (14.2%) |
| Fall | 12 (8.5%) |
| Blunt assault | 9 (6.4%) |
| Penetrating injury | 7 (5.0%) |
| Falling Objects | 3 (2.1%) |
| Duration of monitoring (median, IR) | 5 days (IR 4-8) range 1-16 |
| Duration in ICU (median, IR) | 7.5 days (IR 5-10) range 1-16 |
| Duration of follow-up (mean) | 2.05 ± 1.2 yrs range 0.5- 6 |

Values are expressed as mean ± SD /median with Interquartile range (IQR) or as numbers and proportions.

Baseline clinical characteristics (table 2)

Post resuscitation GCS was 6 (median, IR 5-7) with 60% of patients between GCS 5-7; 78% of the patients had GCS 7 and below. Thirteen patients (15.6%) had a post-resuscitation GCS of 9-11 and subsequently deteriorated to a GCS of 8 or less and were then invasively monitored.

Twenty-seven patients (19.1%) had at least one unresponsive pupil; 73% of subjects had diffuse TBI on CT (Grade II and III as per the Marshall criteria) Although the Marshall criterion has not been validated in pediatric populations, lack of widely accepted alternative CT radiological scoring systems for TBI informed our decision to include it in our analysis¹⁵⁷. Paediatric Trauma Score (PTS) is a composite score inculcating 6 variables: weight, SBP, mental status, airway maintenance, skeletal injury and open wounds. It is used as a marker of the severity of trauma^{158,159}. Likewise the Paediatric Index of Mortality (PIM) consisting of SBP, pupillary reaction (fixed or reactive), PaO₂/FiO₂ ratio, base excess, elective admission (Y/N), mechanical ventilation (Y/N), recovery from surgery (Y/N), cardiac bypass (Y/N), and high risk/ low risk diagnosis is used as an indicator of severity of critical illness¹⁶⁰. The baseline results are summarised in table 2.

Physiological parameters (table 3)

Systemic hypoxia was documented in 26% of patients in the prehospital period, and in 22% during the ICU stay. Similarly, hypotension occurred in 19.9% preadmission, and in 9.2% of patients in the ICU.

Most patients (89 %) experienced an ICP > 20 mmHg, with the median number of hourly-documented episodes being 9. The median ICP during the first 24 hours was 14 mmHg and the mean ICP throughout stay was also 14 mmHg (IQR 11-16).

Episodes of CPP below 40 mmHg and 50 mmHg occurred in 33% and 70% of patients respectively. The median of the lowest CPP for all patients was 64 mmHg (IR 58-70) and ranged from 18-92 mmHg. Physiological parameter results are described in table 3.

Table 2: Clinical profiles at admission (n=141 patients)

| Characteristic | Value (%) |
|--|-----------------------|
| Post resuscitation GCS | 6 (IR 5-7) range 3-11 |
| GCS 3 | 6 (4.3%) |
| GCS 4 | 15 (10.6%) |
| GCS 5 | 21 (14.9%) |
| GCS 6 | 38 (27.0%) |
| GCS 7 | 30 (21.8%) |
| GCS 8 | 18 (12.8%) |
| GCS 9 | 6 (4.3%) |
| GCS 10 | 6 (4.3%) |
| GCS 11 | 1 (0.7%) |
| Motor component of post-resuscitation GCS | 4 (range 1-6) |
| Pupil reactivity on admission | |
| Bilaterally reactive | 114 (80.9%) |
| Unilaterally nonreactive | 14 (9.9%) |
| Bilaterally nonreactive | 13 (9.2%) |
| PTS (median, range) | 6 (-1 to 5) |
| PIM 2 score | 0.08 ± 0.2 |
| CT classification (Marshall criteria) (Appendix 5) | |
| I | 5 (3.5%) |
| II | 56 (39.7%) |
| III | 47 (33.3%) |
| IV | 7 (5%) |
| Evacuated mass lesion | 13 (9.2%) |
| Non-evacuated mass lesion | 8 (5.7%) |

Values are expressed as mean ± SD /median with Interquartile range or as numbers and proportions.

PTS Pediatric Trauma Scale, PIM2 Pediatric Index Of Mortality 2

Table 3: Physiological parameters (n=141 patients)

| Characteristic | Value |
|--|------------------------|
| ICP | |
| mICP (mmHg) | 14 (11-16) range 2-58 |
| mICP24 (mmHg) | 14 (11-18) range 2-58 |
| hICP (mmHg) | 29 (22-38) range 6-99 |
| eICP>20 | 9 (1-24) range 0-128 |
| Number of patients (ICP>20) | 112 (89%) |
| mICP>20 (mmHg) | 25 (23-27) range 0-58 |
| CPP | |
| eCPP<40 | 3 (1-10) range 0-88 |
| Number of patients (CPP<40) | 47 (33%) |
| eCPP<50 | 8 (0-16) range 0-135 |
| Number of patients (CPP<50) | 99 (70%) |
| CPPlow (mmHg) | 44 (36-51) range 0-82 |
| Hypoxia | |
| Prehospital Saturations | |
| Number of patients (SaO2<90) | 37 (26%) |
| Intrahospital Arterial Blood gas PaO2 | |
| PaO2<8kPa (episodes) | 1.5(1-2.75) range 0-16 |
| Number of patients (PaO2<8kPa) | 32 (22%) |
| Hypotension | |
| Prehospital Number of patients with SBP< 90 mmHg | 28 (19.9%) |
| Intrahospital MAP <5 th percentile for age and height | 60 (56-64) range 30-94 |
| Number of patients with MAP< 5 th centile | 13 (9.2%) |

Values are expressed as mean ± SD /median with Interquartile range or as numbers and proportions

PTS Pediatric Trauma Scale, PIM2 Pediatric Index Of Mortality 2, eICP20: number episodes > above 20, hICP: highest ICP recorded mICP, mean ICP or duration of monitoring, mICP20 mean of episodes > above 20, mICP24 mean in initial 24 hours, mCPP24 mean CPP in initial 24 hrs, eCPP40 episodes of CPP<40, episodes CPP<50

Interventions and outcomes

Interventions and outcomes for this group of patients are summarized in Table 4.

Seventy-five percent of patients had a favourable functional outcome (EGOS 1-3) and 22% unfavourable (EGOS 3-8). Functional assessment was not possible from the clinical notes of 5 patients. Overall, 14 patients died (9.9 %).

Table 4: Interventions and outcome (n=141 patients)

| Characteristic | Value |
|----------------------------------|-------------|
| Interventions (number, %) | |
| Hypertonic saline | 102 (72%) |
| Thiopentone | 34 (24%) |
| Mannitol | 29 (20%) |
| Decompressive Craniectomy | 23 (16%) |
| External Ventricular Drainage | 15 (11%) |
| Functional outcome | |
| Favourable EGOS 1-3 | 105 (75%) |
| Unfavourable EGOS 4-8 | 31 (22%) |
| Inadequate functional assessment | 5 (3%) |
| Mortality | |
| Alive | 127 (90.1%) |
| Dead | 14 (9.9%) |

Values are expressed as mean \pm SD /median with Interquartile range or as numbers and proportions

Univariate analysis functional outcome (table 5)

The presence of pupillary abnormalities ($p < 0.001$) and focal deficits ($p < 0.001$) were significantly associated with unfavourable functional outcome. The post-resuscitation GCS approached significance ($p = 0.06$). The use of mannitol ($p = 0.007$) was associated with 3.4 times the odds of unfavourable outcome (95%CI 1.415-8.525). Decompressive craniectomy was significantly ($p = 0.032$) associated with favourable outcome (Odds ratio for unfavorable outcome 0.345 (CI 0.13-0.91).

Inhospital hypotension ($p=0.043$) was associated with 3.3 times the Odds (95% CI 1.037-10) of unfavourable outcome. All the parameters of ICP as well as CPP analyzed had significant associations with the outcome (Table 5).

Univariate analysis mortality outcome (Table 6)

Post resuscitation GCS ($p=0.019$) and the motor response ($p=0.012$) were associated with survival, whilst the pupillary abnormalities ($p=0.011$) and mannitol ($p=0.008$) were associated with mortality. A higher Paediatric Index of Mortality PIM ($p=0.014$) was associated with increased mortality, although with a wide confidence interval (95% CI 1.87-265).

Inhospital MAP less than 5% centile for age and height ($p=0.012$) was associated with 3.1 times the odds of death (95% CI 1.76-13.3). As with functional outcome, all parameters of ICP and CPP analyzed similarly had significant associations with the outcome (Table 6).

Table 5: Univariate analysis Paediatric E-GOS Functional Dichotomized as Favourable (1-3) vs. Unfavourable (4-8)

| | Pseudo R2 | Sig. p=0.05 | Exp (B) Odds ratio | 95% C.I. for EXP (B) | |
|--------------------------|-----------|---------------|--------------------|----------------------|--------|
| | | | | Lower | Upper |
| Age | 0.002 | 0.685 | 0.977 | 0.872 | 1.094 |
| Gender | 0.001 | 0.747 | 0.876 | 0.391 | 1.962 |
| Mechanism | 0.009 | 0.393 | 0.86 | 0.608 | 1.215 |
| Intubated on arrival | 0.010 | 0.358 | 1.504 | 0.630 | 3.590 |
| Post resus GCS | 0.090 | 0.060 | 0.682 | 0.518 | 0.897 |
| Motor component GCS | 0.085 | 0.060 | 0.604 | 0.421 | 0.865 |
| Pupillary | 0.164 | 0.000* | 3.182 | 1.759 | 5.757 |
| Focal deficits | 0.079 | 0.008* | 3.041 | 1.343 | 6.886 |
| PTS | 0.008 | 0.446 | 0.913 | 0.722 | 1.154 |
| PIM2 | 0.020 | 0.249 | 3.254 | 0.438 | 24.176 |
| Marshall CT score | 0.029 | 0.111 | 1.292 | 0.943 | 1.771 |
| Pre Hospital Hypotension | 0.033 | 0.118 | 0.362 | 0.101 | 1.294 |
| Pre Hospital Hypoxia | 0.001 | 0.795 | 1.125 | 0.463 | 2.734 |
| DCC | 0.048 | 0.032* | 0.345 | 0.131 | 0.910 |
| EVD | 0.003 | 0.588 | 1.407 | 0.409 | 4.843 |
| Thiopentone | 0.005 | 0.482 | 1.381 | 0.562 | 3.394 |
| Hypertonic saline | 0.008 | 0.395 | 1.503 | 0.588 | 3.843 |
| Mannitol | 0.078 | 0.007* | 3.474 | 1.415 | 8.525 |
| Hypoxic episodes<8kPa | 0.001 | 0.763 | 1.028 | 0.857 | 1.235 |
| In Hypoxia Category | 0.007 | 0.413 | 1.458 | 0.591 | 3.598 |
| In Hypotension <5% MAP | 0.042 | 0.043* | 3.360 | 1.037 | 10.886 |
| mICP | 0.165 | 0.014* | 1.143 | 1.028 | 1.272 |
| mICP24 | 0.093 | 0.007* | 1.067 | 1.018 | 1.119 |
| hICP | 0.109 | 0.003* | 1.042 | 1.014 | 1.070 |
| eICP20 | 0.049 | 0.035* | 1.018 | 1.001 | 1.035 |
| mICP20 | 0.048 | 0.046* | 1.038 | 1.001 | 1.076 |
| Lowest CPP | 0.073 | 0.012* | 0.965 | 0.938 | 0.992 |
| eCPP40 | 0.160 | 0.005* | 1.132 | 1.038 | 1.236 |
| eCPP50 | 0.087 | 0.012* | 1.028 | 1.006 | 1.050 |

Asterisk (*)denotes significant results (grey shading) PTS Pediatric Trauma Scale, PIM2 Pediatric Index Of Mortality 2, eICP20: number episodes > above 20, hICP: highest ICP recorded mICP, mean ICP or duration of monitoring, mICP20 mean of episodes > above 20,mICP24 mean in initial 24 hours, mCPP24 mean CPP in initial 24 hrs, eCPP40 episodes of CPP<40,episodes CPP<50

Table 6: Univariate analysis GOS Mortality Alive vs. Deceased

| | Pseudo R2 | Sig. p=0.05 | Exp (B) Odds ratio | 95% C.I. for EXP (B) | |
|--|-----------|----------------|-----------------------|-------------------------|---------|
| | | | | Lower | Upper |
| | | | | Age | 0.000 |
| Gender | 0.005 | 0.554 | 0.716 | 0.237 | 2.163 |
| Mechanism | 0.000 | 0.946 | 0.984 | 0.644 | 1.507 |
| Intubated on arrival | 0.000 | 0.970 | 1.022 | 0.323 | 3.233 |
| Post resus GCS | 0.091 | 0.019* | 0.634 | 0.434 | 0.927 |
| Motor response | 0.094 | 0.012* | 0.538 | 0.332 | 0.871 |
| Pupillary | 0.084 | 0.011* | 2.408 | 1.221 | 4.750 |
| Focal deficits | 0.049 | 0.070 | 2.799 | 0.919 | 8.522 |
| PTS | 0.030 | 0.195 | 0.817 | 0.601 | 1.109 |
| PIM2 | 0.125 | 0.014* | 22.289 | 1.870 | 265.658 |
| Marshall CT score | 0.010 | 0.660 | 1.104 | 0.710 | 1.718 |
| Pre Hospital Hypotension | 0.000 | 0.877 | 1.113 | 0.289 | 4.290 |
| Pre Hospital Hypoxia | 0.010 | 0.400 | 1.649 | 0.515 | 5.284 |
| DCC | 0.022 | 0.201 | 0.440 | 0.125 | 1.547 |
| EVD | 0.023 | 0.181 | 2.614 | 0.638 | 10.687 |
| Thiopentone | 0.016 | 0.291 | 1.877 | 0.583 | 6.043 |
| Hypertonic saline | 0.005 | 0.585 | 1.451 | 0.382 | 5.505 |
| Mannitol | 0.098 | 0.008* | 4.727 | 1.506 | 14.843 |
| Hypoxic episodes<8kPa In Hypoxia Category | 0.004 | 0.595 | 1.061 | 0.852 | 1.321 |
| In Hypotension <5% MAP | 0.020 | 0.228 | 2.058 | 0.637 | 6.649 |
| In Hypotension <5% MAP | 0.032 | 0.012* | 3.191 | 1.763 | 13.342 |
| mICP | 0.297 | 0.021* | 1.186 | 1.027 | 1.370 |
| mICP24 | 0.184 | 0.001* | 1.094 | 1.039 | 1.153 |
| hICP | 0.135 | 0.002* | 1.048 | 1.017 | 1.080 |
| eICP20 | 0.039 | 0.083 | 1.017 | 0.998 | 1.037 |
| mICP20 | 0.081 | 0.025* | 1.061 | 1.007 | 1.117 |
| Lowest CPP | 0.178 | 0.001* | 0.936 | 0.901 | 0.973 |
| eCPP40 | 0.176 | 0.007* | 1.099 | 1.026 | 1.176 |
| eCPP50 | 0.059 | 0.033* | 1.021 | 1.002 | 1.041 |

Asterisk (*) denotes significant results (grey shading) PTS Pediatric Trauma Scale, PIM2 Pediatric Index Of Mortality 2, eICP20: number episodes > above 20, hICP: highest ICP recorded mICP, mean ICP or duration of monitoring, mICP20 mean of episodes > above 20, mICP24 mean in initial 24 hours, mCPP24 mean CPP in initial 24 hrs, eCPP40 episodes of CPP<40, episodes CPP<50

Multivariate logistic regression analysis (table 7 and 8)

All significant variables in univariate analysis were subsequently analyzed with logistic regression models. Three variables, namely post resuscitation GCS, mICP and mICP24 were all independently associated with both functional and mortality outcomes. Pupillary anomalies (p=0.02) as well as the motor score (p= 0.02) were independently associated with unfavourable functional outcome.

**Table 7: Multivariate logistic regression analysis for unfavourable outcome
Outcome Dichotomized as Favourable (1-3) vs. Unfavourable (4-8)**

| | Sig. p=0.05 | Odds ratio | 95% C.I. | |
|----------------|----------------|------------|----------|-------|
| | | | Lower | Upper |
| Post resus GCS | 0.01* | 0.65 | 0.45 | 0.92 |
| mICP | 0.01* | 2.71 | 1.22 | 5.99 |
| mICP24 | 0.04* | 1.58 | 1.21 | 3.86 |
| Pupillary | 0.02* | 3.36 | 1.19 | 9.48 |
| Motor score | 0.02* | 0.63 | 0.35 | 0.94 |

Table 8: Multivariate logistic regression analysis Mortality
Dichotomized as Alive vs. Deceased

| | Sig. p=0.05 | Odds ratio | 95% C.I. | |
|----------------|----------------|------------|----------|-------|
| | | | Lower | Upper |
| Post resus GCS | 0.02* | 0.63 | 0.33 | 0.97 |
| mICP | 0.01* | 2.71 | 1.22 | 5.99 |
| mICP24 | 0.04* | 2.39 | 1.38 | 4.05 |
| hICP | 0.04* | 1.28 | 1.09 | 2.93 |
| eCPP<40 | 0.05* | 2.43 | 1.09 | 5.38 |

The highest ICP recorded (p=0.04) independently predicted mortality. An episode of CPP below 40 (p=0.05) was independently associated with 2.43 Odds of mortality (95% CI 1.09 - 5.38).

6. Discussion

Demographics and baseline characteristics

As expected, motor vehicle accidents (MVA) are the leading cause of severe paediatric TBI, perhaps as a result of urbanization¹⁻⁵. Similarly, males have a higher prevalence of TBI, presumably associated with higher risk-taking behavior^{2,5,8}. Most patients (60%) had GCS scores of 5,6 or 7 and hence classified by BTF guidelines as severe TBI. A small proportion (9%) were admitted with a higher GCS and deteriorated to a GCS of less than 8, requiring intubation and monitoring. The predominant pattern of TBI (diffuse in 73%) is also reported by other authors in paediatric TBI studies, distinct from adult TBI literature, and may reflect the unique anatomic-physiological features in children and/or mechanism of injury (see 1.2.3.4 above)⁸¹⁻⁸⁶.

Frequency of Secondary insults and influence on outcome.

Prehospital hypoxia occurred in 26%, and hypotension in 19.9 %, a smaller proportion than reported by other authors (31-68%)^{94,95,96}. Several factors may account for these apparent

differences. First, the physiological parameters reading in the field by emergency personnel is prone to human and technical errors. Second, failure to complete the records immediately introduces recall errors. Third, a patient's records may have been mis-transcribed during handover to trauma staff. It is likely that prehospital insults occurred more frequently but their recording is influenced by the quality of prehospital ambulance services and handover documentation. The fact that prehospital insults were not associated with outcome may reflect under-reporting of these insults, less likely effective prehospital emergency management to reverse hypotension and hypoxia.

As demonstrated by Haque et al, there is a significant influence of height and weight on the normative blood pressure values in children¹⁰¹. Applying the 5th centile age and height-adjusted threshold for MAP, hypotension was found in 9.2% of subjects during their ICU admissions. This may underestimate the prevalence of inhospital hypotension for two reasons: firstly, 50th centile values may be more appropriate in a clinical setting and secondly, weight adjustments need to be further included in assessing appropriate MAP target values. On the other hand, these may be more accurate figures than that reported elsewhere as we are unaware of any other study that has taken both age and height into account in defining hypotension in paediatric TBI. Taking both age and height into account to define a norm for age would appear to be the most robust method to defining hypotension.

In-hospital hypotension was significantly associated with unfavourable functional outcome and mortality, with any episode of hypotension associated with 3.1 times the odds of death ($p=0.012$). Our results are similar to other authors indicating the negative role of hypotension in TBI⁹⁵.

Physiological parameters and associations with outcome

Intracranial hypertension was common (89% of cases) and all the various parameters of raised ICP were associated with both unfavourable outcome and mortality in univariate analysis. On multivariate analysis the mean ICP in the first 24 hours as well as mean ICP for the duration of monitoring were independent predictors of functional outcome as well as mortality.

This finding suggests that in ICP control in the first 24 hours is a strong determinant of outcome. Its association with mortality may reflect the fact that more severely injured patients tend to have higher ICP early on and the risk of death for this group is high within the first 24-48 hours after

injury anyway. There is a paucity of comparative data in other paediatric TBI studies to elucidate this finding. Although the highest ICP recorded independently predicted mortality, we speculate this may also be a surrogate marker of severity of TBI injury. For all the various ways in which the burden of ICP can be assessed though, this is likely true. The adage 'correlation is not causation' is important to keep in mind; therefore, the association of high ICP with poor outcome may reflect its association with a more severely injured brain. It follows therefore that just because high ICP is associated with poor outcome, it does not mean that treating the ICP improves outcome. On the other hand, the observations that high ICP is deleterious to perfusion of the brain, and that perfusion of the brain responds to control of ICP, suggests that it likely is also responsible for true secondary injury^{161,162}.

CPP variables were also associated with functional outcome and mortality. Seventy percent of patients experienced at least 1 episode of CPP less than 50mmHg. Any episode of CPP less than 40mmHg (33% of subjects) had a 2.4 increased odds of mortality. CPP being a derivative of MAP and ICP is challenging in its interpretation, and so may reflect the effects of the associated arterial hypotension or intracranial hypertension.

Interventions and outcome

Although this was not the focus of the study, several interventions were assessed in this cohort. Of these, mannitol and decompressive craniectomy showed significant results. Mannitol was associated with unfavourable functional outcome and mortality. Although it is tempting to suggest a causal relationship, again it must be appreciated that this may be a surrogate marker of TBI severity, i.e. patients with more severely injured brains and high ICP were more likely to receive mannitol.

Decompressive craniectomy ($p=0.032$) was associated with a favourable functional outcome. This finding is similar to the findings of Taylor *et al* in a small-randomized controlled trial in children¹⁶³. A recent randomized controlled study in adult TBI suggested that early decompressive craniectomy may not benefit patients as hoped (as opposed to craniectomy used as a salvage procedure)¹⁶⁴. Although there are several methodological concerns about this particular study that prevent easy generalization, it may also be true that adult and paediatric patients may differ in their response to the intervention.

7. Study limitations

Although the TBI database is an ongoing prospective record, recognized limitations of retrospective studies include loss of records, recall bias and transcription errors.

The paucity of similar studies also places limitations to any comparative value.

The analysis of outcomes as binary outcomes may have contributed to loss of sensitivity, as resolution and small differences between the groups may have been missed.

Although the cohort is relatively large in comparison with many other studies in paediatric TBI with this degree of detail, the size remains relatively small when age-specific groups are considered. Thresholds for ICP and CPP in particular may be sensitive to age-specific factors and so should ideally be assessed in specific age groups. Future work should concentrate on narrow age bands where the inter-age physiological variability is minimized.

Many other studies define children up to the age of 21 years and so increase the size of their overall cohort at the expense of studying the pure paediatric population. The sample of this study is limited to children less than 13 years old and so does not include adolescents, the physiology of whom tends to be more similar to that of adults.

8. Conclusions

Secondary insults such as hypotension, hypoxia, raised ICP and reduced CPP are common after paediatric TBI. Although to some extent these may reflect an association with increased severity of brain injury, rather than independent determinants of outcome, multivariate analysis suggests several relationship with both mortality and functional outcome that are independent of measures of severity. Therefore, these may represent avoidable or treatable factors that potentially may improve outcome. This is the largest cohort of paediatric TBI in which a comprehensive assessment of these variables has been performed and as such provides a useful platform for comparison with adult studies, paediatric studies at other centres, and future studies at the same institution to assess whether the frequency of these secondary insults can be reduced.

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10. Appendices:

Appendix 1

Paediatric Extended Glasgow Outcome Score

- **1 = Upper good recovery**
 - There are no problems associated with the child's head injury that interfere with daily life.
 - Problems that existed before the child's injury may still be present (such as headaches, memory or attention problems, etc.).
- **2 = Lower Good Recovery**
 - The subject participates a bit less in leisure activities due to the injury, but he or she participates at least half as often as before injury.
 - The subject has returned to his or her former level of functioning, with minor problems associated with the head injury such as headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, concentration problems, etc.
- **3 = Upper Moderate Disability:** The subject is experiencing one or more of the following:
 - Reduced work or school capacity due to their injury.
 - Participates much less in leisure activities due to the injury (less than half as often as prior to the injury).
 - Frequent (once a week or more, but tolerable) psychological problems associated with the injury.
- **4 = Lower Moderate Disability:** The subject is experiencing one or more of the following:
 - Constant – daily and intolerable psychological problems associated with the injury.
 - Unable to participate: rarely, if ever, take part in social or leisure activities.
 - Able to work only in a sheltered workshop or non-competitive job (for older adolescents), in a school setting for severely impaired children or tutored at home, or currently unable to work or go to school.
- **5 = Upper Severe Disability:** The subject cannot return to school (only able to engage in life skills training) or work and is experiencing one or more of the following:
 - Unable to travel locally without assistance.
 - Cannot behave age appropriately outside the home.
- **6 = Lower Severe Disability**
 - The subject cannot return to school (only able to engage in life skills training) or work.
 - The subject needs frequent help from a caretaker to accomplish simple tasks that a child this age should be able to accomplish.
 - The subject requires constant supervision.
- **7= Vegetative state**
 - No meaningful interaction with environment
- **8=Death**

Appendix 2

Data Collection Form

| PT day | ICU Day | Date | Time | PbtO2 | Brain Temp | MAP | ICP | CPP | ABG time | ABG pAO2 | pCO2 | ABG PtiO2 | ABG Hb | Hb |
|--------|---------|------|------|-------|------------|-----|-----|-----|----------|----------|------|-----------|--------|----|
| 1 | D0 | | 1 | | | | | | | | | | | |
| 1 | D0 | | 2 | | | | | | | | | | | |
| 1 | D0 | | 3 | | | | | | | | | | | |
| 1 | D0 | | 4 | | | | | | | | | | | |
| 1 | D0 | | 5 | | | | | | | | | | | |
| 1 | D0 | | 6 | | | | | | | | | | | |
| 1 | D0 | | 7 | | | | | | | | | | | |
| 1 | D0 | | 8 | | | | | | | | | | | |
| 1 | D0 | | 9 | | | | | | | | | | | |
| 1 | D0 | | 10 | | | | | | | | | | | |
| 1 | D0 | | 11 | | | | | | | | | | | |
| 1 | D0 | | 12 | | | | | | | | | | | |
| 1 | D0 | | 13 | | | | | | | | | | | |
| 1 | D0 | | 14 | | | | | | | | | | | |
| 1 | D0 | | 15 | | | | | | | | | | | |
| 1 | D0 | | 16 | | | | | | | | | | | |
| 1 | D0 | | 17 | | | | | | | | | | | |
| 1 | D0 | | 18 | | | | | | | | | | | |
| 1 | D0 | | 19 | | | | | | | | | | | |
| 1 | D0 | | 20 | | | | | | | | | | | |
| 1 | D0 | | 21 | | | | | | | | | | | |
| 1 | D0 | | 22 | | | | | | | | | | | |
| 1 | D0 | | 23 | | | | | | | | | | | |

Appendix 3

Paediatric Index of Mortality Instructions for collecting the information needed to calculate PIM

PIM is calculated from information collected at the time a child is admitted to your ICU. Because PIM describes how ill the child was at the time you started intensive care, the observations to be recorded are those made at or about the time of first face-to-face (not telephone) contact between the patient and a doctor from your intensive care unit (or a doctor from a specialist paediatric transport team).

Use the first value of each variable measured within the period from the time of first contact to 1 h after arrival in your ICU. The first contact may be in your ICU, or your emergency department, or a ward in your own hospital, or in another hospital (e.g. on a retrieval). The pupils' reactions to light are used as an index of brain function; do not record an abnormal finding if this is probably caused by drugs, toxins or local injury to the eye.

If information is missing (e.g. base excess not measured), record zero (except for systolic blood pressure, which should be recorded as 120); do not leave the space blank.

1. Booked admission to ICU after elective surgery, or elective admission to ICU for a procedure such as insertion of a central line or monitoring or review of home ventilation (no=0, yes=1):
2. If there is one of these underlying conditions, record the code [number in square brackets]:
[0] none [5] cardiomyopathy or myocarditis
[1] cardiac arrest out of hospital [6] hypoplastic left heart syndrome
[2] severe combined immune deficiency [7] HIV infection
[3] leukaemia/lymphoma after 1st induction [8] IQ probably <35, worse than Down's
[4] cerebral haemorrhage [9] a neurodegenerative disorder
3. Response of pupils to bright light (both >3 mm and both fixed=1, other=0, unknown=0):
4. Base excess in arterial or capillary blood, mmol/l (unknown=0):
5. PaO₂, mmHg (unknown=0):
6. FIO₂ at time of PaO₂ if oxygen via ETT or headbox (unknown=0):
7. Systolic blood pressure, mmHg (unknown=120):
8. Mechanical ventilation at any time during first hour in ICU (no=0, yes=1):
9. Outcome of ICU admission (discharged alive from ICU=0, died in ICU=1):

Also consider collecting: ICU admission number, age, diagnosis, days in PICU, intubation (no=0, or yes=1=an endotracheal tube in situ at any time during the ICU admission), gestational age (neonates), Apgar score at 5 min (neonates).

Appendix 4

Paediatric Trauma Score

The PTS was developed to reflect the children's vulnerability to traumatic injury. It emphasizes the importance of the child's weight and airway. Several studies have confirmed that the PTS is a valid tool in predicting mortality of a traumatically injured child. Mortality is estimated at 9% with a PTS > 8, and at 100% with a PTS ≤ 0. There is a linear relationship between the decrease in PTS and the mortality risk (i.e. the lower the PTS, the higher the mortality risk). The minimal score is -6 and the maximum score is +12.

| Pediatric Trauma Score (PTS) | +2 | +1 | -1 |
|-------------------------------------|------------------------|----------------------------|------------------------------------|
| Weight | >20kg(44lbs) | 10-20kg(22-44lbs) | <10kg(22lbs) |
| Airway | Patent | Maintainable | Unmaintainable |
| Systolic B/P | >90mm Hg | 50-90 mm Hg | <50mm Hg |
| CNS | Awake | +LOC | Unresponsive |
| Fractures | None | Closed or suspected | Multiple closed or open |
| Wounds | None | Minor | Major, penetrating or burns |

Appendix 5
Modified Marshall CT injury grading

Diffuse injury I (no visible pathology)
No visible intracranial pathology seen on CT scan

Diffuse injury II
Cisterns are present with midline shift of 0-5 mm and/or lesions densities present; no high or mixed density lesion $>25 \text{ cm}^3$ may include bone fragments and foreign bodies

Diffuse injury III (swelling)
Cisterns compressed or absent with midline shift of 0-5 mm; no high or mixed density lesion $>25 \text{ cm}^3$

Diffuse injury IV (shift)
Midline shift $>5 \text{ mm}$; no high or mixed density lesion $>25 \text{ cm}^3$
Evacuated mass lesion
Any lesion surgically evacuated

Diffuse injury V
Evacuated mass lesion

Diffuse injury VI
Non-evacuated mass lesion ($>25 \text{ cm}^3$)

Non-evacuated mass lesion
High or mixed density lesion $>25 \text{ cm}^3$; not surgically evacuated

